The reaction product of DPN^+ + PABA and DPN^+ + PABA-substituted compounds were isolated by paper chromatography (1:1 mixture of ethanol and 0.1 *N* acetic acid, ascending, 20 hours, Whatman #1 paper). The spots on the chromatogram were detected with a "Blak-Ray," long wave ultraviolet source. The following R_f values were obtained: DPN^+ = 0.62, DPN^+ + PABA = 0.84, DPN^+ + methyl *p*-aminobenzoate = 0.83, DPN^+ *p*-dimethylaminobenzoic acid = 0.83, DPN^+ + methyl *p*-dimethylaminobenzoate = 0.84, DPN^+ + *p*-acetylaminobenzoic acid = 0.62, DPN^+ + 3,5-dimethyl-4-aminobenzoic acid = 0.62. The spots were eluted from the paper with distilled water and absorption spectra of the eluted material were determined. DPN^+ and DPN^+ + 3,5-dimethyl-4-PABA showed an absorption peak at 260 mμ; DPN^+ + *p*-acetylaminobenzoic acid showed two absorption peaks, one at 260 mμ (R_f 0.62) and the other at 310 mμ (R_f 0.84). DPN^+ + PABA or methyl *p*-aminobenzoate, *p*-dimethylaminobenzoic acid and methyl *p*-dimethylaminobenzoate showed absorption peaks at 310 mμ.

Discussion

Kaplan[11] has reviewed many DPN^+ addition reactions. In this report, on the basis of the data presented, a new type of reaction is presented for consideration. PABA has been found to inhibit the cleavage of DPN^+ by DPNase. The inhibition probably comes about when DPN^+ combines chemically with PABA forming a new compound for which DPNase is no longer specific. Neither the carboxyl nor the amino groups are directly involved in the reaction. The site of reactivity of PABA is likely the 3- or 5-position. Blocking these positions by methylation is shown to prevent inhibition of DPN^+ cleavage probably because the dihydrobenzene ring of the adduct presumably formed cannot regain its aromaticity by loss of proton as in the case of PABA reaction. Acetylation of the amino group decreases the inhibition as expected, since the acetyl group competes with the ring for the pair of unshared electrons of the amino group and decreases the reactivity of the aromatic ring toward electrophilic substitution. *o*-Aminobenzoic acid and *m*-aminobenzoic acid were also found to inhibit DPN^+ cleavage. This is expected since there are positions *ortho* and *para* to the amino group at which an electrophilic substitution reaction involving attack by DPN^+ can occur.

The evidence of DPN^+ reactivity with PABA and related compounds raises the question of the situation existing in the intact cell. Not only does PABA inhibit DPN^+ cleavage, but folic acid, the naturally occurring combined form of PABA, is likewise inhibitory. We are investigating the interrelationships of the cellular co-factors on the basis of chemical structures, in light of the present data and hypothesis.

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LAWRENCE, KANSAS

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Pteridines. XVI. A Synthesis of 2-Aminopyrazine-3-carboxamides by Reductive Ring Cleavage of 3-Hydroxy-1-pyrazolo[b]pyrazines[1-3]

BY E. C. TAYLOR, J. W. BARTON AND T. S. OSDENE[4]

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A new method for the synthesis of 2-amino- and 2-substituted aminopyrazine-3-carboxamides has been developed which involves the following steps: (1) the synthesis of suitably substituted 3-hydroxy-4,5-diaminopyrazoles, (2) ring closure of these intermediates by reaction with α,β-dicarbonyl compounds to give 3-hydroxy-1-pyrazolo[b]pyrazines, and (3) reductive ring cleavage by means of Raney nickel of the -N-N- bond of the 3-hydroxy-1-pyrazolo[b]pyrazines. Each of these steps is considered in detail. Since previous work has shown that pteridines may be formed by ring closure of 2-aminopyrazine-3-carboxamides, the above reaction sequence constitutes a new total synthetic approach to pteridines.

The construction of the bicyclic pteridine ring system may be approached from either of two directions. In the first, a suitable pyrimidine intermediate is initially prepared and the pyrazine ring is closed in the terminal stage of the synthesis. The most widely employed method for the preparation of pteridines, which involves the condensation of a 4,5-diaminopyrimidine with an α,β-dicarbonyl compound, is of this type.[5] Although several variations of this approach have been devised,[6-11] the over-all method suffers from inescapable limitations which previously have been pointed out.[12] In the second approach, a pyrazine intermediate is prepared initially and the fused pyrimidine ring is closed in the terminal stage of the synthesis.[12-20] This method has not been widely

(1) A preliminary note describing the results of the present investigation has been published (T. S. Osdene and E. C. Taylor, THIS JOURNAL, **78**, 5451 (1956)).

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(3) Presented before the Division of Organic Chemistry at the 131st National ACS Meeting in Miami, Fla., April 7-12, 1957.

(4) M. D. Anderson Hospital and Tumor Institute, University of Texas, Houston, Texas.

(5) A. Albert, *Quart. Revs.*, **6**, 197 (1952).

(6) W. R. Boon, W. G. M. Jones and G. R. Ramage, *J. Chem. Soc.*, 96 (1951).

(7) W. R. Boon and T. Leigh, *ibid.*, 1497 (1951).

(8) W. R. Boon and W. G. M. Jones, *ibid.*, 591 (1951).

(9) P. R. Brook and G. R. Ramage, *ibid.*, 896 (1955).

(10) M. Polonovski and H. Jerome, *Compt. rend.*, **230**, 392 (1950).

(11) M. Polonovski, M. Pesson and A. Puister, *ibid.*, **230**, 2205 (1950).

(12) E. C. Taylor, J. A. Carbon and D. R. Hoff, THIS JOURNAL, **75**, 1904 (1953).

(13) E. C. Taylor, R. B. Garland and C. F. Howell, *ibid.*, **78**, 210 (1956).

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(15) A. Albert, D. J. Brown and G. Cheeseman, *J. Chem. Soc.*, 474 (1951).

(16) A. Albert, D. J. Brown and G. Cheeseman, *ibid.*, 4219 (1952).

(17) A. Albert, D. J. Brown and H. C. S. Wood, *ibid.*, 2066 (1956).

(18) G. P. G. Dick and H. C. S. Wood, *ibid.*, 1379 (1955).

(19) G. P. G. Dick, H. C. S. Wood and W. R. Logan, *ibid.*, 2131 (1956).

