

filtration, washed with water and dried at 70° *in vacuo* to give 1.5 g. (75%) of green platelets exhibiting a bright metallic luster. The infrared absorption spectrum of this material was identical with that of an authentic sample of 2-methylthio-4,6-diamino-5-nitrosopyrimidine prepared by nitrosation of 2-methylthio-4,6-diaminopyrimidine.

2-Methylthioadenine (III, R = -SCH₃).—To a suspension of 6.0 g. of 2-methylthio-4,6-diamino-5-nitrosopyrimidine in a mixture of 8 ml. of 98% formic acid and 60 ml. of formamide warmed to 100–110°, was added slowly, in small portions and with stirring, 2.5 g. of sodium dithionite dihydrate. The addition required 15 minutes, during which time the green suspension had changed to a brown solution. The reaction mixture was then heated for 30 minutes at 190–200°, and the clear solution poured with stirring into 500 ml. of water. A yellow precipitate formed gradually on standing. It was filtered, washed with cold water and dried to give a yellow solid which was recrystallized from absolute ethanol and then from water to give 5.2 g. (88.5%) of a light yellow powder, m.p. 295–296° dec. This compound has been reported³² to melt at 290°.

The product was dried *in vacuo* over phosphorus pentoxide for 8 hours at 130° to give a hemi-hydrate.

Anal. Calcd. for C₈H₇N₅S·½H₂O: C, 37.9; H, 4.2; N, 36.9. Found: C, 38.1; H, 4.2; N, 37.3.

Anhydrous material was readily prepared by sublimation at 230° (0.05 mm.). Paper chromatography of the compound before and after sublimation showed only one spot.

Direct conversion of the S-methylisothiuronium salt of isonitrosomalonalonitrile in formamide, formic acid and sodium dithionite, gave a very low yield of product and the simultaneous formation of isoguanine and unidentified products. This latter procedure is thus unsatisfactory in this instance.

Adenine (III, R = -H).—To a suspension of 2.05 g. of 2-methylthioadenine in 400 ml. of water was added freshly prepared Raney nickel saturated with hydrogen (14 g. in 200 ml. of water). The mixture was heated under reflux with vigorous stirring for 16 hours, the hot suspension filtered and the residue extracted with hot water. The combined filtrates were evaporated to 200 ml. and cooled. The white solid which separated was collected by filtration and recrystallized from water to give 0.8 g. (51%) of

adenine, identified by comparison of its ultraviolet absorption spectrum and paper chromatographic behavior with an authentic sample.

Isoguanine (III, R = -OH).—To a solution of 2 g. of 2-methylthioadenine in 50 ml. of absolute ethanol was added 25 ml. of 30% hydrogen peroxide. A white precipitate gradually separated. The mixture was warmed on a water-bath, whereupon vigorous boiling ensued and the precipitated solid slowly redissolved. The clear solution was allowed to reflux overnight until the evolution of gas had ceased. The reaction solution was allowed to stand for two days, and was then filtered to give a light yellow solid. This product was purified by dissolution in dilute potassium hydroxide, decolorization with charcoal and reprecipitation with acetic acid; yield 1.4 g. (94%) of colorless isoguanine, identified by comparison of its ultraviolet absorption spectrum and paper chromatographic behavior with an authentic sample.

2-Phenyladenine (III, R = -C₆H₅).—To a suspension of 28 g. of 2-phenyl-4,6-diamino-5-nitrosopyrimidine in 1200 ml. of boiling water was added, in small portions, 100 g. of sodium dithionite dihydrate. After addition was complete, the mixture was boiled for 2 minutes and filtered. The light yellow filtrate was treated cautiously with 200 ml. of 18 N sulfuric acid (in the hood!), charcoal added and the mixture filtered. The filtrate upon cooling deposited the sulfate salt of 2-phenyl-4,5,6-triaminopyrimidine in the form of white needles; yield 19 g.

A mixture of 6 g. of the above sulfate salt and 90 ml. of a 1:1 molar mixture of ethyl orthoformate and acetic anhydride (which had been allowed to stand for one week prior to use) was heated under reflux for 4 hours. Cooling caused the separation of a light yellow solid which was collected by filtration and dissolved in dilute potassium hydroxide. Acidification with dilute acetic acid yielded a colorless solid which was recrystallized from water to give 2.4 g. of 2-phenyladenine, m.p. 320–321°, identical in every respect with the samples of 2-phenyladenine prepared directly from 2-phenyl-4,6-diamino-5-nitrosopyrimidine or from the benzamidine salt of isonitrosomalonalonitrile (see Table III).

