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Pyrazolo[3,4-b]pyridines and Pyrazolo[3',4':6,5]pyrido[2,3-d]pyrimidines (1)

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3,6-Diamino-5-cyanopyrazolo[3,4-b]pyridine (III) and 1-methyl-3,6-diamino-5-cyanopyrazolo[3,4-b]pyridine (IV) were formed by treatment of 2-amino-6-chloro-3,5-dicyanopyridine with hydrazine and methylhydrazine. Pyrazolo[3',4':6,5]pyrido[2,3-d]pyrimidines were formed from IV and from a number of its derivatives.

Recent investigations have made available a number of 6-substituted-2-amino-3,5-dicyanopyridines (2,3). Among these, 2-amino-3,5-dicyano-6-chloropyridine (I) a vicinal chlorocyanopyridine is a suitable candidate for uninvolved synthesis of pyrazolo[3,4-b]-pyridines. The formation and several reactions of this fused heterocyclic system are reported here.

When I was treated with hydrazine in ethanol, 2-amino-6-hydrazino-3,5-dicyanopyridine (II) was formed. When II was heated in dilute hydrochloric acid or in dimethylformamide, a ring closure occurred which gave 3,6-diamino-5-cyanopyrazolo-[3,4-b]pyridine (III). Direct formation of III was accomplished by heating I with hydrazine in dimethylformamide. Similar treatment of I with methylhydrazine in either ethanol or dimethylformamide gave 1-methyl-3,6-diamino-5-cyanopyrazolo[3,4-b]-pyridine (IV). Attempts to isolate the intermediate 6-(methylhydrazino)pyridine failed. The 5-cyanopyrazolopyridines, III and IV, were readily hydrolyzed to the 5-pyrazolopyridinecarboxamides, V and VI.

The location of the methyl group in the methylpyrazolo[3,4-b]pyridines was established by the following sequence of reactions (Scheme I). 2-Isopropylideneamino-5-cyano-6-chloro-3-pyridinecarboxamide (VII) was formed on the addition of base to an acetone suspension of I. Treatment of VII with methyl hydrazine in ethanol at room temperature gave the corresponding 6-methylhydrazinopyridine (VIII) which gave the hydrazone IX when treated with *n*-butyraldehyde. The latter, in turn, was converted to the pyrazolo[3,4-b]pyridinecarboxamide (X) by boiling in dilute acid. Compound X was obtained directly by boiling VIII in dilute hydrochloric acid. When X was heated in concentrated hydrochloric acid, 1-methyl-3,6-diamino-5-pyrazolo[3,4-b]pyridinecarboxylic acid (XI) was obtained. Boiling VI in concentrated hydrochloric acid also gave XI. The above conversions also showed that the carboxamido group in VII is adjacent to the isopropylideneamino group. It has been previously observed in similar heterocyclic systems that alkylhydrazines displaced chloro- through the α-nitrogen, and that aryl hydrazines react at the β-nitrogen (4,5).

When VI was treated with acetic anhydride and triethyl orthoformate, 1-methyl-3-N-acetamido-5-hydroxypyrazolo[3',4':6,5]pyrido[2,3-d]pyrimidine (XII) was formed. Similar treatment of VI with triethyl orthopropionate gave the 7-ethyl homolog (XIII). An alternate synthesis of XII was accomplished by acetylation of VI followed by fusion with formamide. The 3-amino group of VI was considerably more reactive toward acetylation than was the 6-amino group.

Compound VI and formamide gave 1-methyl-3-N-formamido-5-hydroxypyrazolo[3',4':6,5]pyrido[2,3-d]-pyrimidine (XV). Compound XV was prepared alternately from XI and formamide or from VI and formic acid. The last method gave the highest yields of XV. Refluxing XV in concentrated hydrochloric acid gave 1-methyl-3-amino-5-hydroxypyrazolo[3',4':6,5]-pyrido[2,3-d]pyrimidine (XVI). Compound XVI and acetic anhydride gave 1-methyl-3-N-acetamido-6-acetylpyrazolo[3',4':6,5]pyrido[2,3-d]pyrimidine-5-one (XVII) in a 91% yield. In addition, XVII was formed when XII was treated with acetic anhydride.