(20) E. C. Taylor and W. W. Paudler, *Chemistry & Industry*, 1061 (1955).

used because of the relative inaccessibility of the requisite pyrazine intermediates. We wish to describe in the present communication a new and general synthetic route to 2-amino- and 2-substituted aminopyrazine-3-carboxamides suitable for cyclization to 4-hydroxypteridines and 1-substituted-4-pteridinones, respectively.

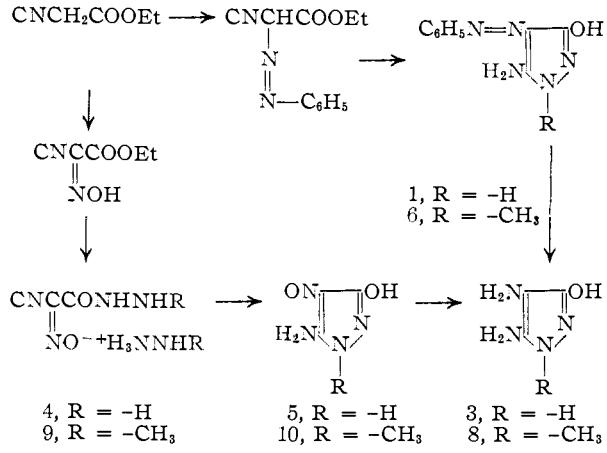
This new approach involves the following steps: (1) the synthesis of suitably substituted 3-hydroxy-4,5-diaminopyrazoles, (2) ring closure of these intermediates by reaction with α,β-dicarbonyl compounds to give 3-hydroxy-1-pyrazolo[b]pyrazines, and (3) reductive ring cleavage of the -N–N- bond of the 3-hydroxy-1-pyrazolo[b]pyrazines to give the 2-aminopyrazine-3-carboxamides. These steps are considered in detail in the discussion which follows.

Synthesis of 3-Hydroxy-4,5-diaminopyrazoles.—Condensation of ethyl phenylazocyanoacetate with hydrazine or hydrazine hydrate in ethanol solution yielded 3-hydroxy-4-phenylazo-5-aminopyrazole (1). Reduction of 1 with hydrogen in 98% formic acid in the presence of palladium-on-charcoal catalyst afforded a diformyl derivative (2) of 3-hydroxy-4,5-diaminopyrazole (3). Formanilide, the other product of the reduction under these conditions, was conveniently separated from the pyrazole by ether extraction. Treatment of 2 with 50% sulfuric acid then resulted in cleavage of the formyl groups to give crystalline 3-hydroxy-4,5-diaminopyrazole[21] (3) sulfate.

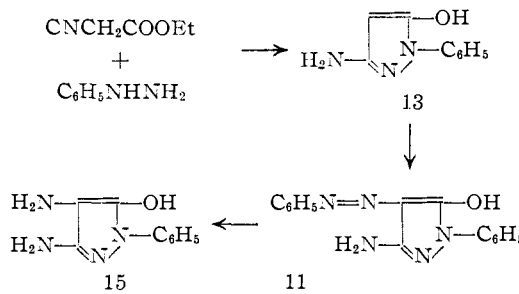
In an alternative synthesis of 3, ethyl isonitrosocyanoacetate was treated with two moles of hydrazine to give the hydrazine salt of isonitrosocyanoacethydrazide[22] (4), which was then cyclized with 40% sodium hydroxide at 60° to 3-hydroxy-4-nitroso-5-aminopyrazole[21] (5) in almost quantitative yield. Catalytic reduction of 5 yielded 3 in high yield.

1-Methyl-3-hydroxy-4-phenylazo-5-aminopyrazole (6) then was prepared similarly by treatment of ethyl phenylazocyanoacetate with methylhydrazine. Catalytic reduction in 90% formic acid gave a monoformyl derivative (7) of 1-methyl-3-hydroxy-4,5-diaminopyrazole (8), which was converted to the sulfate salt of 8 by recrystallization from 50% sulfuric acid. Compound 8 could also be prepared by treatment of ethyl isonitrosocyanoacetate with methylhydrazine as described above for the alternative synthesis of 3, except that the intermediate hydrazine salt 9 was not isolated but was converted directly with alkali to 1-methyl-3-hydroxy-4-nitroso-5-aminopyrazole (10). Reduction of 10 then afforded 8 in good yield.

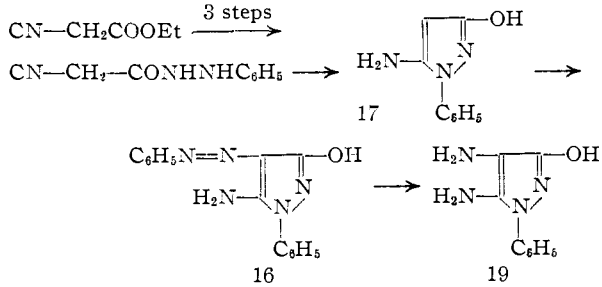
By condensation of phenylhydrazine with ethyl phenylazocyanoacetate, 2-phenyl-3-hydroxy-4-phenylazo-5-aminopyrazole (11) was formed, along with a very small amount (2.5%) of phenylazomalonamide phenylhydrazone-N-phenylhydrazide (12). The structure of 11 was confirmed by an independent synthesis from benzenediazonium chloride and 2-phenyl-3-hydroxy-5-aminopyrazole[23]



(13) and by subsequent conversion (*vide infra*) to 2-aminopyrazine-3-carboxylic acid anilide (40). Reduction of 11 in 90% formic acid, followed by recrystallization of the resulting monoformyl derivative (14) from 50% sulfuric acid, yielded 2-phenyl-3-hydroxy-4,5-diaminopyrazole (15) sulfate.



Base-catalyzed condensation of phenylhydrazine with ethyl phenylazocyanoacetate yielded a mixture of 11 and the isomeric 1-phenyl-3-hydroxy-4-phenylazo-5-aminopyrazole (16), both in poor yield. A much more satisfactory route to 16 involved the coupling of benzenediazonium chloride with 1-phenyl-3-hydroxy-5-aminopyrazole (17), available by a four-stage sequence from ethyl cyanoacetate.[24] Reduction of 16 in 90% formic acid yielded a monoformyl derivative (18) of 1-phenyl-3-hydroxy-4,5-diaminopyrazole (19), which was converted into the sulfate salt of 19 by recrystallization from a mixture of dilute sulfuric acid and ethanol.



