[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

# A Convenient Synthesis of Formamidine and Acetamidine Acetate

BY EDWARD C. TAYLOR AND WENDELL A. EHRHART[1]

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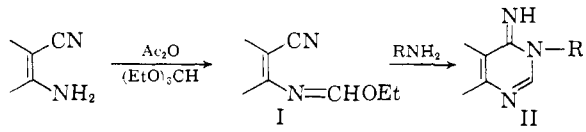
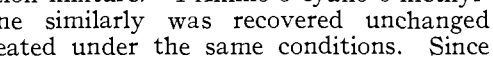
It is shown that the reaction of ethyl orthoformate, ammonia and $1^1/_3$ moles of acetic acid gives pure formamidine acetate in 84% yield. Acetamidine acetate may also be prepared in 84% yield by the reaction of ethyl orthoacetate with ammonia and ammonium acetate. In contrast to formamidine and acetamidine hydrochloride, which are highly deliquescent, the corresponding acetates are not appreciably hygroscopic. Formamidine acetate may be used directly in many condensation reactions without prior liberation of free formamidine. Thus, 4-aminopyrimido[4,5-d]-pyrimidine (IV) may be prepared by reaction of formamidine acetate with (a) 1/3 mole of malononitrile, (b) 4-amino-5-cyanopyrimidine, (c) 4-methylmercapto-5-formyl-6-aminopyrimidine, (d) 4-aminopyrimidine-5-thiocarboxamide or (e) 4-methylmercapto- or 4-mercaptopyrimido-[4,5-d]pyrimidine. Direct condensation of formamidine acetate with ethyl cyanoacetate yields ethyl aminomethylenecyanoacetate, while reaction with *o*-phenylenediamine gives benzimidazole. Reaction of formamidine acetate with acetic anhydride yields triacetylaminomethane (VI), identical with a compound previously prepared by Pinner from formamidine hydrochloride, acetic anhydride and sodium acetate but recently considered to be diacetylformamidine (V).

Previous work in this Laboratory has shown that various *o*-aminonitriles in the pyrazole[2] and imidazole[2,3] series may readily be converted to fused pyrimidine heterocycles by reaction with ethyl orthoformate and acetic anhydride to give an ethoxymethyleneamino derivative I, which upon subsequent reaction with ammonia or primary amines undergoes cyclization to II. In connection with current work on the chemistry and properties of pyrimido[4,5-d]pyrimidines, we attempted a similar series of reactions with some 4-amino-5-cyanopyrimidines, and the unexpected results obtained led to a new synthesis of formamidine which is described in the present paper.




I II

Following the procedures previously employed with other *o*-aminonitriles, a mixture of 4-amino-5-cyanopyrimidine (III), ethyl orthoformate and acetic anhydride was heated under reflux and then evaporated under reduced pressure to a viscous oil. Since this presumed ethoxymethylene derivative could not be crystallized, it was treated directly with ethanolic ammonia. To our surprise, unchanged III separated in quantitative yield from the reaction mixture. 4-Amino-5-cyano-6-methylpyrimidine similarly was recovered unchanged when treated under the same conditions. Since monosubstituted pyrimido[4,5-d]pyrimidines are known to be labile to aqueous base[4] and imino ethers such as (I) are hydrolyzed under the same conditions, it was thought that the failure of this reaction might have been due to the presence of moisture in the alcoholic ammonia. Accordingly, 4-amino-5-cyanopyrimidine (III) was heated with an equimolar mixture of acetic anhydride and ethyl orthoformate while a stream of dry ammonia was bubbled directly through the reaction mixture. Filtration yielded the desired 4-aminopyrimido-[4,5-d]pyrimidine (IV) and a large amount of white water-soluble crystals. It was evident from the bulk of this latter material that it was not a derivative of 4-amino-5-cyanopyrimidine; indeed, it could be prepared in equivalent amount by bubbling ammonia directly into a refluxing solution of ethyl orthoformate in acetic anhydride. Fractional crystallization of this material from ethanol yielded a less soluble fraction (A), m.p. 279–280° dec., and a soluble fraction (B), m.p. 162–164°, as the major constituent. Compound B, $C_3H_8N_2O_2$, was shown to be formamidine acetate by conversion to formamidine hydrochloride by means of dry hydrogen chloride, to formamidine picrate with picric acid and by its utilization in synthesis (*vide infra*). Compound A proved to be identical with a compound previously prepared by Pinner[5] by the reaction of acetic anhydride with an equimolar mixture of formamidine hydrochloride and sodium acetate. Although it was first claimed to be diacetylformamidine (V), it was later stated[6] that the analytical results were better in accord with the structure triacetylaminomethane (VI), although no evidence in support of this assignment could be advanced. An acetyl determination on compound A now definitely confirms this structure.[7] It should be pointed out that triacetylaminomethane (VI) can be prepared directly from formamidine acetate and acetic anhydride and this procedure is preferable to Pinner's original method. Compound VI has recently been prepared by a different procedure by Bredereck,