Compound IV and formic acid gave 1-methyl-3-N-formamido-6-amino-5-cyanopyrazolo[3,4-b]pyridine (XVIII). Formamide and IV gave mainly XVIII, but also, some 1-methyl-3-N-formamido-5-aminopyrazolo[3',4':6,5]pyrido[2,3-d]pyrimidine (XIX). The location of the formamido group in XVIII was assumed and based on the observation that reaction with formamide of amino groups which are *ortho* to cyano groups generally give rise to a fused aminopyrimidine (6,7). Hydrolysis of XIX with concentrated hydrochloric acid gave XVI.

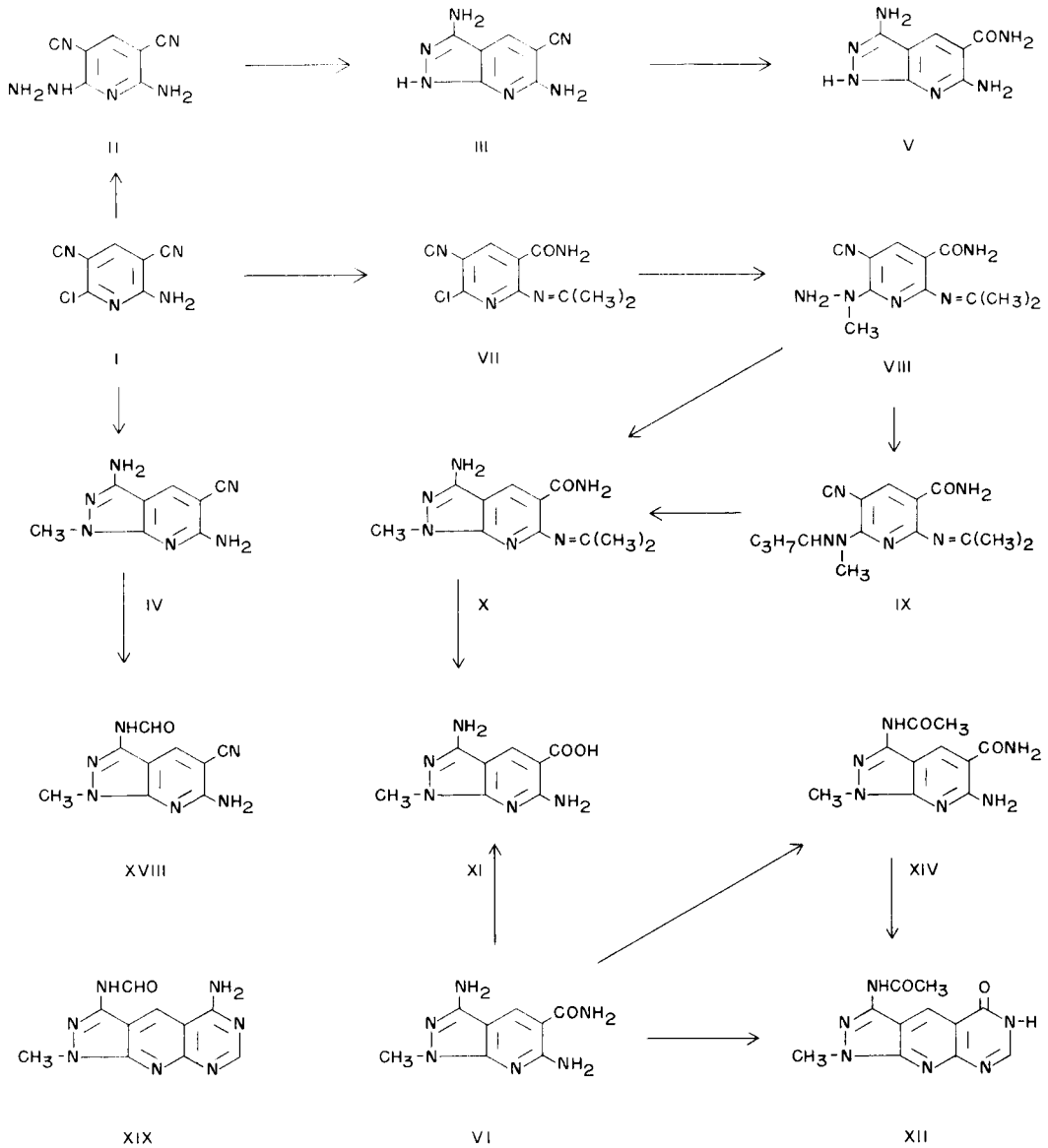
When XI was treated with acetic anhydride, acetylation and ring closure occurred to form 1,7-dimethyl-3-N-acetamidopyrazolo[3',4':6,5]pyrido[2,3-d]-1,3-oxazine-5-one (XX).

