concentrated hydrochloric acid. This acidic mixture was extracted several times with chloroform and the extracts discarded. The residue was made basic with sodium carbonate solution and extracted several times with chloroform. The combined chloroform extracts of the basic solution were dried over sodium sulfate and the solvent distilled. The residue was distilled in vacuum to give 32.5 g. (58.6%) of α-phenyl-γ-(4-pyridyl)-butyronitrile, b.p. 185–187° at 2 mm. *Anal.* Calcd. for $C_{15}H_{14}N_2$: N, 12.61. Found: N, 12.45. Picrate, m.p. 136–137°. *Anal.* Calcd. for $C_{21}H_{17}N_5O_7$: N, 15.52. Found: N, 15.40. From the reaction of phenylacetonitrile and 2-vinylpyridine there was obtained a 39.6% yield of α-phenyl-γ-(2-pyridyl)-butyronitrile, b.p. 158–160° at 1.5 mm. *Anal.* Calcd.: N, 12.61. Found: N, 15.69. Picrate, m.p. 135–136°. *Anal.* Calcd.: N, 15.52. Found: N, 15.69.

From similar experiments between acetonitrile with 2-vinylpyridine and 4-vinylpyridine and isobutyronitrile with 2-vinylpyridine, there were obtained γ-(2-pyridyl)-butyronitrile (8.0%, V), b.p. 95–97° at 1 mm.; γ-(4-pyridyl)-butyronitrile (8.0%, VI), b.p. 122–125° at 1 mm., and α,α-dimethyl-γ-(2-pyridyl)-butyronitrile (27.0%, VII), b.p. 95–97° at 1.5 mm. Isobutyronitrile failed to react with 4-vinylpyridine. *Anal.* Calcd. for $C_9H_{10}N_2$ (V): N, 19.17. Found: N, 19.26. Picrate, m.p. 114–115°. *Anal.* Calcd. for $C_{15}H_{13}N_5O_7$: N, 18.66. Found: N, 18.41. Compound VI behaved erratically on analysis. However it gave an analytically pure picrate, m.p. 132.5–133.5°. *Anal.*: N, 18.66. Found: N, 18.23. *Anal.* Calcd. for $C_{11}H_{15}N_2$ (VII): N, 16.00. Found: N, 15.70. Picrate, m.p. 132–133°. *Anal.* Calcd. for $C_{17}H_{17}N_5O_7$: N, 17.36. Found: N, 17.66.

PITTSBURGH 13, PENNSYLVANIA

[CONTRIBUTION FROM THE BIOLOGICAL LABORATORY OF AMHERST COLLEGE]

The Synthesis of 5-Amino-7-hydroxy-1,3,4-imidazopyridine (1-Deazaguanine) and Related Compounds

BY D. G. MARKEES AND G. W. KIDDER

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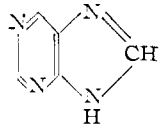
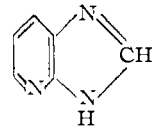
The preparation and Curtius reaction of 4-chloro- and 4-alkoxypyridine-2,6-dicarboxylates is reported. Two of the resulting diamines were aminated in position 3 and the triamines were converted to derivatives of 1,3,4-imidazopyridine.

A number of analogs of naturally occurring purine bases, which differ from the latter by replacement of a CH–group of the ring system by the isosteric N-atom have been shown to inhibit the growth of certain microörganisms. Among the compounds studied are derivatives of imidazo-1,2,3-triazine[1] and 5-amino-7-hydroxy-1-v-triazolo(d)-pyrimidine.[2,3]

We wished to study analogs of purine bases in which one nitrogen atom of the pyrimidine ring is replaced by the isosteric CH– group, and this paper deals with the synthesis of derivatives of 1,3,4-imidazopyridine.



Purine



1,3,4-Imidazopyridine (1-Deazapurine)

The parent compound 1,3,4-imidazopyridine[4] as well as a number of its derivatives are described in the literature.[4–6] However there is little information on their biological activity. Vaughan, *et al.*,[5] reported that their products failed to show any inhibition of the growth of a number of bacterial organisms. This is not too surprising as the positions of the substituents in their compounds were not the same as in the natural products. A publication by Dimmling and Hein[7] gives some information on the *in vitro* antibacterial activity of 7-amino-1,3,4-imidazopyridine (1-deazaadenine).

We were particularly interested in 5-amino-7-hydroxy-1,3,4-imidazopyridine (1-deazaguanine) (XII) and it was hoped that *Tetrahymena pyriformis*, because of its absolute guanine requirement,[8] could be used for the detection of any possible antimetabolite activity. Furthermore it has been established that the guanine antimetabolite 8-azaguanine[2] is incorporated into the nucleic acids of this organism,[9] and a similar metabolic fate of 1-deazaguanine was considered possible. Additional interest was lent to this project by the fact that 8-azaguanine is also an inhibitor of certain tumors in higher animals.[10]

For the synthesis of 1-deazaguanine we started with the pyridine moiety of the molecule and attached to it the imidazole ring. Since derivatives of 4-hydroxypyridine could cause difficulties, due to their tautomerism with isomeric 4-pyridones, we avoided their use and introduced the hydroxyl with the last operation. Esters of 4-chloropyridine-2,6-dicarboxylic acid (Ia, Ib) and 4-alkoxypyridine-2,6-dicarboxylic acids (IIIa, IIIb) were subjected to the Curtius degradation and gave 4-chloro-2,6-diaminopyridine (IVa) and 4-alkoxy-2,6-diaminopyridines (IVb, IVc). In two cases an additional amino group was introduced and gave 4-chloro-2,3,6-triaminopyridine (Xa) and 4-ethoxy-2,3,6-triaminopyridine (Xb), respectively. By ring closure involving the amino groups in position 2 and 3 we prepared 5-amino-7-chloro-1,3,4-imidazopyridine (XIa) and 5-amino-7-ethoxy-1,3,4-imidazo-

(1) D. W. Woolley and E. Shaw, *J. Biol. Chem.*, **189**, 401 (1951).

(2) R. O. Roblin, Jr., J. O. Lampen, J. P. English, Q. P. Cole and J. R. Vaughan, Jr., THIS JOURNAL, **67**, 290 (1945).