V VI

*et al.*,[8] but no physical properties for this substance were given and its relationship to Pinner's compound was not mentioned. A recent review article on amidines[9] assigns structure V to Pinner's compound, apparently unaware of his later structural revision.

The formation of formamidine acetate by the reaction of acetic anhydride, ethyl orthoformate and ammonia is of great interest, for we believe that it represents the first synthesis of an *unsubsti-*

(1) Parke, Davis and Co. Fellow in Chemistry, 1958–1959.

(2) E. C. Taylor and K. S. Hartke, THIS JOURNAL, **81**, 2459 (1959).

(3) E. C. Taylor and P. K. Loeffler, *ibid.*, **82**, 3147 (1960).

(4) R. J. Knopf, Ph.D. Thesis, Princeton University, 1957.

(5) A. Pinner, *Ber.*, **16**, 1659 (1883); **17**, 171 (1884).

(6) A. Pinner, "Die Imidoäther und ihre Derivate," Berlin, 1892.

(7) The acetyl determination was carried out by the method described by Freudenberg (*Ann.*, **433**, 230 (1923)) and indicated *four* acetyl groups. However, it has been shown (ref. 12) that triformylaminomethane gives four formyl groups by this method and it seems reasonable to assume that formic acid would also be produced from VI, thus accounting for the fourth acetyl group.

(8) H. Bredereck, R. Gompper, H. Rempfer, H. Keck and K. Klemm, *Angew. Chem.*, **70**, 269 (1958).

(9) R. L. Shriner and F. W. Newmann, *Chem. Revs.*, **35**, 351 (1944).

*tuted* amidine from ammonia and an ortho ester. The above procedure, however, is not an efficient one for the preparation of formamidine, for a part of the product reacts further with acetic anhydride to give triacetylaminomethane (VI), which also impedes purification. Furthermore, inspection of the many reactions which must be taking place in the reaction mixture leading to the formation of formamidine acetate (1–6) reveals that the acetic anhydride serves primarily as a source of acetic acid. Indeed, it was found that optimum conditions proved to be the reaction of ethyl ortho-

$$HC(OEt)_3 + Ac_2O \longrightarrow CH_3COOCH(OEt)_2 + CH_3COOEt \quad (1)$$

$$HC(OEt)_3 + NH_3 \rightleftharpoons HC(=NH)OEt + 2EtOH \quad (2)$$

$$Ac_2O + 2NH_3 \longrightarrow CH_3CONH_2 + CH_3COO^-{}^+NH_4 \quad (3)$$

$$CH_3COOCH(OEt)_2 + 2NH_3 \longrightarrow CH_3COO^-{}^+NH_4 + EtOH + HC(=NH)OEt \quad (4)$$