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Synthesis of 2-Aminonicotinamides by Raney Nickel Cleavage of Pyrazolo[3,4-b]-pyridines¹

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A new synthesis of 2-aminonicotinamides is described which involves the reductive ring cleavage with Raney nickel of 3-hydroxy- and 3-ketopyrazolo[3,4-b]pyridines. The reaction is used as a means of establishing the structure of pyrazolo-pyridines formed by the condensation of 3-amino-5-pyrazolones with unsymmetrical 1,3-dicarbonyl compounds.

A recent publication from this Laboratory described the reductive ring cleavage of a number of 3-hydroxy-1-pyrazolo[b]pyrazines to yield 2-aminopyrazine-3-carboxamides.² The present paper is concerned with an extension of this work in which a new synthetic route to 2-aminonicotinamides by reductive ring cleavage of pyrazolo[3,4-b]pyridines is described.

Several synthetic routes to derivatives of 2-aminonicotinic acid are known. The parent amino acid may be prepared by the Hofmann reaction on quinolinic acid imide,³ ethyl 2-carboxamidonic-

tinic acid,⁴ 2-carboxamidonicotinic acid^{5–8} or quinolinamide,⁹ by alkaline cleavage of 2,4-dihydroxypyrimido[4,5-b]pyridine,⁹ strong acid hydrolysis of 2-aminonicotinonitrile¹⁰ or by the action of ammonium hydroxide on 2-chloronicotinonitrile or 2-chloronicotinamide.¹⁰ 2-Aminonicotinamide has been prepared by the action of alkaline hydrogen peroxide on 2-aminonicotinonitrile,¹⁰ by the action of sodium amide on nicotinamide¹¹ and by the

(4) E. Ochiai and I. Arai, *J. Pharm. Soc. Japan*, **59**, 458 (1939).

(5) S. Carboni, *Gazz. chim. ital.*, **83**, 637 (1953).

(6) H. H. Fox, *J. Org. Chem.*, **17**, 547 (1952).

(7) A. Philips, *Ber.*, **27**, 839 (1894).

(8) A. Philips, *Ann.*, **288**, 253 (1895).

(9) A. C. McLean and F. S. Spring, *J. Chem. Soc.*, 2582 (1949).

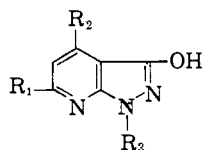
(10) E. C. Taylor and A. J. Crovetti, *J. Org. Chem.*, **19**, 1633 (1954).

(11) W. T. Caldwell, F. T. Tyson and L. Lauer, *THIS JOURNAL*, **66**, 1479 (1944).

(1) This investigation was supported by a grant from the American Cancer Society.

(2) E. C. Taylor, J. W. Barton and T. S. Osdene, *THIS JOURNAL*, **80**, 421 (1958).

(3) E. Sucharda, *Ber.*, **58**, 1727 (1925).