(3) G. W. Kidder and V. C. Dewey, *J. Biol. Chem.*, **179**, 181 (1949).

(4) F. Kögl, G. M. van der Want and C. A. Salemink, *Rec. trav. chim.*, **67**, 29 (1948).

(5) J. R. Vaughan, Jr., J. Krapcho and J. P. English, THIS JOURNAL, **71**, 1885 (1949).

(6) C. A. Salemink and G. M. van der Want, *Rec. trav. chim.*, **68**, 1013 (1949).

(7) T. Dimmling and H. Hein, *Arzneimittel Forsch.*, **2**, 515 (1952).

(8) G. W. Kidder, V. C. Dewey, R. E. Parks, Jr., and M. R. Heinrich, *Proc. Nat. Acad. Sci.*, **36**, 431 (1950).

(9) M. R. Heinrich, V. C. Dewey, R. E. Parks, Jr., and G. W. Kidder, *J. Biol. Chem.*, **197**, 199 (1952).

(10) G. W. Kidder, V. C. Dewey, R. E. Parks, Jr., and G. L. Woodside, *Science*, **109**, 511 (1949); G. W. Kidder, V. C. Dewey, R. E. Parks, Jr., and G. L. Woodside, *Cancer Research*, **11**, 204 (1951).

pyridine (XIb). From the latter we obtained the guanine analog XII by hydrolysis of the ethoxy group.

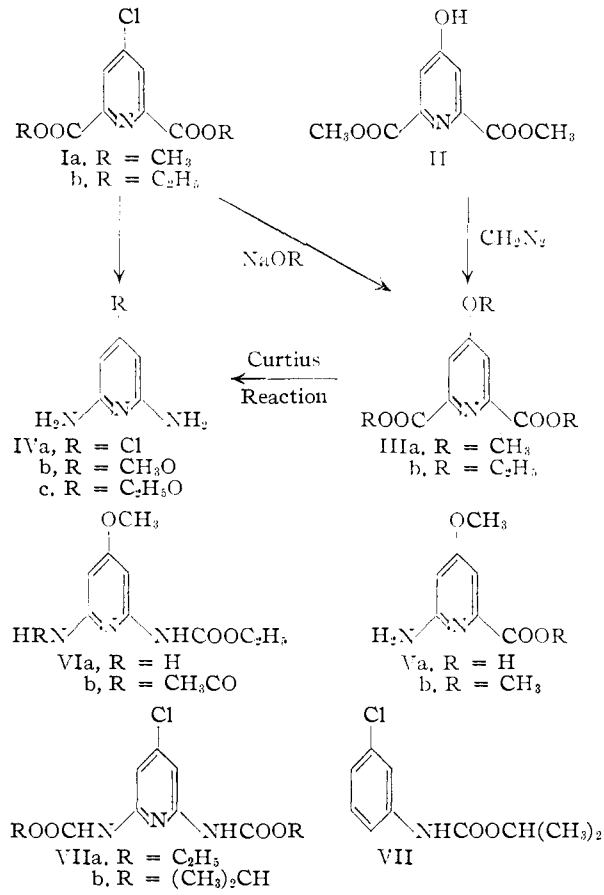
Diethyl 4-chloropyridine-2,6-dicarboxylate (Ib) was prepared by a modification of a method described in the literature.[11] Its Curtius degradation[12] proceeded smoothly. The desired 4-chloro-2,6-diaminopyridine (IVa) could be obtained either by direct rearrangement and decomposition of the intermediate azide or by hydrolysis and decarboxylation of 4-chloro-2,6-dicarbethoxyamidopyridine (VIIa). This diurethan is structurally related to the plant growth inhibitor isopropyl N-3-chlorophenylcarbamate (VII).[13–15] However, in preliminary tests for inhibition of germination it was found to be inactive as was 4-chloro-2,6-dicarboisopropoxyamidopyridine (VIIb).

Diethyl 4-chloropyridine-2,6-dicarboxylate (Ib) gave dimethyl 4-methoxypyridine-2,6-dicarboxylate (IIIa) on reaction with sodium methoxide in methanol. Using dimethyl 4-chloropyridine-2,6-dicarboxylate (Ia) as starting material improved this preparation materially since in this way the yield was not impaired by transesterification. It was also observed that the same ester was formed by methylation of dimethyl chelidamate (II) with diazomethane. Fibel and Spoerri[16] and also Meyer[17] treated chelidamic acid with diazomethane and considered the reaction products to be dimethyl N-methyl-4-pyridone-2,6-dicarboxylate and dimethyl chelidamate, respectively. We assume that our product and the ones obtained by Fibel and Spoerri and Meyer are identical because of their similar mode of formation and the close correspondence of their melting points. However, we assign to it the structure of dimethyl 4-methoxypyridine-2,6-dicarboxylate.

The Curtius reaction carried out with this ester furnished, besides the desired diamine, two additional products. The decomposition of the intermediate diazide in aqueous acetic acid produced 4-methoxy-2-aminopicolinic acid (Va). This compound was characterized further by esterification with diazomethane (Vb).

A product of partial hydrolysis was obtained by refluxing 4-methoxy-2,6-dicarbethoxyamidopyridine with 5% sodium hydroxide. The analytical values indicated the empirical formula $C_9H_{13}N_3O_3$ which corresponds to 4-methoxy-2-amino-6-carbethoxyamidopyridine (VIa). Acetylation gave a compound of the empirical formula $C_{11}H_{15}N_3O_4$, which is assumed to be 4-methoxy-2-acetamido-6-carbethoxyamidopyridine (VIb).

Diethyl 4-ethoxypyridine-2,6-dicarboxylate (IIIb) was obtained from diethyl 4-chloropyridine-2,6-dicarboxylate (Ib) with sodium ethoxide. Its Curtius degradation proceeded smoothly and with acceptable yields.