Synthesis of 3-Hydroxy-1-pyrazolo[b]pyrazines.—Condensation of the 3-hydroxy-4,5-diaminopyrazoles, prepared as described above, with α,β-dicarbonyl compounds proceeded smoothly and in

(21) B. Hepner and S. Fajersztejn, *Bull. soc. chim.*, [5] **4**, 854 (1937).

(22) A. Darapsky and D. Hillers, *J. prakt. Chem.*, **92**, 297 (1915).

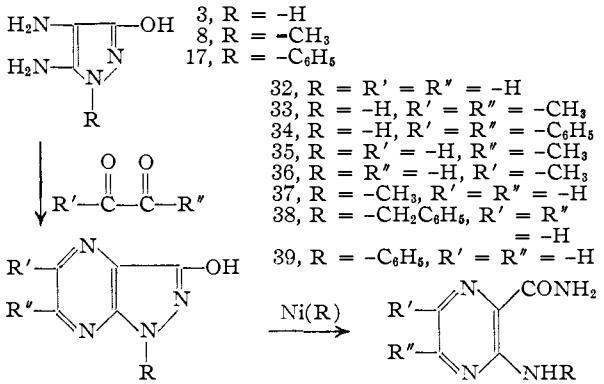
(23) A. Weissberger and H. D. Porter, THIS JOURNAL, **64**, 2133 (1942).

(24) A. Weissberger and H. D. Porter, *ibid.*, **65**, 52 (1943).

almost every case in excellent yield to give derivatives of 3-hydroxy-1-pyrazolo[b]pyrazine. Thus, the parent member of the series, 3-hydroxy-1-pyrazolo[b]pyrazine (20), was prepared by condensation of 3-hydroxy-4,5-diaminopyrazole (3) with glyoxal. It is of interest that 20 is isomeric with the naturally-occurring purine hypoxanthine, and the possibility that derivatives of this condensed heterocyclic system may possess purine antimetabolite activity is under investigation. Condensation of 3 with biacetyl and with benzil yielded 3-hydroxy-5,6-dimethyl-1-pyrazolo[b]pyrazine (21) and 3-hydroxy-5,6-diphenyl-1-pyrazolo[b]pyrazine (22), respectively.

In a similar fashion, condensation of 1-methyl-3-hydroxy-4,5-diaminopyrazole (8) with glyoxal, biacetyl and benzil yielded 1-methyl-3-hydroxy-1-pyrazolo[b]pyrazine (25), 1,5,6-trimethyl-3-hydroxy-1-pyrazolo[b]pyrazine (26) and 1-methyl-3-hydroxy-5,6-diphenyl-1-pyrazolo[b]pyrazine (27), respectively. 1-Phenyl-3-hydroxy-1-pyrazolo[b]-pyrazine (29) was similarly prepared from glyoxal and 1-phenyl-3-hydroxy-4,5-diaminopyrazole (19). Condensation of 2-phenyl-3-hydroxy-4,5-diaminopyrazole (15) with glyoxal and biacetyl yielded 2-phenyl-1-pyrazolo[b]pyrazine-3(2*H*)-one (30) and 2-phenyl-5,6-dimethyl-1-pyrazolo[b]pyrazine-3-(2*H*)-one (31), respectively.

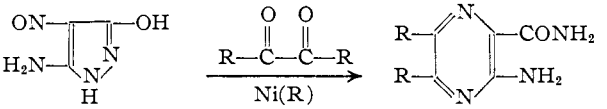
It was found that 1-alkyl-3-hydroxy-1-pyrazolo[b]pyrazines could be prepared directly from 20 by alkylation in basic solution, thus obviating the necessity of utilizing substituted hydrazines for their preparation. Thus, treatment of 20 with methyl iodide in dilute sodium hydroxide solution yielded the 1-methyl derivative 25. The use of benzyl chloride led in high yield to 1-benzyl-3-hydroxy-1-pyrazolo[b]pyrazine (28).



20, R = R' = R'' = -H
21, R = -H, R' = R'' = -CH3
22, R = -H, R' = R'' = -C6H5
23, R = R' = -H, R'' = -CH3
24, R = R'' = -H, R' = -CH3
25, R = -CH3, R' = R'' = -H
26, R = R' = R'' = -CH3
27, R = -CH3, R' = R'' = -C6H5
28, R = -CH2C6H5, R' = R'' = -H
29, R = -C6H5, R' = R'' = -H

All of the above condensation products are yellow, crystalline solids with rather high melting points, which are purified readily by sublimation in high vacuum. Consistent with similar observations in other heterocyclic series, the replacement of the 1-hydrogen atom by methyl, phenyl or benzyl groups results in an increased solubility in organic solvents and a lower melting point, reflecting a decrease in the strength of intermolecular hydrogen bonding so characteristic of hydroxy- and amino-substituted polyazaheterocyclic systems.[25]

Reductive Ring Cleavage of 3-Hydroxy-1-pyrazolo[b]pyrazines.—Reductive cleavage of the -N-N- bond of acid hydrazides to yield amines and amides has been described by Ainsworth.[26] Application of this procedure to the 3-hydroxy-1-pyrazolo[b]pyrazines prepared above resulted in a smooth cleavage of the condensed pyrazole ring with the formation of 2-aminopyrazine-3-carboxamides. Thus, treatment of 3-hydroxy-1-pyrazolo[b]pyrazine (20), 3-hydroxy-5,6-dimethyl-1-pyrazolo[b]pyrazine (21) and 3-hydroxy-5,6-diphenyl-1-pyrazolo[b]pyrazine (22) with Raney nickel yielded 2-aminopyrazine-3-carboxamide (32), 2-amino-5,6-dimethylpyrazine-3-carboxamide (33) and 2-amino-5,6-diphenylpyrazine-3-carboxamide (34), respectively. In a trial experiment, the reaction sequence leading to these pyrazines was shortened by several steps by reaction of 3-hydroxy-4-nitroso-5-aminopyrazole (5) with a mixture of biacetyl and Raney nickel in ethanol solution to give 2-amino-5,6-dimethylpyrazine-3-carboxamide (33) directly, the Raney nickel effecting both the reduction of the nitroso group and the cleavage of the subsequently formed 3-hydroxy-5,6-dimethyl-1-pyrazolo[b]pyrazine (21). In a similar fashion, 2-aminopyrazine-3-carboxamide (32) could be prepared directly from 5 and glyoxal, although in low yield.