TABLE I
 PYRAZOLO(3,4-b)PYRIDINES


Com- pound	R ₁	R ₂	R ₃	Yield, %	Recrystn. solvent	M.p., °C.	Formula	Analyses, %	
								Calcd.	Found
I	-CH ₃	-CH ₃	-H	85	HOAc	338-339 dec.	C ₉ H ₉ N ₃ O	C, 58.9 H, 5.5 N, 25.8	C, 58.8 H, 5.6 N, 26.0
II	-CH ₃	-CH ₂ OCH ₃	-H	75	HOAc	272-273 dec.	C ₉ H ₁₁ N ₃ O ₂	C, 56.0 H, 5.7 N, 21.8	C, 56.1 H, 5.8 N, 21.9
III	-CH ₃	-CH ₃	-CH ₃	94	EtOH	211-212	C ₉ H ₁₁ N ₃ O	C, 61.0 H, 6.2 N, 23.75	C, 61.0 H, 6.2 N, 23.5
IV	-CH ₃	-CH ₂ OCH ₃	-CH ₃	79	10% EtOH	195-196.5	C ₁₀ H ₁₃ N ₃ O ₂	C, 58.0 H, 6.3 N, 20.3	C, 58.1 H, 6.6 N, 20.0
V	-CH ₃	-CH ₃	-C ₆ H ₅	89	CH ₃ OH	235.5-236.5	C ₁₄ H ₁₃ N ₃ O	C, 70.3 H, 5.4 N, 17.6	C, 70.2 H, 5.4 N, 17.2
VI	-CH ₃	-CH ₂ OCH ₃	-C ₆ H ₅	89	EtOH	163-165	C ₁₅ H ₁₅ N ₃ O ₂	C, 67.0 H, 5.4 N, 15.6	C, 66.8 H, 5.4 N, 15.2
VII				79	EtOH-ligroin	196-197	C ₉ H ₁₁ N ₃ O	C, 61.0 H, 6.2	C, 61.2 H, 6.1
VIII				85	Aq. EtOH	199-200	C ₁₄ H ₁₃ N ₃ O	C, 70.3 H, 5.4 N, 17.6	C, 70.4 H, 5.4 N, 17.8

condensation of β -ethoxyacrolein diethylacetal with malonamidamide.¹² A number of 4- and 6-substituted 2-aminonicotinamides were prepared by analogous condensations of malonamidamide with various 1,3-dicarbonyl compounds.^{13,14} Corresponding ethyl 2-aminonicotinate were synthesized by the condensation of the imino ether prepared from ethyl cyanoacetate with 1,3-dicarbonyl compounds.^{15,16} None of the above synthetic methods, however, is suitable for the preparation of 2-substituted amino derivatives of nicotinic acid or nicotinamide, nor can they be readily adapted to the preparation of N-substituted nicotinamides. We describe in the following discussion a new pyridine synthesis involving reductive ring cleavage of pyrazolo(3,4-b)pyridines, which allows the preparation of both of these classes of nicotinic acid derivative.

The requisite pyrazolo(3,4-b)pyridines were prepared by the condensation of 3-amino-5-pyrazolones with 1,3-diketones in dilute sodium hydroxide solution, and are listed in Table I. The 2-substituted pyrazolo(3,4-b)pyridines (VII, VIII) are deep red in color and are thermally unstable, in contrast to the 1-substituted derivatives, which are all colorless and thermally stable. This suggests that the former compounds may well exist in the tautomeric *o*-quinoid form IX.

(12) A. Dornow and K. Peterlein, *Ber.*, **82**, 257 (1949).

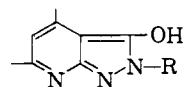
(13) A. Dornow and E. Neuse, *ibid.*, **84**, 296 (1951).

(14) A. Dornow and E. Neuse, *Arch. Pharm.*, **287**, 361 (1954).

(15) A. Dornow and A. Hargesheimer, *Ber.*, **86**, 461 (1953).

(16) A. Dornow and P. Karlson, *ibid.*, **73B**, 542 (1940).

These compounds underwent a smooth reductive ring cleavage of the N-N bond when heated under reflux in ethanol solution with an excess of Raney nickel to give good yields of derivatives of 2-aminonicotinamide. The products formed are listed in Table II. Identification of the products of the cleavages also served as a means of structure proof for the products formed by the condensation of 3-amino-5-pyrazolones with unsymmetrical 1,3-diketones. For example, the reaction of 3-amino-5-py-

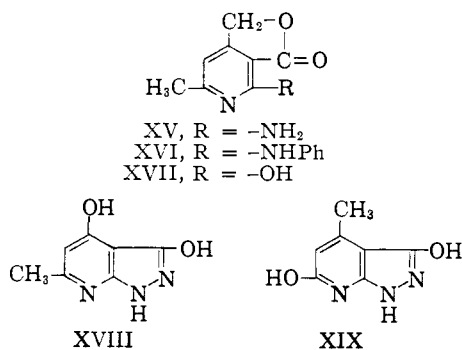


razolone, 1-methyl-3-amino-5-pyrazolone and 1-phenyl-3-amino-5-pyrazolone with methoxyacetylacetone could lead in each case to either of two isomeric pyrazolo(3,4-b)pyridines, or to a mixture of the two isomers. The products were shown to be the 4-methoxymethyl-6-methyl isomers (II and VI) by Raney nickel cleavage to the respective pyridines (XI and XIII). Subsequent treatment with 30% sulfuric acid resulted in each case in simultaneous hydrolysis, demethylation and lactonization to yield the lactones of 2-amino- and 2-anilino-4-hydroxymethyl-6-methylnicotinic acid, respectively (XV and XVI). Deamination of XV yielded the lactone of 2-hydroxy-4-hydroxymethyl-6-methylnicotinic acid (XVII). The structure of IV is assigned by analogy.