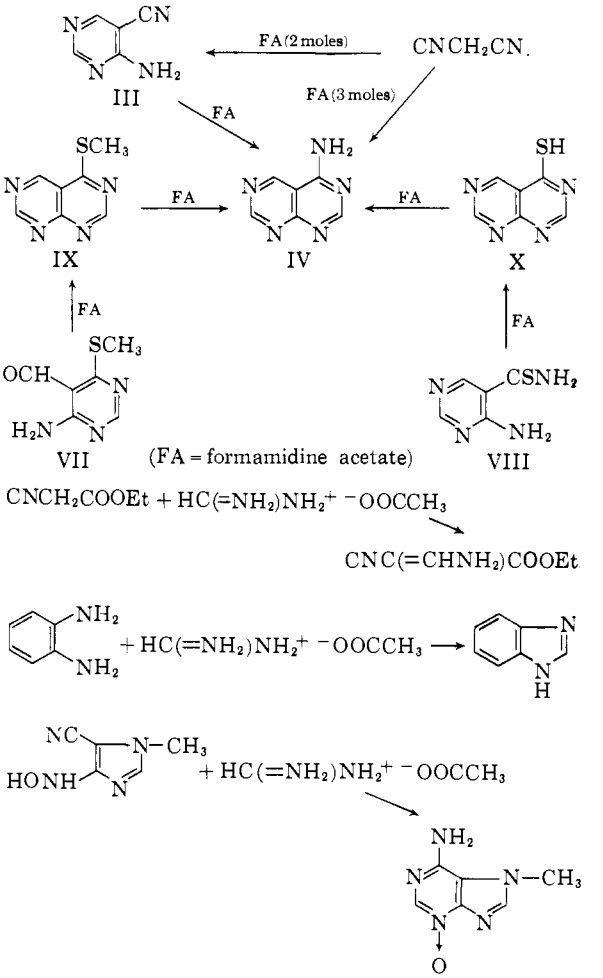
$$HC(=NH)OEt + NH_3 \rightleftharpoons HC(=NH)NH_2 + EtOH \quad (5)$$

$$HC(=NH)NH_2 + CH_3COO^-{}^+NH_4 \rightleftharpoons HC(=NH_2)NH_2{}^+{}^-OOCCH_3 + NH_3 \quad (6)$$

formate with anhydrous ammonia in the presence of $1^1/_3$ moles of acetic acid. The ethanol formed is distilled from the mixture, which is then cooled and filtered to give pure, colorless formamidine acetate in 84% yield. It could also be prepared by heating ethyl orthoformate with two molecular equivalents of ammonium acetate in the absence of additional ammonia, but the product was slightly contaminated with ammonium acetate and yields were somewhat lower.

Formamidine is usually prepared as its hydrochloride, either by the classical method of Pinner[10] from hydrogen cyanide *via* the formimino ether or by desulfurization of thiourea in the presence of ammonium chloride.[11] Formamidine hydrochloride, however, is extremely deliquescent and considerable care to exclude moisture must be exercised in both of the above procedures if satisfactory results are to be achieved. Bredereck, *et al.*,[12] have recently reported the synthesis of the hydrogen methyl sulfate salt of formamidine by reaction of formamide with dimethyl sulfate. Although this method appears to be both convenient and economical, no reactions of the salt have been reported and it would be anticipated that, as with the hydrochloride, the free base must be liberated from the salt when used in condensation reactions. Furthermore, complications in synthesis might be anticipated from the fact that methyl hydrogen sulfate is an effective methylating agent.[13]

In view of the above results, it would appear that the formation of 4-aminopyrimido[4,5-d]-pyrimidine (IV) by the reaction of 4-amino-5-cyanopyrimidine with ammonia, ethyl orthoformate and acetic anhydride may have been the result of a direct condensation of formamidine acetate formed *in situ* with the *o*-aminonitrile. Indeed, it was found that condensation of these two reagents in 2-ethoxyethanol yielded 4-aminopyrimido-(4,5-d)pyrimidine (IV) in 57% yield. Furthermore, since 4-amino-5-cyanopyrimidine itself is prepared by the reaction of 1 mole of malononitrile with 2 moles of formamidine,[14] a one-step synthesis of IV was achieved directly from malononitrile and 3 moles of formamidine acetate. Compound IV could also be formed by the reaction of formamidine acetate either with 4-methylmercapto-5-formyl-6-aminopyrimidine (VII) or with 4-aminopyrimidine-5-thiocarboxamide(VIII). Both syntheses presumably proceed *via* the intermediate mercapto derivatives IX and X, since X was isolated in a reaction between formamidine acetate and VIII when the reaction temperature was lowered by using ethanol rather than 2-ethoxyethanol as solvent. Furthermore, both IX and X could be converted to IV by treatment with formamidine acetate under the reaction conditions.