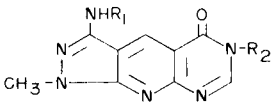
EXPERIMENTAL (8,9)

2-Amino-6-hydrazino-3,5-dicyanopyridine (II).

One gram (5.7 mmoles) of I and 1.0 g. of hydrazine hydrate in 25 ml. of absolute ethanol was heated for 1 hour. After cooling, the solid was collected by filtration, washed with water and dried to yield 0.9 g. of yellow powder, yield 91%, dec. 320°. Attempts to purify

SCHEME I

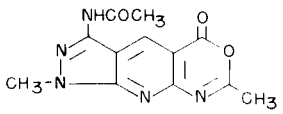




XV R_1 = CHO; R_2 = H

XVI R_1 = R_2 = H

XVII R_1 = R_2 = CH_3CO



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this material by standard procedures led to the formation of III. The sodium pentacyanoammineferroate test was positive for a hydrazino group (10).

3,6-Diamino-5-cyanopyrazolo[3,4-b]pyridine (III). Method A.

Nine-tenths of a gram of II was suspended in 37 ml. of 0.5 N hydrochloric acid and boiled for 1 hour. After cooling, the solid was filtered, washed with water, and dried. The compound gave a negative spot test for a hydrazino group (10); yield, 0.35 g., (40%). It decomposed above 360°.

Method B.

Three grams (0.017 mole) of I, 3.0 g. of hydrazine hydrate and 10 ml. of dimethylformamide were shaken together. A vigorous reaction occurred and upon cooling, a solid mass (2.6 g.) formed; yield, 88%. Recrystallization from dimethylformamide-water gave fine pale yellow needles of III, dec. > 360°. The infrared spectra of the compounds from Methods A and B were identical.

Anal. Calcd. for $C_7H_6N_6$: C, 48.27; H, 3.47; N, 48.26. Found: C, 48.25; H, 3.98; N, 47.81.

1-Methyl-3,6-diamino-5-cyanopyrazolo[3,4-b]pyridine (IV).

Six grams of methylhydrazine was added dropwise, with stirring, to a mixture of 11 g. (0.062 mole) of I and 100 ml. of ethanol. Upon cooling the mixture, the solid was filtered, washed with water, and then with ethanol, to give 11.5 g. of IV; yield, 99%, m.p. 265-266°. Recrystallization from dimethylformamide-water gave yellow needles.

Anal. Calcd. for $C_8H_8N_6$: C, 51.06; H, 4.28; N, 44.66. Found: C, 51.00; H, 4.40; N, 44.63.

3,6-Diamino-5-pyrazolo[3,4-b]pyridinecarboxamide (V).

One gram of III (5.8 mmoles) in 200 ml. of 0.2 *N* potassium hydroxide was boiled for 1.5 hours and the solution filtered while hot. After cooling the solution overnight in a refrigerator, the solid was collected by filtration, washed with water and dried. This gave 0.8 g. (73%) of the amide which was recrystallized from dimethylformamide-water to give fine yellow needles; dec. 350-352°.