TABLE II
 NICOTINAMIDES

Compound					Yield, %	Recrystn. solvent	M.p., °C.	Formula	Analyses, %	
	R ₁	R ₂	R ₃	R ₄					Calcd.	Found
X	-CH ₃	-CH ₃	-H	-H	62	EtOH-ligroin	155-156	Reference 13		
XI	-CH ₃	-CH ₂ OCH ₃	-H	-H	45	CH ₂ Cl ₂ -ligroin	128-130	C ₉ H ₁₃ N ₃ O ₂	C, 55.4 H, 6.7 N, 21.5	C, 55.2 H, 6.7 N, 21.9
XII	-CH ₃	-CH ₃	-H	-C ₆ H ₅	80	Benzene	136-137	C ₁₄ H ₁₆ N ₂ O	N, 17.4	N, 17.4
XIII	-CH ₃	-CH ₂ OCH ₃	-H	-C ₆ H ₅	61	Benzene-ligroin	123-124	C ₁₅ H ₁₇ N ₃ O ₂	C, 66.5 H, 6.3 N, 15.5	C, 66.4 H, 6.4 N, 15.5
XIV	-CH ₃	-CH ₃	-C ₆ H ₅	-H	71	Benzene	207-208	C ₁₄ H ₁₆ N ₃ O	C, 69.7 H, 6.2 N, 17.4	C, 70.3 H, 6.3 N, 17.6

Similarly, the reaction of 3-amino-5-pyrazolone with ethyl acetoacetate could lead to XVIII or XIX, or to a mixture of the two isomers.



The product obtained, m.p. 356-358° dec., was cleaved with Raney nickel in ethanol solution to yield a 2-aminonicotinamide which was isomeric with the known 2-amino-4-methyl-6-hydroxynicotinamide.¹⁴ It follows that the cleavage product must have been 2-amino-4-hydroxy-6-methylnicotinamide, and the original condensation product can thus be assigned structure XVIII.

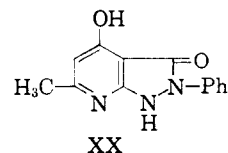
The condensation of 3-amino-5-pyrazolone with ethyl acetoacetate *in acetic acid* has been previously described as leading to a product, m.p. 330°, to which structure XVIII was arbitrarily assigned.¹⁷ In our hands, repetition of these experimental conditions yielded a product, m.p. 300-332°. Recrystallization of this material from aqueous dimethylformamide raised the melting point range but did not yield a pure compound. Confirmation that this product was actually a mixture was obtained by acetylation, which afforded three distinct compounds. One, m.p. 255-256° dec., was found to be identical with the monoacetyl derivative of 3,4-dihydroxy-6-methylpyrazolo(3,4-b)pyridine (XVIII). The second, m.p. 325-327°, was an isomeric monoacetyl derivative, while the third proved to be a diacetyl derivative which, upon heating in ethanol, was partially converted into the second compound, m.p. 325-327°. Alkaline hydrolysis of either of these latter two compounds yielded a pyrazolo(3,4-b)pyridine isomeric with XVIII.

(17) P. Papini, *Gazz. chim. ital.*, **83**, 861 (1953).

Raney nickel cleavage gave the known 2-amino-4-methyl-6-hydroxynicotinamide,¹⁴ thus establishing its structure as 3,6-dihydroxy-4-methylpyrazolo(3,4-b)pyridine (XIX).