For the preparation of 5-amino-7-chloro-1,3,4-imidazopyridine (XIa) we coupled 4-chloro-2,6-diaminopyridine (IVa) with diazotized aniline or sulfanilic acid and reduced the resulting azo dyestuff (VIIIa) to 4-chloro-2,3,6-triaminopyridine (Xa). It is interesting to note that this chlorinated triamine is stable as the free base, in contrast to the unhalogenated 2,3,6-triaminopyridine. This finding has a parallel in the result published by Vaughan, *et al.*,[5] that 5-chloro-2,3-diaminopyridine is more stable than 2,3-diaminopyridine.

Cyclization of 4-chloro-2,3,6-triaminopyridine (Xa) with formic acid gave 5-formamido-7-chloro-1,3,4-imidazopyridine. By acid hydrolysis we could easily remove the formyl group and obtained 5-amino-7-chloro-1,3,4-imidazopyridine (XIa). Although the Cl-atom in position 7 corresponds to the most reactive one in 2,6,8-trichloropurine, it proved to be quite unreactive and we were not able to replace it with a hydroxyl or an acetoxy group. This is in agreement with the generally decreased reactivity of pyridine halides as compared with the isosteric pyrimidine or triazine derivatives.[18]

For our further experiments we used 4-ethoxy-2,6-diaminopyridine (IVc) since its preparation gave generally better yields than that of the 4-methoxy compound. The intermediate 4-ethoxy-2,3,6-triaminopyridine (Xb), obtained by a coupling reaction and subsequent reduction, was much less stable than the corresponding chlorotriamine

(11) E. Koenigs and W. Jaeschke, *Ber.*, **54**, 1351 (1921).

(12) For a survey of this method see P. A. S. Smith in R. Adams, "Organic Reactions," Vol. 3, John Wiley and Sons, New York, N. Y., 1946, p. 337.

(13) J. R. W. Wilson, *Agr. Chem.*, **6** [2], 34 (1951).

(14) E. D. Witman and F. D. Newton, *Proc. 5th. Ann. Meet. Northeastern WCC.*, 45 (1951).

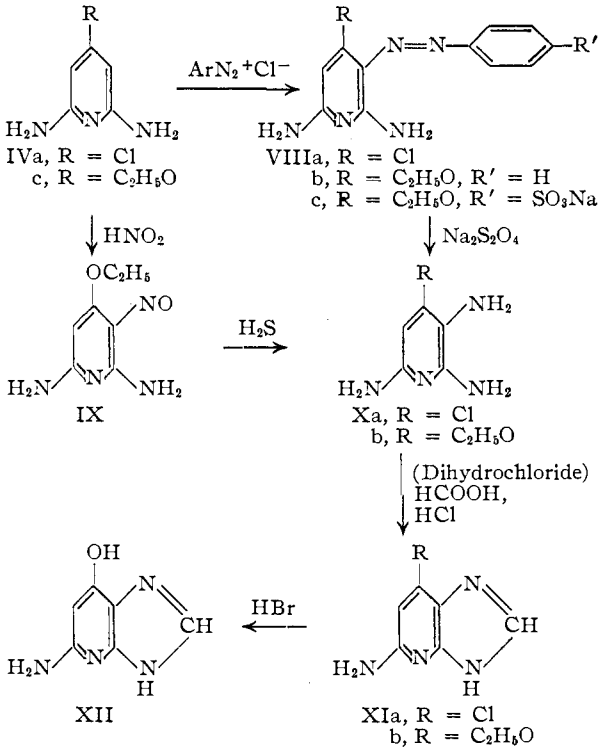
(15) E. D. Witman, *Agr. Chem.*, **8** [10], 50 (1953).

(16) L. R. Fibel and P. E. Spoerri, THIS JOURNAL, **70**, 3908 (1948).

(17) H. Meyer, *Monatsh.*, **26**, 1311 (1905); **25**, 1193 (1904).

(18) See for instance H. S. Mosher in R. C. Elderfield, "Heterocyclic Compounds," Vol. 1, John Wiley and Sons, New York, N. Y., 1950, p. 522.

and could be purified for analysis only as the dihydrochloride. For that reason, we had only a small amount of somewhat impure material available for the following steps of the synthesis. We treated the crude triamine with formic acid and hydrolyzed the primary reaction product with hydrochloric acid without further purification. Thus we obtained 5-amino-7-ethoxy-1,3,4-imidazopyridine (XIb) which, subjected to hydrolysis in 48% hydrobromic acid, afforded a small amount of 5-amino-7-hydroxy-1,3,4-imidazopyridine (XII).



In order to avoid the isolation of the sensitive 4-ethoxy-2,3,6-triaminopyridine (Xb) in our preparation, we nitrosated[19] the diamine to 4-ethoxy-2,6-diamino-3-nitrosopyridine (IX) which in turn could be reduced with hydrogen sulfide[20] to the triamine and stabilized immediately as a salt. The latter could be used just as well as the free base in the subsequent cyclization[21] with formic acid.

The results of the biological investigation of the derivatives of 1-deazapurine will be reported elsewhere.

Acknowledgment.—This work was supported by the Office of Naval Research Contract Nonr. 1058(00).

Experimental[22]

Diethyl 4-Chloropyridine-2,6-dicarboxylate (Ib).—A mixture of 61.0 g. of crude dry chelidamic acid, 209.5 g. of phosphorus pentachloride and 300 ml. of carbon tetrachloride was refluxed until the evolution of hydrogen chloride gas ceased and a dark solution was obtained. Gradually 250 ml. of commercial absolute ethanol was added to the lively boiling mixture. After the addition was complete and the evolution of hydrogen chloride had ceased again, most of the volatile material was distilled off. Another 50 ml. of absolute ethanol was added and distilled off to remove as much of the carbon tetrachloride as possible. The mixture was then poured into one l. of ice and water. The ester crystallized immediately, was filtered and dissolved in about 250 ml. of dioxane. After treatment with charcoal the solution was poured into ice-water and the ester crystallized, filtered and air-dried. The average yield (5 runs) was 56.1 g. (65%) and the m.p. was 89–91°. A sample recrystallized from dilute ethanol melted at 92° (lit. 92–94°).[2]

Dimethyl 4-Chloropyridine-2,6-dicarboxylate (Ia).—This ester was obtained by substituting methanol for ethanol in the procedure above. The average yield (3 runs) of air-dried material was 52.4 g. (69%). After recrystallization from methanol the colorless needles melted at 142–143°.