Anal. Calcd. for $C_7H_8N_6O$: C, 43.75; H, 4.19; N, 43.73. Found: C, 43.82; H, 4.30; N, 43.23.

1-Methyl-3,6-diamino-5-pyrazolo[3,4-b]pyridinecarboxamide (VI).

Four grams of IV (0.021 mole) in 200 ml. of 0.5 *N* potassium hydroxide was boiled until most of the compound dissolved. The solution was filtered and cooled overnight in a refrigerator. The solid which formed was collected by filtration, washed with water, followed by ethanol, and dried. This gave 2.5 g. (57%) of yellow powder which was recrystallized from water giving yellow needles, m.p. 242-244°.

Anal. Calcd. for $C_8H_{10}N_6O$: C, 46.60; H, 4.89; N, 40.76. Found: C, 46.54; H, 5.08; N, 40.88.

2-Isopropylideneamino-5-cyano-6-chloro-3-pyridinecarboxamide (VII).

One gram (5.7 mmoles) of I was stirred with 75 ml. of acetone and 50 ml. of 1 *N* potassium hydroxide for 2 minutes. The mixture was diluted to 200 ml. with water and stirred again for 10 minutes. After cooling in a refrigerator overnight, the green-yellow precipitate was collected by filtration, washed with water and dried. The crude VII (0.62 g., 46%) was recrystallized from acetone-water to give pale yellow-green needles, dec. 320-325°.

Anal. Calcd. for $C_{10}H_9N_4ClO$: C, 50.76; H, 3.83; Cl, 14.98. Found: C, 50.42; H, 4.03; Cl, 14.30.

2-Isopropylideneamino-5-cyano-6-α-methylhydrazino-3-pyridinecarboxamide (VIII).

To a mixture of 5 g. (0.021 mole) of VII and 100 ml. of ethanol, 5 g. of methylhydrazine was added dropwise, with stirring. During the addition, VII slowly went into solution and later VIII precipitated. After stirring for 20 minutes, the mixture was refrigerated for 3 hours and the solid material collected and washed with water. Prolonged standing of the reaction mixture led to the formation of X. A second crop was obtained by concentrating the ethanolic filtrate; yield 5.1 g., 73%; dec. 285°. The infrared spectrum of this material showed a nitrile band (4.55 μ) and gave a positive spot test with sodium pentacyanoammineferroate (10). Attempts to purify this material led to the formation of X.

2-Isopropylideneamino-5-cyano-6-(β-butylidene-α-methylhydrazino)-3-pyridinecarboxamide (IX).

A mixture of 35 ml. of butyraldehyde and 0.8 g. (3.2 mmoles) of VIII was refluxed for 0.5 hours. After the mixture was allowed to stand overnight the solid was collected, washed with a little ethanol, and dried to give 0.55 g. (57%). The analytical sample was recrystallized from ethanol after which it decomposed at 279-280°.

Anal. Calcd. for $C_{15}H_{20}N_6O$: C, 59.98; H, 6.71; N, 27.98. Found: C, 59.94; H, 6.72; N, 27.97.

1-Methyl-3-amino-6-isopropylideneamino-5-pyrazolo[3,4-b]pyridinecarboxamide (X). Method A.

A solution of IX (0.3 g., 1 mmole), and 75 ml. of 0.2 *N* hydrochloric acid was boiled for 15 minutes and evaporated to dryness under reduced pressure. The residue was dissolved in 35 ml. water, filtered and the filtrate made basic with 0.1 *N* sodium hydroxide to *p*H 8. The yellow crystals were collected, washed with water and dried to yield 0.15 g. (61%).

Method B.

A solution of VIII (1.5 g., 6.1 mmoles) and 75 ml. of 0.1 *N* hydrochloric acid was boiled for 15 minutes and evaporated to dryness. The residue was dissolved in 100 ml. water, filtered and the filtrate made basic with 0.1 *N* sodium hydroxide to *p*H 8. The yellow crystals were collected, washed with water and dried to give 0.74 g. (50%). Recrystallization from ethanol-benzene gave 0.25 g., m.p. 328-332° dec.