Cleavage of the 1-substituted 3-hydroxy-1-pyrazolo[b]pyrazines 25, 28 and 29 led to 2-methylamino-, 2-benzylamino- and 2-anilinopyrazine-3-carboxamide (37, 38 and 39), respectively. A similar cleavage of 2-phenyl-1-pyrazolo[b]-pyrazine-3-one (30) yielded 2-aminopyrazine-3-carboxylic acid anilide (40), the structure of which was established by alkaline hydrolysis to 2-aminopyrazine-3-carboxylic acid (41) and aniline. Similar alkaline hydrolysis of 38 gave 2-benzylaminopyrazine-3-carboxylic acid (42).

One of the disadvantages of the conventional approach to pteridine synthesis *via* the condensation of a 4,5-diaminopyrimidine with an α-ketoaldehyde is the lack of specificity in isomer formation, and the resulting difficulty often experienced in devising reaction conditions suitable for the formation of adequate amounts of the desired (usually the 6-substituted) isomer. It was thus of interest to investigate the possibility that the condensation of a 4,5-diaminopyrazole with similar α-ketoaldehydes might lead to more specific isomer formation. However, condensation of 3-hydroxy-4,5-diaminopyrazole (3) with methylglyoxal led to the forma-

(25) A. Albert in "Recent Work on Naturally Occurring Nitrogel Heterocyclic Compounds," The Chemical Society, London, Special Publication No. 3, 1955, p. 124.

(26) C. Ainsworth, THIS JOURNAL, **76**, 5774 (1954); **78**, 1636 (1956).

tion of both 3-hydroxy-5-methyl-1-pyrazolo[b]-pyrazine (24) and 3-hydroxy-6-methyl-1-pyrazolo-[b]pyrazine (23) in the ratio 1:3. The structures of these isomers were readily established by Raney nickel cleavage to the respective pyrazines. Thus, cleavage of 24 with Raney nickel yielded 2-amino-5-methylpyrazine-3-carboxamide (36), identical with an authentic sample prepared independently.[27] Similarly, reductive cleavage of 23 yielded 2-amino-6-methylpyrazine-3-carboxamide (35) which upon alkaline hydrolysis was converted to the known 2-amino-6-methylpyrazine-3-carboxylic acid (43).[28]

Since 2-aminopyrazine-3-carboxamides have previously been cyclized to pteridines by a variety of methods,[12-18] the reaction sequences outlined above constitute a new total synthetic approach to these important heterocycles. It is of particular interest that a convenient method for the synthesis of 1-substituted pteridines may now be at hand, since a route to the requisite intermediates, 2-substituted aminopyrazine-3-carboxamides, is provided. Experiments directed toward the utilization of the above reaction sequences for the formation of 1-glycosyl derivatives of pteridines are in progress.

Experimental[29]

3-Hydroxy-4-phenylazo-5-aminopyrazole (1).—To a solution of 4.1 g. of ethyl phenylazocyanoacetate in 25 ml. of ethanol was added 1.4 g. of hydrazine hydrate. The deep red solution was then heated under reflux for 15 minutes, cooled to 0° and filtered. The bright red crystalline solid was recrystallized from aqueous ethanol to give 3.6 g. (94%) of deep red needles, m.p. 256° dec.

Anal. Calcd. for $C_9H_9N_5O$: C, 53.2; H, 4.5; N, 34.5. Found: C, 53.2; H, 4.3; N, 34.3.

3-Hydroxy-4-nitroso-5-aminopyrazole (5). Method A.—A solution of 5.0 g. of the hydrazine salt of isonitrosocyanoacethydrazide[22] in 25 ml. of 40% sodium hydroxide was allowed to stand at 60° for one hour, and the deep red solution was then acidified with glacial acetic acid. The heavy red solid which immediately separated was collected by filtration, washed with ice-cold water and dried; yield 3.87 g. (97%). When the same reaction was carried out by heating the reactants on a steam-bath for 30 minutes, the yield was decreased to 2.56 g. (64%).

Method B.—A mixture of 5.0 g. of the hydrazine salt of isonitrosocyanoacethydrazide[22] in 100 ml. of ethanol containing 6 g. of sodium was heated under reflux for four hours with continuous mechanical stirring. The deep red sodium salt was then removed by filtration and dissolved in 25 ml. of water. Acidification with glacial acetic acid and cooling caused the separation of 4.0 g. (quantitative) of the deep red nitroso derivative.

Diformyl Derivative of 3-Hydroxy-4,5-diaminopyrazole (2). Method A.—A solution of 4.0 g. of 3-hydroxy-4-phenylazo-5-aminopyrazole in 50 ml. of 98% formic acid was hydrogenated at 3 atmospheres pressure, using 0.4 g. of 10% palladium-on-carbon as catalyst, until the hydrogen uptake ceased and the color of the reduction solution had become pale yellow. The catalyst was removed by filtration and the filtrate evaporated to dryness under reduced pressure. The residue was triturated with ethanol–ether (1:1), the light yellow solid filtered off and recrystallized from water with the use of charcoal to give 2.05 g. (61%) of colorless crystals, m.p. 212–213° dec.

Anal. Calcd. for $C_5H_6N_4O_3$: C, 35.3; H, 3.5; N, 32.9. Found: C, 35.4; H, 3.2; N, 32.4.

Method B.—Hydrogenation of 2.0 g. of 3-hydroxy-4-nitroso-5-aminopyrazole in 40 ml. of 98% formic acid, using 10% palladium-on-charcoal as catalyst, and isolation of the product as described above, yielded 2.05 g. (77%) of the diformyl derivative of 3-hydroxy-4,5-diaminopyrazole, m.p. 213°, identical with the material prepared by method A above.

3-Hydroxy-4,5-diaminopyrazole (3) Sulfate.—A solution of 8 g. of the diformyl derivative of 3-hydroxy-4,5-diaminopyrazole in 30 ml. of 50% sulfuric acid was warmed until crystallization of the sulfate salt of 3-hydroxy-4,5-diaminopyrazole commenced. Boiling water was then added until complete solution was achieved, and the solution was then allowed to cool slowly to give 9.4 g. (94%) of light yellow crystals.

1-Methyl-3-hydroxy-4-phenylazo-5-aminopyrazole (6).—A mixture of 32.5 g. of ethyl phenylazocyanoacetate, 7.5 ml. of methylhydrazine (99%) and 250 ml. of ethanol was heated under reflux for 4 hours. Cooling the reaction mixture to 0° caused the separation of a golden yellow crystalline solid which was collected by filtration, washed with ether and recrystallized from ethanol; yield 27 g. (83%), m.p. 265° dec.