Anal. Calcd. for $C_9H_8ClNO_4$: N, 6.10. Found: N, 6.05.

Dimethyl 4-Methoxypyridine-2,6-dicarboxylate (IIIa).—A solution of 4.0 g. of sodium in 125 ml. of commercial absolute methanol was mixed with a suspension of 40.0 g. of dimethyl 4-chloropyridine-2,6-dicarboxylate in 50 ml. of dry methanol. The dark clear solution was concentrated after reflux for 0.75 hour. The partly crystalline residue was diluted with water, cooled and filtered. A crop of 36.8 g. (94%) of crude material was obtained. A sample was recrystallized from water; m.p. 125–127°.

Anal. Calcd. for $C_{10}H_{11}NO_5$: C, 53.32; H, 4.92; N, 6.22. Found: C, 53.10; H, 4.84; N, 6.20.

The same compound was obtained by treating a suspension of 26.0 g. of dry diethyl 4-chloropyridine-2,6-dicarboxylate in 30 ml. of methanol with a solution of 2.3 g. of sodium in 50 ml. of methanol. The yield was 11.3 g. (49%) of crude material. A sample was recrystallized from methanol; m.p. 125–127°.

Anal. Calcd. for $C_{10}H_{11}NO_5$: C, 53.32; H, 4.92; N, 6.22. Found: C, 53.38; H, 4.74; N, 6.35.

We obtained this compound also by treating a suspension of 3.1 g. of dimethyl chelidamate hydrate[16] in 25 ml. of dioxane with an excess of an ethereal diazomethane solution. After the excess of diazomethane was destroyed with a little acetic acid a first crop of 0.8 g. of dimethyl 4-methoxypyridine-2,6-dicarboxylate was filtered off. The mother liquor was washed with dilute sodium bicarbonate and the ether evaporated down. Upon addition of petroleum benzin to the semi-solid residue another 0.35 g. of the same material was obtained, and on standing a third crop of 0.9 g. separated from the washings. The three crops were combined and recrystallized from methanol; m.p. 126.5–128° (lit. 128–129° (uncor.)).[16]

Anal. Calcd. for $C_{10}H_{11}NO_5$: N, 6.22. Found: N, 6.21. No depression of the m.p. was observed by mixing any two of these preparations.

Diethyl 4-Ethoxypyridine-2,6-dicarboxylate (IIIb).—A solution of 32.2 g. of diethyl 4-chloropyridine-2,6-dicarboxylate in 150 ml. of commercial absolute ethanol was added to a solution of 3.0 g. of sodium in 100 ml. of absolute ethanol. The spontaneous reaction was completed by heating to reflux for 1.5 hours. The mixture was then poured into 1200 ml. of ice-water, whereupon 24.1 g. (69%) of the ester crystallized out. Recrystallization from heptane gave colorless needles, m.p. 85°.

Anal. Calcd. for $C_{13}H_{17}NO_5$: C, 58.41; H, 6.41; N, 5.25. Found: C, 58.43; H, 6.34; N, 5.03.

4-Chloropyridine-2,6-dicarboxylic Acid Dihydrazide.—A solution of 66.4 g. of diethyl 4-chloropyridine-2,6-dicarboxylate in 300 ml. of 95% ethanol was mixed with 35.0 ml. of 85% hydrazine hydrate. Reaction took place instantaneously and the solid precipitate was filtered after a short while, washed with water and alcohol and air-dried. The yield of crude material was 47.5 g. (80.5%). A sample, recrystallized from water, was obtained as colorless needles which did not melt below 300°.

Anal. Calcd. for $C_7H_8ClN_5O_2$: C, 36.61; H, 3.52; N, 30.5. Found: C, 36.73; H, 3.49; N, 30.2.

4-Methoxypyridine-2,6-dicarboxylic Acid Dihydrazide.—This compound was obtained in a similar way by refluxing

(19) A. I. Titov, *J. Gen. Chem.* (*U.S.S.R.*), **8**, 1483 (1938); *C.A.*, **33**, 4248[2] (1939).

(20) M. Engelmann, U. S. Patent 2,136,044 (1938); *C.A.*, **33**, P 1348[5] (1939).

(21) *Cf.* M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).

(22) All melting points were determined on a Fisher–Johns apparatus and are corrected.

the ester with an equimolecular amount of hydrazine hydrate for 1.5 hours. The yield was 84.5% and the m.p. of the colorless needles (from water) was 252–254°.

Anal. Calcd. for $C_8H_{11}N_5O_3$: C, 42.66; H, 4.92; N, 31.1. Found: C, 42.78; H, 4.93; N, 31.2.

4-Ethoxypyridine-2,6-dicarboxylic Acid Dihydrazide.—Refluxing of the appropriate ester with an excess of hydrazine hydrate for 1.5 hours gave the desired product in 90.5% yield. The colorless crystals (from water) melted at 229–230°.

Anal. Calcd. for $C_9H_{13}N_5O_3$: N, 29.3. Found: N, 29.0.

4-Chloro-2,6-dicarbethoxyamidopyridine (VIIa).—To a solution of 42.0 g. of crude 4-chloropyridine-2,6-dicarboxylic acid dihydrazide in 360 ml. of 10% hydrochloric acid was added with stirring the solution of 30.0 g. of sodium nitrite in 100 ml. of water, over a period of 1.25 hours while the temperature was kept between 10 and 15° with an ice-bath. The diazide crystallized immediately and the mixture was stirred for an additional hour. The product was then filtered off, air-dried (41.5 g.), dissolved in 550 ml. of absolute ethanol and refluxed for 4 hours. Concentrated to about 150 ml. it separated 21.5 g. (42.5%) of diurethan. Recrystallization from dilute ethanol gave colorless crystals of m.p. 143.5–144.5°.

Anal. Calcd. for $C_{11}H_{14}ClN_3O_4$: N, 14.6; Cl, 12.35. Found: N, 14.6; Cl, 12.18.