It should be pointed out that Papini has prepared a number of pyrazolo(3,4-b)pyridines by the condensation of 1,3-dicarbonyl compounds with 1-phenyl-3-amino-5-pyrazolone.¹⁷ The structures assigned to these products are all incorrect, however, for Papini assumed his starting material to be 2-phenyl-3-amino-5-pyrazolone.^{18,19} The product of the reaction of 1-phenyl-3-amino-5-pyrazolone with ethyl acetoacetate in glacial acetic acid solution¹⁸ is probably 2-phenyl-3-keto-2,3-dihydro-4-hydroxy-6-methylpyrazolo(3,4-b)pyridine (XX). Since the same product is formed when the condensation is carried out in ethanol in the presence of sodium ethoxide.^{20,21}

However, an attempt to verify this structural assignment by Raney nickel cleavage of the product to 2-amino-4-hydroxy-6-methylnicotinic acid anilide was unsuccessful. The difficulty experienced



in this cleavage illustrates to an extreme degree the detrimental effect of 4- and 6-hydroxy groups on the yield of this reaction, presumably because of complex formation with the nickel.

Experimental²²

Starting Materials.—3-Amino-5-pyrazolone was prepared by the method of Hepner and Fajersztejn.²³ 1- and 2-

(18) P. Papini, S. Checchi and M. Ridi, *ibid.*, **87**, 931 (1957).

(19) For the proof of structure of this pyrazole, see A. Weissberger and H. D. Porter, *THIS JOURNAL*, **64**, 2133 (1942).

(20) S. L. Lasker and T. N. Ghosh, *Science and Culture*, **11**, 306 (1946).

(21) It is interesting that XX is colorless in contrast to VII and VIII, which are deep red. This suggests that XX, as a γ -pyridone, does not exist in the *o*-quinoid form suggested for the other 2-substituted derivatives.

(22) We are indebted to Dr. Joseph F. Alicino, Metuchen, N. J., and Drs. G. Weiler and F. B. Strauss, Oxford, England, for the microanalyses. All melting points are corrected.

(23) B. Hepner and S. Fajersztejn, *Bull. soc. chim.*, **4**, 854 (1937).

phenyl-3-amino-5-pyrazolones were prepared according to Weissberger and Porter.^{19,24,25} 2-Methyl-3-amino-5-pyrazolone was prepared from ethyl β -amino- β -ethoxyacrylate and methylhydrazine according to method (a) of Graham, Porter and Weissberger,²⁶ and attempts were made to obtain 1-methyl-3-amino-5-pyrazolone from ethyl cyanoacetate and methylhydrazine according to method (b). In our hands, this condensation gave poor and variable yields, and an improved procedure is given below.

Condensation of Ethyl Cyanoacetate with Methylhydrazine.—A mixture of 22.6 g. of ethyl cyanoacetate, 10 ml. of 98% methylhydrazine and 200 ml. of ethanol was heated under reflux for 48 hours. Chilling the amber reaction mixture at 0° for 3 hours caused the separation of 1-methyl-3-amino-5-pyrazolone as fine colorless needles, which were recrystallized from ethanol; yield 6.1 g. (27%), m.p. 197–198°. Slow evaporation of the mother liquor over a period of one week led to the separation of colorless prisms of 2-methyl-3-amino-5-pyrazolone; yield 7.0 g. (31%), m.p. 180–182°.

Condensation of 3-Amino-5-pyrazolones with 1,3-Diketones.—To a solution of 0.2 mole of the pyrazolone in 20 ml. of 5% sodium hydroxide at 40–50° was added 0.3 mole of the diketone. After one hour of stirring, the reaction mixture was adjusted to pH 5 with acetic acid, cooled to 0° and filtered. The collected pyrazolo(3,4-b)pyridine was washed, dried and recrystallized from an appropriate solvent (see Table I).

Raney Nickel Cleavage of Pyrazolo(3,4-b)pyridines.—A mixture of 10 g. of the pyrazolo(3,4-b)pyridine, 100 g. of settled Raney nickel catalyst and 1 l. of ethanol was stirred and heated under reflux for 3 hours. It was then filtered from the Raney nickel, which was extracted with hot ethanol. The combined ethanol filtrates were concentrated to dryness under reduced pressure and the residual 2-aminonicotinamide recrystallized from an appropriate solvent (see Table II).