Anal. Calcd. for $C_{10}H_{11}N_5O$: C, 55.3; H, 5.1; N, 32.2. Found: C, 55.5; H, 5.0; N, 32.5.

1-Methyl-3-hydroxy-4-nitroso-5-aminopyrazole (10).—A mixture of 7.1 g. of ethyl isonitrosocyanoacetate, 5 ml. of methylhydrazine (99%) and 30 ml. of ethanol was heated under reflux for 3 hours. To the resulting solution was added 30 ml. of 30% ethanolic potassium hydroxide, and the mixture heated under reflux with stirring for an additional hour. The reaction mixture was then chilled to 0° and the deep red potassium salt of 1-methyl-3-hydroxy-4-nitroso-5-aminopyrazole collected by filtration and then dissolved in 20 ml. of water. Acetic acid was added to *p*H 5. The product separated from the acidic solution as red-brown microcrystals; yield 2.9 g., m.p. 184–186°. Long chilling of the mother liquor yielded an additional 0.3 g. of product, total yield 3.2 g. (45%).

Monoformyl Derivative of 1-Methyl-3-hydroxy-4,5-diaminopyrazole (7). Method A.—A solution of 20 g. of 1-methyl-3-hydroxy-4-phenylazo-5-aminopyrazole in 100 ml. of 90% formic acid was hydrogenated at 3 atmospheres pressure, using 1 g. of 10% palladium-on-carbon as catalyst, until hydrogen uptake ceased (45 minutes). The catalyst was removed by filtration and the filtrate evaporated to dryness under reduced pressure. The residual yellow oil was washed several times by decantation with ether and then dissolved in 70 ml. of ethanol. Cooling caused the separation of a white, microcrystalline solid; yield 12.8 g. (89%), m.p. 210–211°. Recrystallization from aqueous ethanol gave glistening white crystals, m.p. 210°. However, further recrystallization from aqueous ethanol yielded a lower melting hydrate, m.p. 188–190° (with loss of moisture at 133–135°).

Method B.—A solution of 2.0 g. of 1-methyl-3-hydroxy-4-nitroso-5-aminopyrazole in 40 ml. of 90% formic acid was hydrogenated as described above, and the filtered hydrogenation solution was evaporated to dryness under reduced pressure. The residual brown oil was dissolved in a small amount of ethanol and the resulting solution chilled at 0° to yield 1.5 g. (68%) of light brown crystals. Recrystallization from aqueous ethanol then gave pale yellow needles, m.p. 188–190° (with loss of moisture at 133–155°). This material was identical with the product obtained by method A above; it was dried for analysis at 100° to constant weight.

Anal. Calcd. for $C_5H_8N_4O_2$: N, 35.9. Found: N, 35.8.

1-Methyl-3-hydroxy-4,5-diaminopyrazole (8) Sulfate.—Ten grams of the monoformyl derivative of 1-methyl-3-hydroxy-4,5-diaminopyrazole prepared as described above was recrystallized from 30 ml. of 20% sulfuric acid containing 25 ml. of ethanol to yield 13.9 g. (96%) of colorless crystals, m.p. > 300°. This material was recrystallized for analysis from 2 *N* sulfuric acid.

Anal. Calcd. for $C_4H_8N_4O \cdot H_2SO_4$: C, 21.2; H, 4.5; N, 24.8; S, 14.2. Found: C, 21.3; H, 4.7; N, 25.2; S, 14.2.

1-Phenyl-3-hydroxy-4-phenylazo-5-aminopyrazole (16).—A solution of 5.25 g. of 1-phenyl-3-hydroxy-5-aminopyrazole[24] in 50 ml. of 10% sodium hydroxide was added dropwise to a sodium acetate-buffered solution of benzenediazonium chloride prepared in the usual manner from 3 g. of

(27) O. Vogl and E. C. Taylor, unpublished observations.

(28) J. Weijlard, M. Tishler and A. E. Erickson, THIS JOURNAL, **67**, 802 (1945).

(29) All melting points are uncorrected. The microanalyses were performed by Dr. Joseph F. Alicino, Metuchen, N. J., and by Drs. G. Weiler and F. B. Strauss, Oxford, England.

aniline, 6 ml. of concentrated hydrochloric acid, 2.1 g. of sodium nitrite and 12 ml. of water. The reaction mixture was stirred for 30 minutes and then filtered to give 7.95 g. (95%) of a yellow solid, m.p. 260–265° dec. The product was obtained in the form of small, deep yellow plates, m.p. 266–268° dec., upon recrystallization from Cellosolve.

Anal. Calcd. for $C_{15}H_{13}N_5O$: C, 64.5; H, 4.7; N, 25.1. Found: C, 64.5; H, 4.9; N, 24.8.

2-Phenyl-3-hydroxy-4-phenylazo-5-aminopyrazole (11). Method A.—Using the above procedure, 2-phenyl-3-hydroxy-5-aminopyrazole[23] yielded the corresponding 4-phenylazo derivative in 91% yield. Recrystallization of the crude deep-red powder from ethanol yielded purple-red needles, m.p. 194–195°.

Anal. Found: C, 64.5; H, 4.8; N, 25.3.

Method B.—A mixture of 40 g. of ethyl phenylazocyanoacetate, 20 ml. of phenylhydrazine and 200 ml. of isoamyl alcohol was heated under reflux for 24 hours and then cooled to room temperature. The deep red solid which separated was collected by filtration and washed with 100 ml. of cold ethanol to give 24.2 g. (47%), m.p. 188–190° dec. Recrystallization of this material from ethanol yielded glistening deep red needles, m.p. 194–195° dec., identical with the material prepared by method A above.

Anal. Calcd. for $C_{15}H_{13}N_5O$: C, 64.5; H, 4.7; N, 25.1. Found: C, 64.5; H, 4.8; N, 25.3.

Phenylazomalonamide Phenylhydrazone-N-phenylhydrazide (12).—The combined mother liquor and washings from the above preparation of 2-phenyl-3-hydroxy-4-phenylazo-5-aminopyrazole were maintained at 0° overnight to give 1.8 g. (2.5%) of a yellow solid, m.p. 175–180°. The product was obtained as yellow, feathery needles, m.p. 187–188° upon recrystallization from ethanol.

Anal. Calcd. for $C_{21}H_{21}N_7O$: C, 65.1; H, 5.4; N, 25.3. Found: C, 65.1; N, 5.1; N, 24.8.