The infrared spectra of the products from Method A and B were identical.

Anal. Calcd. for $C_{11}H_{14}N_6O$: C, 53.64; H, 5.73; N, 34.13. Found: C, 53.58; H, 5.76; N, 34.28.

1-Methyl-3,6-diamino-5-pyrazolo[3,4-b]pyridinecarboxylic acid (XI). Method A.

One gram (4.9 mmoles) of VI in 50 ml. of concentrated hydrochloric acid was boiled gently for 1 hour. After cooling and carefully diluting the solution to 200 ml. with water, the mixture was refrigerated overnight. The yellow-orange crystals were collected, washed with water and dried to yield 0.5 g. (50%). An analytical sample was prepared by recrystallization from dimethylformamide-water, which gave XI in the form of fine, light yellow flakes; dec. 288-289°.

Method B.

Three grams (0.014 mole) of VI in 75 ml. of 1 *N* potassium hydroxide was boiled for 2 hours. The mixture was cooled to 5°, acidified with glacial acetic acid, diluted to 250 ml. with water and refrigerated overnight. The solid was collected, washed with water and dried to yield 3.0 g. of XI.

Method C.

One gram (4 mmoles) of X and 50 ml. of concentrated hydrochloric acid was boiled gently for 1 hour. After standing overnight in a refrigerator 0.4 g. (41%) was collected by filtration and washed with water. The washings were added to the original filtrate, the mixture diluted to 250 ml. with water and refrigerated overnight. This gave a second crop weighing 0.19 g. The combined product was recrystallized from dimethylformamide-water to give the analytical sample.

Anal. Calcd. for $C_8H_9N_5O_2$: C, 46.36; H, 4.38; N, 33.80. Found: C, 46.56; H, 4.29; N, 33.74.

The infrared spectra and melting points of the products from the above three methods were identical. A mixture of the purified samples from methods B and C melted at 287-288° with effervescence.

1-Methyl-3-N-acetamido-5-hydroxypyrazolo[3',4':6,5]pyrido[2,3-d]-pyrimidine (XII). Method A.

Two grams (9.6 mmoles) of VI, 20 ml. of acetic anhydride and 20 ml. of triethyl orthoformate were refluxed for 1/2 hour. After cooling to room temperature, the solid was collected and washed with ethanol, followed by ether. After drying, the solid was dissolved in 100 ml. of 1 *N* potassium hydroxide, the mixture was filtered and the filtrate acidified with glacial acetic acid. The solid precipitate was collected, washed with water, then ethanol and dried to give 1.4 g. (57%); dec. > 400°. An analytical sample was obtained by recrystallization from glacial acetic acid.

Method B.

One gram (4 mmoles) of XIV in 50 ml. of formamide was heated at 175° for about 40 minutes. After cooling to 5°, 75 ml. of water was introduced, the mixture shaken, and the solid collected by filtration. After washing with water, then ethanol and drying, the solid was shaken with 50 ml. of 1 *N* potassium hydroxide and the mixture filtered. Ethanol (200 ml.) was added to the filtrate and the solution acidified with glacial acetic acid. After refrigerating the mixture overnight, the solid was collected, washed with water, ethanol, then ether and dried to yield 0.3 g. (30%).

Anal. Calcd. for $C_{11}H_{10}N_6O_2$: C, 51.16; H, 3.90; N, 32.55. Found: C, 50.68; H, 3.85; N, 32.63.

The infrared spectra of the products from methods A and B were identical.

1-Methyl-3-N-acetamido-5-hydroxy-7-ethylpyrazolo[3',4':6,5]pyrido-[2,3-d]pyrimidine (XIII).

Procedure A in the preparation of XII was followed except that 20

ml. of triethyl orthopropionate was used instead of the formate and that the mixture was refluxed for 1 hour. Seventy milliliters of 50% aqueous methanol was added to the reaction mixture before refrigerating in order to prevent gel formation. In this reaction, 0.6 g. (24%) of a pale yellow powder was obtained which was recrystallized from dimethylformamide-water to yield a fine white powder, m.p. 364-366°.