It was found, as expected, that formamidine acetate could replace formamidine hydrochloride in syntheses previously reported using the latter. In addition, formamidine acetate, as the salt of a strong base and a weak acid, could often be used directly without prior liberation of free formamidine. In addition to the examples given above,

(10) A. Pinner, *Ber.*, **16**, 352, 1643 (1883).

(11) D. J. Brown, *J. Appl. Chem.*, **2**, 202 (1952).

(12) H. Bredereck, R. Gompper, H. Rempfer, K. Klemm and H. Keck, *Ber.*, **92**, 329 (1959).

(13) "Chemistry of Carbon Compounds," ed. by E. H. Rodd, Elsevier Publishing Co., New York, N. Y., 1951, Vol. IA, p. 339.

(14) J. Baddiley, B. Lythgoe and A. R. Todd, *J. Chem. Soc.*, 386 (1943).

the direct condensation of formamidine acetate with ethyl cyanoacetate in ethanol solution gave ethyl aminomethylenecyanoacetate in 63% yield, and condensation with *o*-phenylenediamine gave benzimidazole in 76% yield. The formation in high yield of 7-methyladenine-3-N-oxide by the condensation of formamidine acetate with 1-methyl-4-hydroxylamino-5-cyanoimidazole has already been reported.[15]

Evidence that the synthesis of other unsubstituted amidines could be carried out under similar conditions with other ortho esters was obtained by the reaction of ethyl orthoacetate with ammonium acetate and ammonia to give acetamidine acetate in 84% yield. Acetic acid could not be used to advantage in place of ammonium acetate in this instance because of rapid decomposition of ethyl orthoacetate. Although this synthesis of acetamidine is more expensive than the Pinner procedure from acetonitrile, it requires only a few hours rather than several days, no precautions need be taken for the exclusion of moisture, and the slightly hydroscopic acetate rather than the highly deliquescent hydrochloride is formed.

We have also found that aliphatic primary amines react with ethyl orthoformate and other ortho esters in the presence of the acetate salt of the amine to give *sym*-N,N′-dialkylamidine acetates in good yield. This work will be discussed in detail in a subsequent paper.

## Experimental[16]

**Formamidine Acetate. Method A.**—A mixture of 30.0 g. of ethyl orthoformate and 16.4 g. of glacial acetic acid in a three-necked flask equipped with a condenser and gas inlet tube was heated to boiling by immersion in an oil-bath held at 130–135° and a rapid stream of dry ammonia passed through. Formamidine acetate started to separate from the boiling mixture after 30 minutes; after 45 minutes the ammonia was turned off, the condenser was set for distillation, and ethanol was slowly distilled off at an oil-bath temperature of 155–160° until the temperature of the condensing vapor dropped below 75°. This required about 30 minutes and 27 ml. of ethanol was collected. The mixture was then cooled to 20° and filtered and the collected white crystals washed with ethanol followed by ether; yield 16.05 g., m.p. 162–164°. An additional 1.65 g. was recovered from the filtrate to give a total yield of 17.7 g. (84.2%). The product was recrystallized from ethanol for analysis without change in the melting point.

*Anal.* Calcd. for $C_3H_8N_2O_2$: C, 34.6; H, 7.75; N, 26.9. Found: C, 34.8; H, 7.7; N, 27.1.

Treatment of an ethanolic solution of formamidine acetate with dry hydrogen chloride, followed by addition of ether, resulted in the separation of formamidine hydrochloride, m.p. 80°, identical with an authentic sample. Addition of picric acid to an ethanol solution of formamidine acetate yielded the picrate, m.p. 251–253°, identical with an authentic sample. The reported melting point for formamidine picrate is 248°.[17]

**Method B.**—A mixture of 30.0 g. of ethyl orthoformate and 31.2 g. of finely ground ammonium acetate was heated under reflux in an oil-bath at 130–135° for 2.75 hours and then evaporated to near dryness under reduced pressure. Addition of ethanol to the residue and filtration yielded 12.5 g. of white crystals, m.p. 162–164°. An additional 2.8 g. of product was obtained from the filtrate for a total yield of 15.3 g. (73%).