Base-catalyzed Reaction of Ethyl Phenylazocyanoacetate with Phenylhydrazine.—To a solution of 0.87 g. of sodium in 75 ml. of isoamyl alcohol was added 4 g. of ethyl phenylazocyanoacetate and 2 ml. of phenylhydrazine. The mixture was heated under reflux for 20 hours and then evaporated to dryness under reduced pressure. Trituration of the residue with 50% acetic acid gave a brown, gummy solid which was extracted with 200 ml. of boiling ethanol. Concentration of this ethanol extract to 50 ml. followed by cooling yielded 1.39 g. (27%) of 2-phenyl-3-hydroxy-4-phenylazo-5-aminopyrazole, m.p. 185–190°. Recrystallization of the ethanol-insoluble material from Cellosolve yielded 0.82 g. (16%) of 1-phenyl-3-hydroxy-4-phenylazo-5-aminopyrazole, m.p. 266–268° dec.

Monoformyl Derivative of 1-Phenyl-3-hydroxy-4,5-diaminopyrazole (18).—A solution of 5.0 g. of 1-phenyl-3-hydroxy-4-phenylazo-5-aminopyrazole in 50 ml. of 90% formic acid was hydrogenated at room temperature under 3 atmospheres pressure in the presence of 0.5 g. of 10% palladium-on-charcoal. Hydrogen absorption had ceased after 1 hour, and the hydrogenation mixture was then filtered and the filtrate evaporated to a brown oil under reduced pressure. Trituration of this oil with 50 ml. of ethanol: ether (1:3) yielded 3.6 g. of a tan powder. Recrystallization from aqueous ethanol yielded 3.1 g. (79.5%) of colorless plates, m.p. 223–225° dec.

Anal. Calcd. for $C_{10}H_{10}N_4O_2$: C, 55.0; H, 4.6; N, 25.7. Found: C, 55.1; H, 4.9; N, 25.4.

1-Phenyl-3-hydroxy-4,5-diaminopyrazole (19) Sulfate.—The above preparation was repeated as described and the crude monoformyl derivative obtained was warmed on a water-bath with a mixture of 3 ml. of concentrated sulfuric acid, 7 ml. of water and 3 ml. of ethanol. Addition of 4 ml. of ethanol and then cooling resulted in the separation of 4.8 g. (93%) of yellow needles which were purified by recrystallization from a mixture of 2 *N* sulfuric acid and ethanol (1:1).

Anal. Calcd. for $C_9H_{12}N_4O_5S$: N, 19.5. Found: N, 19.7.

Monoformyl Derivative of 2-Phenyl-3-hydroxy-4,5-diaminopyrazole (14).—A mixture of 8.0 g. of 2-phenyl-3-hydroxy-4-phenylazo-5-aminopyrazole, 100 ml. of 90% formic acid and 0.8 g. of 10% palladium-on-carbon catalyst was shaken under 3 atmospheres of hydrogen until hydrogen uptake ceased. The catalyst was removed by filtration and the filtrate evaporated to dryness under reduced pressure. The dark, rather sticky residue was triturated with ether to give a brown powder; yield 4.8 g. (77%). Recrystallization of this material from aqueous ethanol with the use of charcoal yielded white crystals, m.p. 235° dec.

Anal. Calcd. for $C_{10}H_{10}N_4O$: C, 55.0; H, 4.6; N, 25.7. Found: C, 55.4; H, 4.7; N, 25.4.

2-Phenyl-3-hydroxy-4,5-diaminopyrazole (15) Sulfate.—Reduction of 12 g. of 2-phenyl-3-hydroxy-4-phenylazo-5-aminopyrazole was carried out as described above, and the crude formyl derivative was crystallized from 30% sulfuric acid–ethanol (1:1) to yield 11.6 g. (94%) of 2-phenyl-3-hydroxy-4,5-diaminopyrazole sulfate in the form of small orange plates. The material could not be purified by recrystallization because of rapid decomposition and was used directly in subsequent condensations.

3-Hydroxy-1-pyrazolo(b)pyrazine (20).—A suspension of 20 g. of 3-hydroxy-4,5-diaminopyrazole sulfate and 28 g. of glyoxal bisulfite in 250 ml. of water at 60° was stirred rapidly while ammonium hydroxide was added dropwise. The material went into solution, and then a solid started to separate as the *p*H approached 7. The reaction mixture was stirred for 30 minutes, adjusted to *p*H 5, cooled to 0° and filtered to give 9.9 g. (77%) of a pale yellow solid, m.p. 314–315° dec. The compound was purified for analysis by sublimation at 230° (0.1 mm.) without change in the melting point; $\lambda_{max}^{ethanol}$ 231, 289, 333 mμ; log ε 4.07, 3.70, 3.26.

Anal. Calcd. for $C_5H_4N_4O$: C, 44.1; H, 3.0; N, 41.2. Found: C, 44.4; H, 3.0; N, 41.2.

3-Hydroxy-5,6-dimethyl-1-pyrazolo(b)pyrazine (21).—To a solution of 1.5 g. of 3-hydroxy-4,5-diaminopyrazole sulfate in 10 ml. of water was added 1 ml. of biacetyl with shaking. The pale yellow precipitate which rapidly separated was collected by filtration, washed well with water and dried; yield 0.93 g. (80%), m.p. 324° dec. The compound was recrystallized from water and then sublimed at 230° (0.1 mm.) to give a light yellow solid, m.p. 325° dec.; $\lambda_{max}^{ethanol}$ 239, 294 mμ; log ε 3.95, 3.54.

Anal. Calcd. for $C_7H_8N_4O$: C, 51.2; H, 4.9; N, 34.1. Found: C, 50.9; H, 4.7; N, 34.4.

3-Hydroxy-5,6-diphenyl-1-pyrazolo(b)pyrazine (22).—A mixture of 4.2 g. of 3-hydroxy-4,5-diaminopyrazole sulfate, 6.3 g. of benzil, 1.2 g. of sodium hydroxide, 30 ml. of ethyl methyl ketone, 30 ml. of ethanol and 20 ml. of water was heated under reflux for 1.5 hours. The resulting deep red solution was then concentrated under reduced pressure to approximately one-sixth its volume and made alkaline with aqueous sodium hydroxide. The basic solution was treated with charcoal and filtered, and the filtrate was acidified with hydrochloric acid to give a yellow solid. A preliminary purification was effected by dissolving this material in dilute sodium hydroxide and reprecipitating by the addition of hydrochloric acid. The resulting yellow solid was thoroughly dried in a vacuum desiccator and then suspended in boiling benzene, the water released being removed azeotropically. Recrystallization of the product from ethyl acetate then yielded 3.5 g. (61.5%) of yellow crystals, m.p. 269° dec.; $\lambda_{max}^{ethanol}$ 247, 257–264 (shoulder), 332 mμ; log ε 4.26, 4.22, 3.86.