Lactone of 2-Amino-4-hydroxymethyl-6-methylnicotinic Acid (XV).—A mixture of 0.5 g. of 2-amino-4-methoxymethyl-6-methylnicotinamide and 20 ml. of 50% sulfuric acid was heated under reflux for 3 hours, cooled, and poured over ice. Addition of ammonium hydroxide (to pH 4–5) followed by chilling at 0° yielded 0.38 g. (90.5%) of a pale, yellow solid, m.p. 249–251°, which crystallized from ethanol in the form of light yellow needles, m.p. 253–254°.

Anal. Calcd. for C₉H₉N₃O₂: C, 58.5; H, 4.9; N, 17.1. Found: C, 58.5; H, 4.9; N, 17.0.

Lactone of 2-Hydroxy-4-hydroxymethyl-6-methylnicotinic Acid (XVII).—A mixture of 1 g. of 2-amino-4-methoxymethyl-6-methylnicotinamide and 40 ml. of 50% sulfuric acid was refluxed for 3 hours, cooled and then poured into 100 ml. of cold water. After chilling to 0°, the solution was treated with 0.4 g. of sodium nitrite dissolved in 5 ml. of cold water. The reaction mixture was warmed at 80° for 15 minutes and then filtered to yield 0.41 g. (48%) of a pale yellow solid, m.p. 332–334° dec. This compound was identical with an authentic sample of the lactone of 2-hydroxy-4-hydroxymethyl-6-methylnicotinic acid prepared by the method of Harris, Stiller and Folkers.²⁷

Lactone of 2-Anilino-4-hydroxymethyl-6-methylnicotinic Acid (XVI).—A mixture of 1 g. of 2-anilino-4-methoxymethyl-6-methylnicotinamide and 40 ml. of 50% sulfuric acid was heated under reflux for 3 hours, cooled, poured over ice and the resulting solution adjusted to pH 5 with ammonium hydroxide. The sticky brown solid which separated was recrystallized from aqueous ethanol to give 0.54 g. (61%) of pale yellow needles, m.p. 151–152°.

Anal. Calcd. for C₁₄H₁₂N₂O₂: C, 70.0; H, 5.0; N, 11.7. Found: C, 69.6; H, 4.9; N, 11.9.

Condensation of Ethyl Acetoacetate with 3-Amino-5-pyrazolone. Method A.—A mixture of 10 g. of 3-amino-5-pyrazolone, 20 ml. of ethyl acetoacetate and 100 ml. of 5% sodium hydroxide was stirred at 50–60° for one hour.

Addition of 100 ml. of water to the resulting thick paste, followed by addition of acetic acid to pH 5, yielded a pale yellow solid which was collected by filtration, washed with water and dried; yield 16.7 g. (quantitative), m.p. 340–344° dec. Recrystallization from dimethylformamide yielded a white microcrystalline powder, m.p. 356–358° dec., which was shown to be 3,4-dihydroxy-6-methylpyrazolo(3,4-b)pyridine by Raney nickel cleavage (see below).

A monoacetyl derivative was formed by heating the product with a 1:1 mixture of acetic acid and acetic anhydride. Recrystallization from ethanol yielded small, colorless needles, m.p. 255–256° dec.

Anal. Calcd. for C₉H₉N₃O₃: C, 52.2; H, 4.35; N, 20.3. Found: C, 52.3; H, 4.6; N, 19.8.

Method B.—A mixture of 16.6 g. of 3-amino-5-pyrazolone, 35 ml. of ethyl acetoacetate and 100 ml. of glacial acetic acid was heated under reflux for 45 minutes, cooled, and the resulting solid mass ground with ethanol and filtered. Repetition of this process yielded, after drying, 27.6 g. of a white powder, m.p. 300–322° dec. Acetylation of 25 g. of this material with 100 ml. of a 1:1 mixture of acetic acid and acetic anhydride, followed by cooling of the reaction mixture overnight, yielded orange needles. Recrystallization from ethanol yielded 6.2 g. of colorless needles, m.p. 254–256° dec., identical with the monoacetyl derivative of 3,4-dihydroxy-6-methylpyrazolo(3,4-b)pyridine prepared as described above.

The filtrate from the acetylation reaction was evaporated to dryness and the residue was extracted with boiling ethanol to leave 4.7 g. of a white powder, m.p. 280–290° dec. Recrystallization from a large volume of ethanol yielded colorless microcrystals, m.p. 325–327°.