4-Chloro-2,6-dicarboisopropoxyamidopyridine (VIIb).—This urethan was obtained in a 36% yield by decomposition of 4-chloropyridine-2,6-dicarboxylic acid diazide in isopropyl alcohol. It was purified by recrystallization from dilute isopropyl alcohol; m.p. 118.5°.

Anal. Calcd. for $C_{13}H_{18}ClN_3O_4$: C, 49.45; H, 5.75; N, 13.3. Found: C, 49.74; H, 5.86; N, 13.6.

4-Methoxy-2,6-dicarbethoxyamidopyridine.—This compound was obtained by decomposing in absolute ethanol the reaction product of 2.5 g. of 4-methoxypyridine-2,6-dicarboxylic acid dihydrazide and 1.5 g. of sodium nitrite in dilute hydrochloric acid. The yield was 0.7 g. (22%) and the m.p. of a purified sample (from dilute ethanol) was 142–144°.

Anal. Calcd. for $C_{12}H_{17}N_3O_4$: C, 50.87; H, 6.05; N, 14.8. Found: C, 51.13; H, 5.99; N, 14.6.

4-Methoxy-2,6-dicarbomethoxyamidopyridine.—Decomposition of the azide in methanol furnished this carbamate in a 30.8% yield. Recrystallization from 50% acetic acid gave colorless needles, m.p. 205°.

Anal. Calcd. for $C_{10}H_{13}N_3O_5$: C, 47.06; H, 5.13; N, 16.5. Found: C, 47.08; H, 5.01; N, 16.5.

4-Ethoxy-2,6-dicarbethoxyamidopyridine.—A batch of 16.0 g. of 4-ethoxypyridine-2,6-dicarboxylic acid dihydrazide was converted to the azide with 10.2 g. of sodium nitrite in dilute hydrochloric acid. The dried intermediate (16.2 g.) was refluxed for 4 hours in 160 ml. of absolute ethanol, the solution concentrated to about half of the original volume and then diluted with water. A crop of 11.2 g. (61.5%) of crude material was obtained. Recrystallization from dilute ethanol gave colorless flakes, m.p. 128.5°.

Anal. Calcd. for $C_{13}H_{19}N_3O_5$: C, 52.52; H, 6.44; N, 14.1. Found: C, 52.64; H, 6.51; N, 14.2.

4-Chloro-2,6-diaminopyridine (IVa).—A solution of 8.0 g. of 4-chloro-2,6-dicarbethoxyamidopyridine and 10.0 g. of potassium hydroxide in a total of 180 ml. of ethanol was refluxed for 3 hours. The solid precipitate was filtered after cooling, dried (8.8 g.) and decomposed by refluxing with 25 ml. of water for 0.5 hour. The diamine separated as an oil which crystallized on cooling. Filtered and dried it weighed 2.5 g. (62.5%). A sample was recrystallized several times from benzene and finally sublimed at 78° (0.2 mm.); m.p. 102.5°.

Anal. Calcd. for $C_5H_6ClN_3$: C, 41.82; H, 4.21; N, 29.3. Found: C, 42.03; H, 4.09; N, 29.0.

The same diamine was also obtained by heating a mixture of 20.0 g. of crude 4-chloropyridine-2,6-dicarboxylic acid diazide with a mixture of 80 ml. of glacial acetic acid and 20 ml. of water. The mixture was then made alkaline with 30% sodium hydroxide and extracted with ethyl acetate. After drying and evaporating, a crop of 5.2 g. of 4-chloro-2,6-diaminopyridine (43.5%) was left. After one sublimation the m.p. of this material was 102° and the m.p. of a mixture of the two preparations was 101–102°.

4-Chloro-2,6-diacetamidopyridine.—A mixture of 0.5 g. of crude 4-chloro-2,6-diaminopyridine, 3 ml. of acetic anhydride and a drop of sulfuric acid was warmed on the steam-bath for 20 minutes. After standing overnight, water was added to the mixture and 0.7 g. (88%) of crude acetylated material filtered off. Recrystallization from water gave colorless needles, m.p. 206–208°.

Anal. Calcd. for $C_9H_{10}ClN_3O_2$: N, 18.5. Found: N, 18.2.

4-Methoxy-2,6-diaminopyridine (IVb).—A solution of 2.0 g. of crude 4-methoxy-2,6-dicarbethoxyamidopyridine and 2.0 g. of potassium hydroxide in 50 ml. of 95% ethanol was refluxed for 3 hours. The solid precipitate was filtered off, extracted with ethyl acetate and the alcoholic filtrate was evaporated down. Some water was added to the residue and the resulting suspension was extracted with ethyl acetate. The two extracts were dried with sodium sulfate and evaporated down, leaving behind 0.7 g. (65.5%) of crude diamine. Recrystallization from benzene gave colorless leaflets, m.p. 132–134°.

Anal. Calcd. for $C_6H_9N_3O$: C, 51.78; H, 6.52; N, 30.2. Found: C, 51.89; H, 6.54; N, 30.4.

4-Methoxy-2,6-diacetamidopyridine.—A 300-mg. sample of crude 4-methoxy-2,6-diaminopyridine was acetylated with 3 ml. of acetic anhydride and a trace of sulfuric acid. The volatile parts were evaporated upon destroying the excess of acetic anhydride with methanol and the residue triturated with a little water. A crop of 480 mg. (96%) of solid material was obtained. Recrystallized from water the colorless needles melted at 181.5–183°, after losing water at about 80°.

Anal. Calcd. for $C_{10}H_{13}N_3O_3 \cdot {}^1/_2H_2O$: N, 18.1. Found: N, 18.2, 18.2.

4-Ethoxy-2,6-diaminopyridine (IVc).—Heating of 11.5 g. of crude 4-ethoxy-2,6-dicarbethoxyamidopyridine in 150 ml. of 6.6% sodium hydroxide under reflux for 3 hours gave 5.4 g. (91%) of the diamine, isolated by filtration and extraction of the mother liquor with ethyl acetate. Recrystallization from water gave colorless needles of m.p. 134–135°.

Anal. Calcd. for $C_7H_{11}N_3O$: C, 54.88; H, 7.24; N, 27.4. Found: C, 54.89; H, 7.01; N, 27.4.