Anal. Calcd. for $C_{17}H_{12}N_4O$: C, 70.8; H, 4.2; N, 19.4. Found: C, 70.8; H, 4.0; N, 19.4.

1-Methyl-3-hydroxy-1-pyrazolo(b)pyrazine (25). Method A.—A mixture of 4.52 g. of 1-methyl-3-hydroxy-4,5-diaminopyrazole sulfate, 5.6 g. of glyoxal bisulfite and 40 ml. of water was well stirred, slowly adjusted to *p*H 5 with ammonium hydroxide, and then allowed to stand at room temperature overnight. The yellow solid which separated was collected by filtration, washed with cold water and sublimed at 200° (0.1 mm.) to give bright yellow needles; yield 2.84 g. (95%), m.p. 242–243°.

Method B.—A solution of 1.0 g. of 3-hydroxy-1-pyrazolo-(b)pyrazine in 10 ml. of 10% sodium hydroxide was stirred at 60° and treated with 1.4 g. (0.62 ml.) of methyl iodide in one portion. After 45 minutes, the solution was evaporated to dryness under reduced pressure, the residue dissolved in a little ice-water and acetic acid added to *p*H 5. A pale brown solid was obtained; yield 0.62 g. (56%), m.p. 238–240°. Recrystallization from water or vacuum sublimation at 200° (0.1 mm.) yielded yellow needles, m.p. 242–243° alone and when admixed with a sample of the

product obtained by method A above; $\lambda_{max}^{ethanol}$ 235, 290, 354 mμ; log ε 4.13, 3.68, 3.20.

Anal. Calcd. for $C_6H_6N_4O$: C, 48.0; H, 4.0; N, 37.3. Found: C, 48.1; H, 4.2; N, 37.1.

1,5,6-Trimethyl-3-hydroxy-1-pyrazolo(b)pyrazine (26).—A mixture of 1.13 g. of 1-methyl-3-hydroxy-4,5-diaminopyrazole sulfate, 0.5 ml. of biacetyl and 10 ml. of water was well stirred and slowly adjusted to *p*H 7–8 with ammonium hydroxide. After 10 minutes, the *p*H was readjusted to 5 with dilute acetic acid and the pale yellow solid which separated was collected by filtration, washed with cold water and dried; yield 0.78 g. (87.5%), m.p. 268–269°. The material was purified for analysis by sublimation at 200° (0.1 mm.) followed by recrystallization from ethanol; $\lambda_{max}^{ethanol}$ 237, 292, 344 mμ; log ε 4.17, 3.74, 3.35.

Anal. Calcd. for $C_8H_{10}N_4O$: C, 53.9; H, 5.7; N, 31.5. Found: C, 54.1; H, 5.7; N, 31.6.

1-Methyl-5,6-diphenyl-3-hydroxy-1-pyrazolo(b)pyrazine (27).—A mixture of 1.0 g. of 1-methyl-3-hydroxy-4,5-diaminopyrazole sulfate, 1 g. of benzil, 10 ml. of water, 10 ml. of ethyl methyl ketone and 10 ml. of ethanol was adjusted to *p*H 8 with 40% sodium hydroxide and the resulting solution was heated under reflux for 90 minutes. It was then allowed to stand at room temperature overnight and evaporated to dryness under reduced pressure. The solid residue was taken up in water, the *p*H of the suspension adjusted to 9 with sodium hydroxide, and the resulting solution heated to boiling, treated with charcoal and filtered. Acidification of the filtrate with acetic acid yielded 0.35 g. (26%) of a yellow solid. This material was purified by recrystallization from ethanol followed by sublimation at 200° (0.1 mm.); m.p. 258–260°; $\lambda_{max}^{ethanol}$ 250, 273, 300–306 (shoulder) 330–340 (shoulder) mμ; log ε 4.21, 4.20, 4.13–4.08, 3.85–3.79.

Anal. Calcd. for $C_{18}H_{14}N_4O$: C, 71.5; H, 4.7; N, 18.5. Found: C, 71.7; H, 4.3; N, 18.4.

1-Benzyl-3-hydroxy-1-pyrazolo(b)pyrazine (28).—To a solution of 15 g. (0.11 mole) of 3-hydroxy-1-pyrazolo(b) pyrazine in a mixture of 150 ml. of 10% sodium hydroxide and 15 ml. of ethanol was added in one portion 15 ml. (16.5 g., 0.13 mole) of benzyl chloride. After 1 hour, the reaction mixture was evaporated to dryness *in vacuo* and the residue acidified with 50% acetic acid. The resulting solid was collected by filtration, washed well with water, dried in the air and then recrystallized from methanol to give 18.4 g. (74%) of pale brown needles, m.p. 173–174°. The product could be obtained as pale yellow needles, m.p. 175–176°, upon further recrystallization from methanol; $\lambda_{max}^{ethanol}$ 237, 291, 350 mμ; log ε 5.00, 4.42, 4.40.

Anal. Calcd. for $C_{12}H_{10}N_4O$: C, 63.7; H, 4.5. Found: C, 63.9; H, 4.4.

1-Phenyl-3-hydroxy-1-pyrazolo(b)pyrazine (29).—To a rapidly-stirred suspension of 12 g. of 1-phenyl-3-hydroxy-4,5-diaminopyrazole sulfate and 13 g. of glyoxal bisulfite in 150 ml. of water at 60° was added dropwise concentrated ammonium hydroxide until the *p*H had reached 7–8. The reaction mixture was stirred for 45 minutes, the *p*H adjusted to 5 with glacial acetic acid, and the mixture cooled to 0°. Filtration yielded 7.7 g. (87%) of a green solid, m.p. 223–225°. Recrystallization from aqueous ethanol gave lime-green needles, m.p. 227–228°; $\lambda_{max}^{ethanol}$ 268, 364 mμ; log ε 4.33, 3.17.

Anal. Calcd. for $C_{11}H_8N_4O$: C, 62.3; H, 3.8; N, 26.4. Found: C, 62.3; H, 3.7; N, 26.1.