Anal. Calcd. for $C_{13}H_{14}N_6O_2$: C, 54.53; H, 4.93; N, 29.36. Found: C, 54.68; H, 4.89; N, 29.15.

1-Methyl-3-N-acetamido-6-amino-5-pyrazolo[3,4-b]pyridinecarboxamide (XIV).

A mixture of 2 g. (9.6 mmoles) of VI and 50 ml. of acetic anhydride was refluxed for 1/2 hour. The mixture was filtered after standing at room temperature overnight. The solid was washed with ethanol and dried. This gave 1.8 g. (76%) of white powder, which was recrystallized from dimethylformamide-water; dec. 354-356°.

Anal. Calcd. for $C_{10}H_{12}N_6O_2$: C, 48.38; H, 4.87; N, 33.86. Found: C, 48.60; H, 5.03; N, 34.90.

1-Methyl-3-N-formamido-6-amino-5-cyanopyrazolo[3,4-b]pyridine XVIII. Method A.

A mixture of 2 g. (0.011 mole) of IV and 50 ml. of formic acid was refluxed for 1 hour. After cooling to 5°, 200 ml. of ethanol was introduced and the mixture refrigerated overnight. The solid, 1.95 g. (83%) was collected, washed with ethanol and dried. An analytical sample was obtained in the form of a light green powder by recrystallization from glacial acetic acid, dec. 365-369°.

Anal. Calcd. for $C_9H_8N_6O$: C, 50.00; H, 3.73; N, 38.87. Found: C, 49.73; H, 3.49; N, 38.12.

Method B. Two grams (0.011 mole) of IV and 60 ml. of formamide were heated at 175° for 50 minutes. After cooling, the mixture was filtered into 175 ml. of glacial acetic acid and this mixture heated to boiling. After filtering the mixture while hot and allowing the filtrate to stand overnight, 0.78 g. (33%) of XVIII was obtained. Recrystallization from glacial acetic acid gave a sample whose infrared spectrum was identical to that of the product from method A.

The residue (5%) which was insoluble in boiling acetic acid was the corresponding pyrazolo[3',4':6,5]pyrido[2,3-d]pyrimidine (XIX). The analytical sample was recrystallized from large volumes of dimethylformamide, dec. > 350°.

Anal. Calcd. for $C_{10}H_9N_7O$: C, 49.37; H, 3.74. Found: C, 48.81; H, 4.05.

1-Methyl-3-N-formamido-5-hydroxypyrazolo[3',4':6,5]pyrido[2,3-d]-pyrimidine (XV). Method A.

Four grams (0.019 mole) of VI in 65 ml. of formamide was heated at 175° for 45 minutes. After refrigerating the mixture overnight, the solid was collected, washed with water and dried. After dissolving the solid in 100 ml. of 1 *N* potassium hydroxide, the solution was filtered and the filtrate mixed with 200 ml. of ethanol. Upon acidification with glacial acetic acid and cooling overnight, a solid weighing 2.1 g. (44%) was obtained. This was collected by filtration, washed with ethanol and dried. An analytical sample was obtained by recrystallization from dimethylformamide, dec. > 360°.

Anal. Calcd. for $C_{10}H_8N_6O_2$: C, 49.18; H, 3.30; N, 34.42. Found: C, 48.83; H, 3.22; N, 34.86.

Method B.

Two grams (9.6 mmoles) of VI and 50 ml. of formic acid were refluxed for 1 hour and the mixture cooled to 5°. After the addition of 200 ml. of ethanol, the mixture was refrigerated overnight. This gave 2.1 g. (90%) of a yellow solid which was collected by filtration, washed with ethanol and dried. The product had an infrared spectrum identical to that of the product from method A.

1-Methyl-3-amino-5-hydroxypyrazolo[3',4':6,5]pyrido[2,3-d]pyrimidine (XVI). Method A.