4-Ethoxy-2,6-diacetamidopyridine.—Acetylation of 0.5 g. of 4-ethoxy-2,6-diaminopyridine with 3 ml. of acetic anhydride gave a crop of 0.6 g. (74%) of crude material. It melted unsharply between 60 and 70° after repeated recrystallization from water.

Anal. Calcd. for $C_{11}H_{15}N_3O_3 \cdot {}^1/_2H_2O$: C, 53.64; H, 6.55; N, 17.1. Found: C, 53.78; H, 6.63; N, 16.8.

4-Methoxy-2-amino-6-carbethoxyamidopyridine (VIa).—A solution of 15.9 g. of 4-methoxy-2,6-dicarbethoxyamidopyridine was refluxed with 8.0 g. of potassium hydroxide in 125 ml. of 95% ethanol for 5 hours. The mixture was concentrated to about 70 ml. and diluted with water until a clear solution was obtained. It then was acidified with 10% hydrochloric acid, again made alkaline with 10% sodium hydroxide, and 3.6 g. (28%) of material was filtered off. After several recrystallizations from benzene the m.p. of the colorless crystals was 120.5–121.5°.

Anal. Calcd. for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 19.9. Found: C, 51.40, 51.65; H, 6.02, 6.07; N, 19.9, 20.0.

4-Methoxy-2-acetamido-6-carbethoxyamidopyridine (VIb).—A 200-mg. sample of 4-methoxy-2-amino-6-carbethoxyamidopyridine was acetylated with 1 ml. of acetic anhydride and a trace of sulfuric acid. Upon dilution with water 210 mg. (93%) of acetylated product were filtered off. Recrystallization from dilute ethanol gave colorless crystals, m.p. 147–149°.

Anal. Calcd. for $C_{11}H_{15}N_3O_4$: C, 52.16; H, 5.97; N, 16.6. Found: C, 52.19; H, 5.96; N, 16.5, 16.7.

4-Methoxy-2-aminopicolinic Acid (Va).—A mixture of 10.0 g. of crude 4-methoxypyridine-2,6-dicarboxylic acid diazide and 55 ml. of glacial acetic acid and 11 ml. of water was warmed gently on the steam-bath. After the evolution of gas had ceased it was concentrated somewhat until crystallization set in, then cooled and the solid filtered off. The yield was 3.5 g. (46%). A sample recrystallized

several times from 50% acetic acid and finally from water melted at 280–282°, losing water of crystallization at about 130°.

Anal. Calcd. for $C_7H_8N_2O_3 \cdot H_2O$: C, 45.16; H, 5.41; N, 15.1. Found: C, 45.39; H, 5.51; N, 15.1.

Methyl 4-Methoxy-2-aminopicolinate (Vb).—A one-gram sample of 4-methoxy-2-aminopyridine-6-carboxylic acid was treated with an excess of ethereal diazomethane. The reaction proceeded rather sluggishly. The volatile parts were allowed to evaporate and the residue was extracted with ethyl acetate and ether, leaving a small amount of crude ester after evaporation. Recrystallized from benzene–petroleum ether with charcoal, then from benzene alone, a colorless sample was obtained, m.p. 129–131°.

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.4. Found: C, 52.68; H, 5.62; N, 15.5.

4-Chloro-2,6-diamino-3-phenylazopyridine (VIIIa).—A solution of 0.9 ml. of aniline in 5 ml. of concentrated hydrochloric acid and water each was diazotized by addition of 0.7 g. of sodium nitrite in 10 ml. of water. This solution was added to a suspension of 1.44 g. of 4-chloro-2,6-diaminopyridine (Ia) in 10 ml. each of water and concentrated hydrochloric acid. It was diluted with a little water and allowed to stand overnight. A solution of 20.0 g. of sodium acetate trihydrate in 30 ml. of water was then added. A crop of 2.4 g. (97%) of crude azo compound was obtained. A sample, recrystallized from ethanol containing a little aqueous ammonia, then several times from aqueous ethanol, was obtained as orange needles melting at 157–158°.

Anal. Calcd. for $C_{11}H_{10}ClN_5$: N, 28.28. Found: N, 28.36.

4-Chloro-2,3,6-triaminopyridine (Xa).—A solution of 2.0 g. of recrystallized 4-chloro-2,6-diamino-3-phenylazopyridine in 15 ml. of ethanol was added in portions to a solution of 10 g. of sodium dithionite in 40 ml. of water. The mixture was stirred mechanically and warmed by immersion in a warm water-bath. The suspension which was formed initially dissolved, and the color changed to light yellow. Some unchanged material was removed by filtration and the filtrate was made distinctly alkaline with 25 ml. of 10% sodium hydroxide. The triamine crystallized out on cooling and was filtered and dried. The yield was 0.65 g. (50.5%), and the m.p. of a sample purified by sublimation was 169–171° dec.

Anal. Calcd. for $C_5H_7ClN_4$: N, 35.3. Found: N, 35.5.

This compound was also obtained by coupling 3.6 g. of 4-chloro-2,6-diaminopyridine with diazotized sulfanilic acid. The resulting dyestuff, not further purified, was reduced with two 20-g. portions of sodium dithionite in 40 ml. of water on the steam-bath. Upon addition of 60 ml. of 10% sodium hydroxide 2.2 g. (69%) of the triamine crystallized out. A sample was purified by sublimation *in vacuo* and melted at 169–171° dec.

Anal. Calcd. for $C_5H_7ClN_4$: C, 37.86; H, 4.31. Found: C, 37.77; H, 4.25.

5-Formamido-7-chloro-1,3,4-imidazopyridine.—A mixture of 1.0 g. of crude 4-chloro-2,3,6-triaminopyridine and 20 ml. of 98% formic acid was refluxed for 19 hours. It was then concentrated to about one half of the original volume and diluted with water. A crop of 1.0 g. (80%) of crystalline material was obtained, of which a sample was recrystallized from water. Its m.p. was above 300°.

Anal. Calcd. for $C_7H_5ClN_4O$: C, 42.76; H, 2.56. Found: C, 43.23; H, 2.58.