**Method C.**—Thirty milliliters of an equimolar mixture of ethyl orthoformate and acetic anhydride was heated under reflux by means of an oil-bath at 150° while a rapid stream of dry ammonia was bubbled through. After 40 minutes the mixture was cooled to room temperature, filtered, and the collected solid washed with cold ethanol and dried; yield 7.5 g., m.p. (incomplete) 162.5–164°. Extraction of this material with hot ethanol yielded 1.0 g. of an insoluble colorless solid, m.p. 279–280° dec., which was identical with an authentic sample of triacetylaminomethane prepared by the method of Pinner (see also below). Concentration *in vacuo* of the ethanol extract above and chilling yielded 6.2 g. of formamidine acetate, m.p. 162–164°.

**Triacetylaminomethane** was prepared by the method of Pinner and also as described below. A mixture of 20 g. of formamidine acetate and 60 ml. of acetic anhydride was heated under reflux for 80 minutes. It was then allowed to stand at room temperature for 2 hours, filtered, and the collected solid washed with ethanol; yield 9.8 g., m.p. 276–278° dec. Recrystallization from water raised the decomposition point to 279–280°.

*Anal.* Calcd. for $C_7H_{13}N_3O_3$: C, 44.9; H, 7.0; N, 22.45; acetyl, 92.0. Found: C, 44.9; H, 6.9; N, 22.1; acetyl, 92.0.

**4-Aminopyrimido(4,5-d)pyrimidine. Method A.**—A mixture of 0.50 g. of 4-amino-5-cyanopyrimidine and 5 ml. of an equimolar mixture of ethyl orthoformate and acetic anhydride was heated under reflux for 70 minutes and then a stream of dry ammonia was bubbled through for 20 minutes. The mixture was cooled and filtered and the collected solid washed thoroughly with water to give 0.35 g. (57%) of a light tan solid, m.p. >340° dec. This material was identical in every respect with an authentic sample of 4-aminopyrimido[4,5-d]pyrimidine.[18]

**Method B.**—A mixture of 0.50 g. of 4-amino-5-cyanopyrimidine, 0.87 g. of formamidine acetate and 10 ml. of 2-ethoxyethanol was heated under reflux for 30 minutes, cooled, filtered, and the collected solid washed with water to give 0.35 g. (57%) of a light tan solid, m.p. >340° dec. identical, with the product obtained by method A.

**Method C.**—A mixture of 1.0 g. of malononitrile, 6.0 g. of formamidine acetate and 15 ml. of 2-ethoxyethanol was heated under reflux in an oil-bath for 25 minutes. It was then cooled, filtered, and the collected solid washed with ethanol. Dissolution in dilute hydrochloric acid followed by reprecipitation with ammonium hydroxide yielded 0.62 g. of a light brown solid, m.p. >320° dec. Sublimation of this material at 240° (0.1 mm.) yielded 0.52 g. (23%) of a light tan solid which was identical in every respect with the products prepared by methods A and B above.

**Method D.**—A mixture of 0.25 g. of 4-methylmercapto-5-formyl-6-aminopyrimidine, 0.50 g. of formamidine acetate and 5 ml. of 2-ethoxyethanol was heated under reflux for 20 minutes and then cooled and filtered. The collected solid was washed thoroughly with water followed by ethanol to give 0.11 g. (50.5%) of a light tan solid, m.p. >340°, dec. identical with the products obtained above.

**Method E.**—Treatment of a mixture of 4-aminopyrimidine-5-thiocarboxamide, formamidine acetate and 2-ethoxyethanol under the above conditions gave 4-aminopyrimido-(4,5-d)pyrimidine in 44% yield.