One gram (4.1 mmoles) of XV in 50 ml. of concentrated hydrochloric acid was refluxed for 4 hours. The solution was cooled and 200 ml. of water carefully introduced. After refrigeration, the mixture was filtered and the solid washed with water. Upon drying 0.7 g. (79%) of a yellow-orange powder was obtained. The analytical sample was obtained by recrystallization from water to give fine, yellow flakes which decomposed above 380°.

Anal. Calcd. for $C_9H_8N_6O$: C, 50.00; H, 3.73; N, 38.88. Found: C, 49.94; H, 3.43; N, 38.30.

Method B.

A mixture of 1.9 g. (7.8 mmoles) of XIX and 50 ml. of concentrated hydrochloric acid was refluxed for 3.5 hours. Procedure A was followed from this point to give 1 g. (57%) of product which was recrystallized from dimethylformamide-water. The infrared spectrum was identical to that of the analytical sample obtained from method A.

1,7-Dimethyl-3-N-acetamidopyrazolo[3',4':6,5]pyrido[2,3-d]-1,3-oxazine-5-one (XX).

A mixture of 1.5 g. (7.8 mmoles) of XI and 50 ml. of acetic anhydride was refluxed for 1/2 hour. After cooling the solid was collected, washed with absolute ethanol and dried. This gave 1.1 g. (56%) of a pale yellow powder, which when recrystallized from absolute ethanol-dimethylformamide gave fine light green flakes which decomposed above 300°.

Anal. Calcd. for $C_{12}H_{11}N_5O_3$: C, 52.75; H, 4.05; N, 25.63. Found: C, 53.09; H, 4.19; N, 25.25.

1-Methyl-3-N-acetamido-6-acetylpyrazolo[3',4':6,5]pyrido[2,3-d]-pyrimidine-5-one (XVII). Method A.

A mixture of 0.2 g. (1 mmole) of XVI and 15 ml. of acetic anhydride was refluxed for 10-20 minutes. After cooling, 0.19 g. (70%) of solid was collected and dried. It decomposed above 370°.

Anal. Calcd. for $C_{13}H_{12}N_6O_3$: C, 52.00; H, 4.03; N, 27.99. Found: C, 51.88; H, 3.98; N, 28.26.

Method B.

One-half gram (1.9 mmoles) of XII and 40 ml. of acetic anhydride were heated to boiling and the mixture filtered. After refrigerating the filtrate, 0.33 g. (57%) of a pale yellow powder was collected and dried. Recrystallization from acetic anhydride gave fine yellow flakes. The infrared spectrum of the product was identical to that of the product obtained in method A.

REFERENCES

(1) This investigation was supported by Public Health Service Research Grant No. CA-02857 from the National Cancer Institute.

(2) E. L. Little, Jr., W. J. Middleton, D. D. Coffman, V. A. Engelhardt, and G. N. Sausen, *J. Am. Chem. Soc.*, 80, 2832 (1958).

(3) S. G. Cottis and H. Tieckelmann, *J. Org. Chem.*, 26, 79 (1961).

(4) P. Schmidt, K. Eichenberger, M. Wilhelm and J. Druey, *Helv. Chim. Acta*, 42, 763 (1959).

(5) M. Hauser, E. Peters, and H. Tieckelmann, *J. Org. Chem.*, 25, 1570 (1960).

(6) E. C. Taylor, R. J. Knopf, R. F. Meyer, A. Holmes, and M. L. Hoefle, *J. Am. Chem. Soc.*, 82, 5711 (1960).

(7) R. K. Robins, *ibid.*, 78, 784 (1956).

(8) The authors acknowledge the technical aid of Mr. Richard D. Erb.

(9) Microanalyses by Galbraith Microanalytical Laboratories, Knoxville, Tenn., and Alfred Bernhardt, Mülheim, Germany. Melting points are uncorrected.

(10) F. Feigl, "Spot Tests in Organic Analysis," Elsevier Publishing Company, New York, N. Y., 1956, p. 292.

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