5-Amino-7-chloro-1,3,4-imidazopyridine (6-Chloro-2-amino-1-deazapurine) (XIa).—A mixture of 150 mg. of 6-chloro-2-formamido-1-deazapurine and 2 ml. of 15% hydrochloric acid was heated on the steam-bath for 0.5 hour. After cooling, 0.7 g. of solid sodium bicarbonate was added and the formed precipitate was filtered off (100 mg.). This product was warmed on the steam-bath with 2 ml. of concentrated hydrochloric acid for 0.5 hour. After removal of the volatile parts, the free base was obtained by addition of saturated sodium bicarbonate solution to the residue. Recrystallized from water the colorless product melted at 229–231° after giving off water above 130°.

Anal. Calcd. for $C_6H_5ClN_4 \cdot H_2O$: N, 30.0; Cl, 19.00. Found: N, 30.3; Cl, 19.15.

4-Ethoxy-2,6-diamino-3-phenylazopyridine (VIIIb).—A solution of 0.9 ml. of aniline in 5 ml. of concentrated hydrochloric acid and 5 ml. of water was diazotized with 0.7 g. of sodium nitrite in 10 ml. of water. This solution was added to 1.53 g. of 4-ethoxy-2,6-diaminopyridine (Ib) dissolved in 10 ml. of water and 10 ml. of concentrated hydrochloric acid. Coupling took place slowly and the mixture was kept in the refrigerator overnight. A solution of 20 g. of sodium acetate trihydrate in 30 ml. of water was then added and a crop of 2.0 g. (78%) of crude azo dyestuff filtered off. Recrystallized from ethanol containing some aqueous ammonia, then several times from aqueous ethanol, it was obtained as yellow needles, m.p. 167.5–168.5°.

Anal. Calcd. for $C_{13}H_{15}N_5O$: N, 27.2. Found: N, 27.4.

4-Ethoxy-2,6-diamino-3-*p*-sulfophenylazopyridine (VIIIc).—This compound was obtained when 6.0 g. of crude 4-ethoxy-2,6-diaminopyridine were coupled with diazotized sulfanilic acid. The yield of crude azo dyestuff was 10.1 g. (89%). For analysis a sample was converted to the sodium salt and recrystallized from ethanol.

Anal. Calcd. for $C_{13}H_{14}N_5O_4SNa \cdot C_2H_5OH$: N, 17.3; Na, 5.68. Found: N, 17.9; Na, 5.61.

4-Ethoxy-2,6-diamino-3-nitrosopyridine (IX).—A solution of 1.4 g. of sodium nitrite in 15 ml. of water was added slowly to a cooled, stirred solution of 3.0 g. of 4-ethoxy-2,6-diaminopyridine in 40 ml. of 10% acetic acid. The temperature was kept between 5 and 8°. To the suspension of crystals which had formed was added a mixture of 20 ml. of saturated sodium bicarbonate and 10 ml. of water. The crystalline material was filtered, the yield being 3.4 g. (95%). A sample, recrystallized from water, was obtained as shiny fuchsia-colored leaflets which decompose gradually above 230° without melting.

Anal. Calcd. for $C_7H_{10}N_4O_2$: C, 46.15; H, 5.53; N, 30.8. Found: C, 45.67; H, 5.65; N, 30.6.

4-Ethoxy-2,3,6-triaminopyridine Dihydrochloride (Xb).—(a).—A solution of 3.6 g. of 4-ethoxy-2,6-diamino-3-*p*-sulfophenylazopyridine in 40 ml. of 5% sodium hydroxide was reduced with 6.0 g. of sodium dithionite. The mixture was then made distinctly alkaline with 5% sodium hydroxide and extracted with 6 portions of ethyl acetate. An excess of alcoholic hydrochloric acid was added to the extract. A crop of 1.3 g. (50.5%) of solid material was filtered off. For analysis a sample was dissolved in ethanol and reprecipitated with ethanolic hydrochloric acid.

Anal. Calcd. for $C_7H_{12}N_4O \cdot 2HCl$: C, 34.87; H, 5.85; N, 23.3. Found: C, 35.09; H, 6.08; N, 23.7.

(b).—A slow stream of hydrogen sulfide was bubbled through a stirred suspension of 3.0 g. of 4-ethoxy-2,6-diamino-3-nitrosopyridine in 40 ml. of water at 80°. The mixture was cooled after decolorization and acidified with 20 ml. of 10% hydrochloric acid. The residue obtained on evaporation *in vacuo* was taken up in a little water, filtered and evaporated again, leaving 4.2 g. of slightly moist material. A sample was recrystallized several times from dilute ethanolic hydrochloric acid.

Anal. Calcd. for $C_7H_{12}N_4O \cdot 2HCl$: N, 23.3; Cl, 29.4. Found: N, 23.3; Cl, 29.9.

5-Amino-7-ethoxy-1,3,4-imidazopyridine (6-Ethoxy-2-amino-1-deazapurine) (XIb). (a).—A warm solution of 3.7 g. of crude 4-ethoxy-2,6-diamino-3-*p*-sulfophenylazopyridine in 20 ml. of 5% sodium hydroxide was reduced with 4.6 g. of sodium dithionite. The decolorized solution was made distinctly alkaline with 30 ml. of 5% sodium hydroxide and after cooling extracted with ethyl acetate. The extract was dried with sodium sulfate and evaporated to dryness, leaving 1.1 g. of a dark tarry residue. This was dissolved in 15 ml. of 98% formic acid and refluxed for 19 hours. The volatile parts were then distilled off in an air stream leaving 1.2 g. of light brown material, which in turn was dissolved in a mixture of 10 ml. each of hydrochloric acid and water and refluxed for 4 hours. The solution was evaporated down and the residue (1.3 g.) was taken up in 20 ml. of water and neutralized with 15 ml. of saturated sodium bicarbonate. The reddish crystalline material was filtered off after standing in the refrigerator for 6 hours and air-dried; the yield was 1.1 g. (56% from azo compound) and a colorless sample, recrystallized from water, melted at 240–241°.

Anal. Calcd. for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.4. Found: C, 53.98; H, 5.75; N, 31.5.