Anal. Calcd. for C₉H₉N₃O₃: C, 52.2; H, 4.35; N, 20.3. Found: C, 52.2; H, 4.7; N, 19.7.

Cooling of the above ethanol extract yielded 12.0 g. of small, colorless needles which lost form on heating at 180–185° and decomposed above 260°.

Anal. Calcd. for C₁₁H₁₁N₃O₄: C, 53.0; H, 4.4; N, 16.9. Found: C, 52.7; H, 4.2; N, 16.4.

Prolonged boiling of this material in ethanol yielded a monoacetyl derivative, m.p. 325–327° dec., identical with the material prepared above.

Hydrolysis of the monoacetyl derivative (m.p. 325–327° dec.) or the diacetyl derivative with 10% sodium hydroxide, followed by acidification with acetic acid, yielded a white powder, m.p. 334–336° dec., in almost quantitative yield. The product was shown to be 3,6-dihydroxy-4-methylpyrazolo(3,4-b)pyridine by Raney nickel cleavage to 2-amino-4-methyl-6-hydroxynicotinamide as described below.

2-Amino-4-hydroxy-6-methylnicotinamide.—A suspension of 10 g. of 3,4-dihydroxy-6-methylpyrazolo(3,4-b)pyridine and 100 g. of settled Raney nickel catalyst in 1 l. of ethanol was stirred and heated under reflux for 3 hours. The reaction mixture was filtered, the Raney nickel extracted with boiling ethanol, and the combined ethanol filtrates evaporated to dryness. Recrystallization of the residual greenish powder from ethanol with the aid of charcoal yielded 2.1 g. (21%) of colorless needles, m.p. 242–243°. The product gave no color with ethanolic ferric chloride.

Anal. Calcd. for C₇H₉N₃O₂: C, 50.3; H, 5.4; N, 25.15. Found: C, 50.4; H, 5.5; N, 24.9.

2-Amino-4-methyl-6-hydroxynicotinamide.—Raney nickel cleavage of 10 g. of 3,6-dihydroxy-4-methylpyrazolo(3,4-b)pyridine was carried out as described above to yield 3.3 g. (33%) of a white powder, m.p. 239–242° dec. Recrystallization from water yielded small colorless prisms, m.p. 249–251° dec. A mixture melting point determination with an authentic sample¹⁴ of 2-amino-4-methyl-6-hydroxynicotinamide, m.p. 250–251° dec., showed no depression (249–251°). The product gave a red-brown color with ethanolic ferric chloride.

Condensation of Ethyl Acetoacetate with 1-Phenyl-3-amino-5-pyrazolone. Method A.—A mixture of 8.75 g. of 1-phenyl-3-amino-5-pyrazolone, 10 ml. of ethyl acetoacetate and 50 ml. of glacial acetic acid was heated under reflux for 45 minutes. Crystalline material separated from the reaction mixture after 20 minutes. The mixture was cooled, diluted with an equal volume of ethanol and filtered to give 9.6 g. (80%) of a light tan solid which darkened above 295° and melted at 306–308° with decomposition.

(24) H. D. Porter and A. Weissberger, "Organic Syntheses," Coll. Vol. III, ed. by E. C. Horning, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 708.

(25) A. Weissberger and H. D. Porter, *THIS JOURNAL*, **65**, 52 (1943).

(26) B. Graham, H. D. Porter and A. Weissberger, *ibid.*, **71**, 983 (1949).

(27) S. A. Harris, E. T. Stiller and K. Folkers, *ibid.*, **61**, 1242 (1939).

Method B.—A mixture of 4.4 g. of 1-phenyl-3-amino-5-pyrazolone, 4 ml. of ethyl acetoacetate and 50 ml. of ethanol, in which was dissolved 0.5 g. of sodium, was heated under reflux and stirred for 1 hour. The reaction mixture, which contained a cream-colored precipitate, was cooled, diluted with ether and filtered. The collected solid was dissolved in 50 ml. of water and the pH adjusted to 4–5 with acetic acid. Filtration then yielded 3.4 g. (56%) of a color-

less solid, which darkened above 295° and melted at 305–307° with decomposition.

Acetylation of the product from method A above with a 1:1 mixture of acetic acid and acetic anhydride yielded a colorless acetyl derivative, m.p. 145–146°, identical with the acetyl derivative prepared in a similar manner from the product of method B above.