**Method F.**—Treatment of a mixture of 4-methylmercaptopyrimido(4,5-d)pyrimidine,[4] formamidine acetate and 2-ethoxyethanol under the above conditions gave 4-aminopyrimido(4,5-d)pyrimidine in 77% yield.

**Ethyl Aminomethylenecyanoacetate.**—A mixture of 3.0 g. of ethyl cyanoacetate, 5.5 g. of formamidine acetate and 60 ml. of ethanol was heated under reflux for 15 hours, evaporated to near dryness, and the residue triturated with water and filtered; yield 2.35 g. (63%), m.p. 131–133°. Recrystallization from toluene–tetrahydrofuran yielded colorless crystals, m.p. 140.5–142.5°. This material is reported to melt at 140°.[19]

*Anal.* Calcd. for $C_6H_8N_2O_2$: C, 51.4; H, 5.75; N, 19.9. Found: C, 51.6; H, 5.95; N, 20.2.

**Benzimidazole.**—A mixture of 1.0 g. of *o*-phenylenediamine, 2.0 g. of formamidine acetate and 15 ml. of 2-ethoxyethanol was heated under reflux for 1.5 hours and then evaporated to a small volume *in vacuo*. Water was added to the

(15) E. C. Taylor and P. K. Loeffler, *J. Org. Chem.*, **25**, in press (1960).

(16) We are indebted for the microanalyses to Dr. Joseph F. Alicino, Metuchen, N. J. All melting points are uncorrected.

(17) W. Dieckmann, *Ber.*, **25**, 546 (1892).

(18) E. C. Taylor, R. J. Knopf, M. L. Hoeffle, R. F. Meyer and A. Holmes, THIS JOURNAL, **82**, in press (1960).

(19) G. W. Kenner, B. Lythgoe, A. R. Todd and A. Topham, *J. Chem. Soc.*, 388 (1943).

residue and the resulting slurry was again evaporated to a small volume. Addition of water and filtration then gave 0.53 g. of a gray solid, m.p. 170–171°. An additional 0.30 g. of product was recovered from the filtrate to give a total yield of 0.83 g. (76%). The product was recrystallized from water without change in the melting point. Benzimidazole is reported to melt at 170°.[20]

**Acetamidine Acetate.**—A mixture of 32.4 g. of ethyl orthoacetate and 15.4 g. of ammonium acetate was heated under reflux for 45 minutes, while a stream of dry ammonia was bubbled through. The reaction mixture was then distilled at an oil bath temperature of 155-160° until the temperature of the condensing vapors fell below 75°. This required about 25 minutes and yielded 18.5 g. of distillate. The residue was cooled to room temperature and filtered and the collected solid washed with a small amount of ethanol and dried; yield 16.5 g., m.p. 189–191°. An additional 3.25 g. of product was obtained from the filtrate for a total yield of 19.75 g. (84%). Acetamidine acetate is reported to melt at 185–187°.[21] Furthermore, this material was identical with an authentic sample of acetamidine acetate prepared by treatment of acetamidine hydrochloride with sodium acetate.

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

(21) H. G. Rule, *ibid.*, **113**, 3 (1918).

PRINCETON, N. J.

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

# Pyridine-1-oxides. V. 4-Substituted Nicotinic Acid-1-oxides[1]

BY EDWARD C. TAYLOR AND JOHN S. DRISCOLL[2]

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4-Nitronicotinic acid-1-oxide (I), prepared from 3-picoline by conversion to the 1-oxide, nitration and subsequent oxidation, was utilized as an intermediate for the synthesis of 4-chloronicotinic acid-1-oxide (II), 4-hydroxynicotinic acid-1-oxide (III), 4-benzyloxynicotinic acid-1-oxide (IV), 4-hydroxynicotinic acid (V), 4-mercaptonicotinic acid-1-oxide (VI), 4-aminonicotinic acid-1-oxide (VII), 4-aminonicotinic acid (VIII), 4-hydrazinonicotinic acid-1-oxide (IX) and 4-hydroxylaminonicotinic acid-1-oxide (X).