(b).—A batch of 3.5 g. of crude 4-ethoxy-2,3,6-triaminopyridine dihydrochloride was refluxed with 20 ml. of 98% formic acid for 19 hours. The volatile material was then evaporated and the residue was refluxed for 4 hours with 20 ml. of concentrated hydrochloric acid. Upon removal of the excess hydrochloric acid the residue was taken up with a little water, then made weakly alkaline with sodium bicarbonate. The crystalline material which separated weighed 1.4 g. (57% from nitroso compound). A sample was charcoaled and recrystallized from water, m.p. 238–240°.

Anal. Calcd. for $C_8H_{10}N_4O$: N, 31.4. Found: N, 31.6.

5-Amino-7-hydroxy-1,3,4-imidazopyridine (6-Hydroxy-2-amino-1-deazapurine, 1-Deazaguanine) (XII). (a).—A mixture of 1.1 g. of 6-ethoxy-2-amino-1-deazapurine and 15 ml. of 48% hydrobromic acid was refluxed for 4 hours. The crystalline material which separated on cooling was filtered off (0.8 g.) and dissolved in 5 ml. of water. This solution was neutralized with sodium bicarbonate and the separated solid material was filtered off. The yield was 0.3 g. (29.5%). Recrystallized several times from water, once with the addition of charcoal, deazaguanine was obtained as a monohydrate, m.p. above 300°.

Anal. Calcd. for $C_6H_6N_4O \cdot H_2O$: C, 42.86; H, 4.80; N, 33.3. Found: C, 43.07, 43.11; H, 4.77, 4.86; N, 33.5, 33.2.

(b).—A 4.6-g. sample of 4-ethoxy-2,6-diamino-3-nitrosopyridine was reduced with hydrogen sulfide as above and the reduction product condensed with formic acid. The crude cyclization product was refluxed with 50 ml. of 48% hydrogen bromide for several hours. The crystals were filtered off after cooling, dissolved in a little water and made weakly alkaline with aqueous sodium bicarbonate. A crop of 2.3 g. (54%) of crude material was separated. Recrystallized several times from water, once with charcoal, it was obtained as shiny, colorless leaflets, m.p. above 300°.

Anal. Calcd. for $C_6H_6N_4O \cdot H_2O$: C, 42.86; H, 4.80; N, 33.3. Found: C, 42.94; H, 4.82; N, 33.2.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF CALIFORNIA]

The Willgerodt Reaction with Acylmesitylenes. The Mechanism of the Reaction

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The Willgerodt reaction with acylmesitylenes has been investigated. In all cases, keto-thioamides are formed. Such results suggest that carbonyl addition and reduction are not necessary steps for this reaction and a modification of previously postulated mechanisms is presented.

The mechanism of the Willgerodt reaction has attracted considerable attention during the past decade, and to date there still is doubt as to exactly what processes are involved. To a large degree, this has been due to the failure to isolate intermediates directly[2] or to identify them.

The technique of treating theoretically possible intermediates under conditions of the Willgerodt reaction in order to determine whether or not they are actual possible intermediates has revealed the fact that the reaction is not limited to ketones, as originally supposed, but is applicable to olefins,[2-5] acetylenes,[4,5] alcohols,[3-5] halides,[6] amines[6] and even alkyl-substituted aromatic compounds.[2]

Perhaps the most satisfactory mechanism yet suggested for the conversion of ketones into amides (or thioamides) under Willgerodt conditions is that of King and McMillan[7] which envisions reduction of the carbonyl group to a hydroxyl (or thiol) followed by elimination to an olefin. This latter functional group is regarded as proceeding along the carbon chain by a series of reversible additions and eliminations of hydrogen sulfide until the terminal carbon is reached, at which point irreversible oxidations occurs. A similar mechanism was suggested by Carmack and DeTar[4] except an acetylenic intermediate was postulated.

In any event, both mechanisms require initial attack at the carbonyl group. In an attempt to determine whether or not such a step is in reality a necessary requirement, acetylmesitylene was allowed to react under the conditions of the Willgerodt reaction. The decreased reactivity toward carbonyl addition of such a hindered ketone is well known.[8]

From the reaction of acetylmesitylene, sulfur and morpholine there was isolated an orange-yellow crystalline solid (I) in 34% yield which contained both nitrogen and sulfur. Although no recognizable product could be obtained from acid hydrolysis, prolonged saponification afforded a mixture of an acid (II) and a neutral nitrogen-containing material (III). These latter two compounds were shown to be mesitylglyoxylic acid and its morpholide, respectively, by comparison with authentic samples. When the original reaction product I was allowed to react with Raney nickel, both desulfurization and reduction of the carbonyl group occurred and an amino alcohol IV was obtained. The structure of this material was established as α-mesityl-β-(N-morpholino)-ethanol by comparison with a sample prepared by the lithium aluminum hydride reduction of ω-(N-morpholino)-acetylmesitylene, which in turn was prepared by allowing ω-bromoacetylmesitylene to react with morpholine. On the basis of the foregoing degradations, the acetylmesitylene Willgerodt product can be assigned the structure I.

The compound I may be regarded either as a nor

(1) Recipient of the U. S. Rubber Co. Fellowship in Chemistry, 1954–1955.

(2) One notable exception (M. A. Naylor and A. W. Anderson, THIS JOURNAL, **75**, 5392 (1953)) is the isolation of what appears to be diisobutyl disulfide and trisulfide from the reaction of isobutylene, sulfur and aqueous ammonia. These compounds were capable of being transformed into isobutyramide when resubjected to Willgerodt conditions.

(3) J. A. King and F. H. McMillan, THIS JOURNAL, **68**, 525 (1946).

(4) M. Carmack and D. F. DeTar, *ibid.*, **68**, 2029 (1946).

(5) D. B. Pattison and M. Carmack, *ibid.*, **68**, 2033 (1946).

(6) R. T. Gerry and E. V. Brown, *ibid.*, **75**, 749 (1953).

(7) J. A. King and F. H. McMillan, *ibid.*, **68**, 632 (1946).

(8) R. G. Kadesch, *ibid.*, **66**, 1207 (1944); L. H. Schwartzman, *ibid.*, **76**, 78 (1954); D. B. Pearson and P. Greer, *ibid.*, **77**, 1294 (1955).