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

The Reaction of Malononitrile with Hydrazine^{1,2}

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The reaction of malononitrile or malononitrile dimer (1,1,3-tricyano-2-aminopropene-1) with hydrazine has been shown to give 3-cyanomethyl-4-cyano-5-aminopyrazole (I). A number of reactions of I are described which illustrate its versatility as an intermediate for the synthesis of condensed pyrazole heterocycles.

The reaction of malononitrile with hydrazine is reported⁴ to yield a dark brown oil to which the structure 3,5-diaminopyrazole was assigned. Support for this structure consisted of a nitrogen determination on a poorly crystalline benzal derivative, since the parent substance could neither be crystallized nor purified. A picrate of "3,5-diaminopyrazole" was prepared but not analyzed, since it was formed only in very poor yield. Ten years later, Knorr⁵ claimed an independent synthesis of 3,5-diaminopyrazole, which he described as a honey-yellow sirup, by a Curtius degradation sequence from pyrazole-3,5-dicarboxylic acid. The product proved to be too unstable to purify, but a nitrogen determination on the crude material was approximately in agreement with the calculated value for 3,5-diaminopyrazole. A dibenzoyl and a dibenzal derivative were prepared but not analyzed. Further details on the intermediates in the Curtius degradation and on the nature of the final product were promised but have not appeared.

Our attention was drawn to this work because of the unusual physical characteristics claimed for "3,5-diaminopyrazole." 5-Amino-3-pyrazolone is a high melting solid (m.p. 204° dec.) rather than a sirup, and indeed, all simple di- and poly-amino substituted nitrogen heterocycles are high melting solids as a result of strong intermolecularly hydrogen bonded crystal lattices. We therefore reinvestigated the reaction of malononitrile with hydrazine, and the present communication describes our results.

The reaction of equivalent amounts of malononitrile and hydrazine in ethanol solution, as described by von Rothenburg,⁴ resulted in a mildly exothermic reaction to give a dark oil with prop-

erties similar to those previously reported. Apparently von Rothenburg failed to notice that the reaction was accompanied by the evolution of ammonia. However, crystallization of this oil from glacial acetic acid yielded a colorless, crystalline solid, m.p. 198°, which was shown to have the molecular formula C₆H₅N₅ by microanalysis and by a molecular weight determination. Upon mixing malononitrile and hydrazine in a smaller volume of ethanol, the reaction proceeded so exothermically that it boiled without external heating within a few minutes, with concomitant vigorous ammonia evolution, and cooling of the reaction mixture resulted in the separation of the compound C₆H₅N₅ as a mass of tan crystals. On the basis of the above observations, it appeared that the product was formed from two moles of malononitrile and one mole of hydrazine, with loss of one mole of ammonia, according to the equation



and combination of the reactants in this proportion indeed led to the expected product in increased yield and in a higher state of purity.

The product C₆H₅N₅ formed a monoacetyl derivative, m.p. 215°, and an unstable monobenzal derivative, m.p. ~168°, apparently identical with the product claimed by von Rothenburg to be the dibenzal derivative of 3,5-diaminopyrazole. The difference of 1.5% in the nitrogen value found by von Rothenburg as compared with that calculated for the monobenzal derivative of C₆H₅N₅ may be ascribed either to the recognized unreliability of nitrogen determinations on such nitrogen-containing heterocycles, or to the presence of impurities in the admittedly crude sample which was analyzed. The infrared spectrum of the product C₆H₅N₅ showed strong N–H bonds at 2.98, 3.04 and 3.20 μ, and two sharp nitrile bands, one at 4.45 (unconjugated) and one at 4.55 μ (conjugated). The ultraviolet absorption spectrum showed only decreasing absorption with increasing wave length with no maximum above 220 mμ. It was recovered unchanged after heating for long periods in ethanol solution in the presence of sodium ethoxide. Thus, of the three structures (I, II and III) which could reasonably be con-

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(3) Visiting Scholar from the University of Marburg, sponsored by Der Stifterverband für die Deutsche Wissenschaft.

(4) R. von Rothenburg, *Ber.*, **27**, 685 (1894).

(5) L. Knorr, *ibid.*, **37**, 3520 (1904).