The utility of the N-oxide grouping as an intermediate in heterocyclic synthesis has received wide recognition,[3] and it is to be anticipated that many new synthetic applications will be found. The present paper extends our earlier work[1,4–6] dealing with the utilization of the N-oxide grouping in pyridine chemistry and is concerned with the synthesis of a number of 4-substituted nicotinic acid derivatives starting with the readily accessible 4-nitronicotinic acid-1-oxide (I).[5]

It was reported earlier[5] that the reaction of 4-nitronicotinic acid-1-oxide(I) with acetyl chloride yielded 4-chloronicotinic acid-1-oxide (II). We have now found that this reaction, when run at 100°, is accompanied by the formation of significant amounts (15–20%) of 4-hydroxynicotinic acid-1-oxide (III), whereas less than 1% of the latter contaminant is formed at 70°. An improved preparation of pure II is reported in the Experimental. Alkaline hydrolysis of II gave 4-hydroxynicotinic acid-1-oxide (III), from which 4-hydroxynicotinic acid (V) was prepared by catalytic reduction.

Alternate routes to III and V were found in the acid hydrolysis and catalytic reduction, respectively, of 4-benzyloxynicotinic acid-1-oxide (IV), which was prepared by the action of sodium benzylate on I.

The lability of the chloro substituent in 4-chloronicotinic acid-1-oxide(II) was further demonstrated by treatment with potassium hydrosulfide to give 4-mercaptonicotinic acid-1-oxide (VI) and by treatment with ammonium hydroxide to give 4-aminonicotinic acid-1-oxide (VII). Catalytic reduction of the latter compound yielded 4-aminonicotinic acid (VIII), identical with the product of reduction of 4-nitronicotinic acid-1-oxide (I). Treatment of VIII with nitrous acid provided a third synthetic route to 4-hydroxynicotinic acid (V).

Since hydrazine hydrate in the presence of a small amount of Raney nickel has been reported to be effective for the reduction of aromatic nitro groups[7] but to be ineffective for the reduction of the N-oxide grouping in 4-picoline-1-oxide,[8] it was thought that these conditions might make possible a direct conversion of I to 4-aminonicotinic acid-1-oxide (VII). However, treatment of I with hydrazine hydrate in the presence of Raney nickel yielded predominately 4-hydrazinonicotinic acid-1-oxide (IX) along with a small amount of the expected 4-aminonicotinic acid-1-oxide (VII).

A possible alternative procedure for carrying out the direct conversion of I to VII appeared to be treatment of I with boiling ammonium sulfide solution, since it has been reported[9,10] that this reagent is effective for the conversion of 4-nitropyridine-1-oxide and its methyl homologs to the corresponding 4-aminopyridine-1-oxides. The product of the reaction of I with this reagent, however, proved to be 4-hydroxylaminonicotinic acid-1-oxide (X). Catalytic reduction of X yielded 4-aminonicotinic acid (VIII), although in one instance 4-aminonicotinic acid-1-oxide (VII) was obtained, apparently as a result of poisoning of the catalyst by residual sulfur.

## Experimental[11]

**4-Chloronicotinic Acid-1-oxide (II).**—A suspension of 4.0 g. of 4-nitronicotinic acid-1-oxide in 20 ml. of acetyl chloride

(1) For the previous paper in this series, see E. C. Taylor and N. E. Boyer, *J. Org. Chem.*, **24**, 275 (1959).

(2) Parke, Davis and Co. Fellow, 1957–1958.

(3) For a recent review of this field, see A. R. Katritzky, *Quart. Revs.*, **10**, 395 (1956).

(4) E. C. Taylor, A. J. Crovetti and N. E. Boyer, THIS JOURNAL, **79**, 3549 (1957).

(5) E. C. Taylor and A. J. Crovetti, *ibid.*, **78**, 214 (1956).

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

(7) D. Balcom and A. Furst, THIS JOURNAL, **75**, 4334 (1953).

(8) R. L. Bixler and C. Niemann, *J. Org. Chem.*, **23**, 575 (1958).

(9) R. W. Faessinger and E. V. Brown, Abstracts of Papers, 121st A.C.S. Meeting 1952, p. 24-K.

(10) E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

(11) All melting points are uncorrected.