2-Phenyl-1-pyrazolo(b)pyrazine-3(2*H*)one (30).—A suspension of 37 g. of 2-phenyl-3-hydroxy-4,5-diaminopyrazole sulfate and 40 g. of glyoxal bisulfite in 400 ml. of water at 60° was adjusted to *p*H 7–8 with concentrated ammonium hydroxide. Immediate separation of the red ammonium salt of 2-phenyl-1-pyrazolo(b)pyrazine-3-one occurred. The reaction mixture was stirred for 45 minutes and then adjusted to *p*H 5 with glacial acetic acid. Cooling and filtering yielded 23.2 g. (85%) of a deep green solid, m.p. 228–230°, which was recrystallized from ethanol to give pale green plates, m.p. 232–233.5°; $\lambda_{max}^{ethanol}$ 263, 300, 435 (infl.) mμ; log ε 4.05, 3.96, 2.85.

Anal. Found: C, 62.3; H, 3.8; N, 26.8.

2-Phenyl-5,6-dimethyl-1-pyrazolo(b)pyrazine-3(2*H*)-one (31).—A mixture of 0.96 g. of 2-phenyl-3-hydroxy-4,5-diamino pyrazole sulfate, 0.4 ml. of biacetyl and 10 ml. of water was adjusted to *p*H 8 with ammonium hydroxide, allowed to stand at room temperature for 15 minutes and then adjusted to *p*H 5 with acetic acid. The brown solid which separated was collected by filtration, washed with cold water and dried to give 0.8 g. (100%), m.p. 239–240°. The product was obtained in another polymorphic form by recrystallization from ethanol followed by sublimation at 200° (0.1 mm.), for it then melted at 193–195°; $\lambda_{max}^{ethanol}$ 261, 366 mμ; log ε 4.16, 4.09.

Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 65.0; H, 5.0; N, 23.3. Found: C, 65.1; H, 4.8; N, 23.4.

3-Hydroxy-6-methyl-1-pyrazolo(b)pyrazine (23).—To a solution of 8.5 g. of 3-hydroxy-4,5-diaminopyrazole sulfate and 8.8 g. of sodium bisulfite in 100 ml. of water was added 6 ml. of a 47.5% solution of methylglyoxal. Concentrated ammonium hydroxide was added dropwise to this mixture, which was maintained at 60° with stirring, until the *p*H had been adjusted to 7–8. Stirring was continued for 45 minutes, and the reaction mixture was then adjusted to *p*H 4–5 with dilute acetic acid and cooled to 0°. The pale yellow solid which separated was collected, washed well with water and dried to give 3.83 g. (64%), m.p. 275–285°. The product was obtained in the form of thick light-yellow needles m.p. 319–321°, upon recrystallization from water; $\lambda_{max}^{ethanol}$ 229, 292 mμ; log ε 4.03, 3.74.

Anal. Calcd. for $C_6H_6N_4O$: C, 48.0; H, 4.0; N, 37.4. Found: C, 48.3; H, 4.1; N, 37.4.

3-Hydroxy-5-methyl-1-pyrazolo(b)pyrazine (24).—The mother liquor from the above preparation of 3-hydroxy-6-methyl-1-pyrazolo(b)pyrazine was evaporated *in vacuo* to one-third its original volume and chilled at 0° for 24 hours. The solid which separated (1.15 g., 19%) was recrystallized from ethanol to give small buff-colored prisms, m.p. 234–235°; $\lambda_{max}^{ethanol}$ 230.5, 292, 335 (infl.) mμ; log ε 4.51, 3.64, 3.28.

Anal. Found: C, 48.3; H, 4.2.

2-Aminopyrazine-3-carboxamide (32).—A mixture of 1.0 g. of 3-hydroxy-1-pyrazolo(b)pyrazine, 20 ml. of formamide and 3 g. of Raney nickel catalyst was heated in an oil-bath with mechanical stirring for 90 minutes at 115–120°. An additional 2 g. of catalyst was added and heating and stirring were continued for 90 minutes. The hot solution was then filtered and the filtrate cooled to yield 0.58 g. (57%) of pure 2-aminopyrazine-3-carboxamide, m.p. 244–245°, alone and admixed with an authentic sample.[27,30,31]

2-Amino-5,6-dimethylpyrazine-3-carboxamide (33).

Method A.—A mixture of 0.5 g. of 3-hydroxy-5,6-dimethyl-1-pyrazolo(b)pyrazine, 50 ml. of 95% ethanol and 6 g. of Raney nickel catalyst was heated under reflux for two hours. A strong blue fluorescence was apparent in the reaction mixture after the first 15 minutes (the starting material does not fluoresce, while the pyrazine does). The reaction mixture was filtered and the filtrate evaporated to dryness. Sublimation of the solid residue at 200° (0.1 mm.) gave a light yellow crystalline solid; yield 0.28 g. (55%), m.p. 255°.

Anal. Calcd. for $C_7H_{10}N_4O$: C, 50.6; H, 6.1; N, 33.7. Found: C, 50.6; H, 6.1; N, 33.2.

Method B.—To a solution of 1.28 g. of 3-hydroxy-4-nitroso-5-aminopyrazole in 40 ml. of water containing 2 ml. of concentrated ammonium hydroxide was added 1.2 ml. of biacetyl and 4 g. of Raney nickel catalyst, and the mixture was heated under reflux for 7 hours. The hot reaction mixture was filtered and the filtrate cooled to 0° to give a yellow crystalline solid; yield 0.32 g., m.p. 251–253°. Extraction of the Raney nickel with four portions of boiling ethanol yielded an additional 0.06 g. of product; total yield 0.38 g. (23%). The material was purified readily by sublimation at 200° (0.01 mm.); m.p. 255° alone and admixed with the product prepared by method A above.

2-Amino-5,6-diphenylpyrazine-3-carboxamide (34).—A mixture of 1.0 g. of 3-hydroxy-5,6-diphenyl-1-pyrazolo(b)-pyrazine, 50 ml. of 95% ethanol and 8 g. of Raney nickel catalyst was heated under reflux for 3 hours, filtered, and the filtrate evaporated to dryness under reduced pressure. The solid residue was triturated with water, filtered and the

(30) R. C. Ellingson, R. L. Henry and F. G. McDonald, THIS JOURNAL, 67, 1711 (1945).

(31) A. Albert, D. J. Brown and G. Cheeseman, *J. Chem. Soc.*, 474 (1951).

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).