tions of liquid ammonia, and the combined filtrate was evaporated at room temperature under a stream of nitrogen. The residue was dried to constant weight and analyzed for its ammonia content.

In a typical experiment, 11.7 g. of dried Amberlite IRC-50 (K^+), with an equivalent capacity of 6 meq./g., was heated at 70° for 5 hr. with a solution of 4.3 g. of ammonium chloride in 240 ml. of liquid ammonia. The cooled mixture was filtered, and the precipitate was washed with 200 ml. of liquid ammonia. Evaporation of the filtrate left 1.4 g. of crystalline residue (dried to constant weight over phosphorus pentoxide). The residue analyzed for an ammonia content of 17.3%, corresponding to 0.76 g. (18% recovery) of ammonium chloride.

(B) Ammonolysis Reactions.—In a typical experiment, the 750-ml. reactor was charged with 44 g. (0.3 mole) of α-chloro-ε-caprolactam, 25 g. (0.18 mole) of potassium carbonate and 350 ml. (14.8 moles) of liquid ammonia. The mixture was heated with agitation at 85° for 24 hr. The reactor was cooled in a Dry Ice–methanol-bath, and the liquid ammonia was drawn off under suction through a sintered glass filter stick into a cooled trap. The insoluble residue was washed with two 50-ml. portions of liquid ammonia. The combined filtrates were evaporated, and the dried residue was dissolved in 65 ml. of absolute ethanol and filtered. The ethanol solution was diluted with additional solvent, concentrated under reduced pressure, and rediluted to a volume of 140 ml. Acidification by addition of ethanol saturated with hydrogen chloride resulted in precipitation of crystalline product which was collected and washed with acetone. The ethanol filtrate was evaporated, and the residue was extracted with acetone. The combined acetone-insoluble materials were dried to yield 21.8 g. (67.4% yield) of α-amino-ε-caprolactam hydrochloride, m.p. 289–293°. The infrared spectrum corresponded to that of an authentic sample[22] and showed no pipecolamide or other impurity to be present. This material burned to leave no ash, and analyzed correctly for the calculated chloride ion content of 21.5%.

The combined acetone extracts were evaporated under vacuum, and the dried residue was recrystallized from ligroin to yield 15 g. (34% recovery) of α-chloro-ε-caprolactam, m.p. 89–91°. Evaporation of the ligroin filtrate yielded 5.1 g. of sirupy residue. The infrared spectrum of this material indicated it to contain more than 50% unreacted α-chloro-ε-caprolactam.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF CHAS. PFIZER AND CO., INC.]

The Synthesis of 6-Chloropyridoxine. The Hydride Reduction of Pyridinedicarboxylic Acids

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6-Chloropyridoxine was synthesized *via* a six-step sequence from methyl acetopyruvate and cyanacetamide. The key step in this sequence was a novel reaction involving catalytic hydrogenation of a nitro group with simultaneous hydrolysis of an ester group and a nitrile group, but without simultaneous loss of a labile chloro group by hydrolysis or hydrogenolysis. Also of importance in the synthesis of 6-chloropyridoxine (and in related syntheses of pyridoxine studied coincidentally) was the hydride reduction of various substituted pyridinedicarboxylic acids to bis-(hydroxymethyl)-pyridines without prior esterification. Sodium borohydride—aluminum chloride in diethylene glycol dimethyl ether was found to be a system well suited for this purpose.

In connection with a broader study on the synthesis of potential antimetabolites, we have found occasion to synthesize a compound closely related in structure to vitamin B_6 (pyridoxine, XII). This compound is 6-chloropyridoxine (VIII). Although 6-chloropyridoxine has not shown any unusual activity in biological systems which would characterize it as an antimetabolite, the synthetic route by which it was obtained is of considerable interest. Thus the synthesis of 6-chloropyridoxine (and related syntheses of pyridoxine studied coincidentally) involve a surprising catalytic reduction–hydrolysis reaction. The syntheses also employ the hydride reduction of various pyridinedicarboxylic acids to bis-(hydroxymethyl)-pyridines without prior formation of esters. All of the intermediates and steps involved in these syntheses are outlined in the accompanying flow sheet.

The Synthesis of 6-Chloropyridoxine.—The first three steps in the synthesis of 6-chloropyridoxine—condensation of cyanacetamide with acetopyruvate ester, nitration of the pyridine so formed (I → II) and replacement of the hydroxyl by chlorine (II→ III)—were closely analogous to steps which have been carried out with the corresponding ethyl esters on at least three occasions in the past.[1-3] Only the first step of the sequence—condensation—was modified appreciably from the original processes[1] employed with the ethyl esters. Thus the sodium salt of methyl acetopyruvate was condensed directly with cyanacetamide without prior conversion of the former to free methyl acetopyruvate and without use of diethylamine as a catalyst.

With 2-methyl-3-nitro-4-carbomethoxy-5-cyano-6-chloropyridine (III) in hand, several synthetic routes to 6-chloropyridoxine (VIII) appear feasible. To summarize we might consider some possible transformations at individual positions in the pyridine ring

3-position	$-NO_2 \longrightarrow -NH_2 \longrightarrow -OH$
4-position[4]	$-COOCH_3 \longrightarrow -CH_2OH$ or
	$-COOCH_3 \longrightarrow -COOH \longrightarrow -CH_2OH$
5-position[4]	$-CN \longrightarrow -CH_2NH_2 \longrightarrow -CH_2OH$ or
	$-CN \longrightarrow -COOH \longrightarrow -CH_2OH$

Similar transformations have been carried out in the past,[1,2,5,6] but only with prior or simultaneous

(1) A. Itiba and S. Emoto, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **38**, 347 (1941).

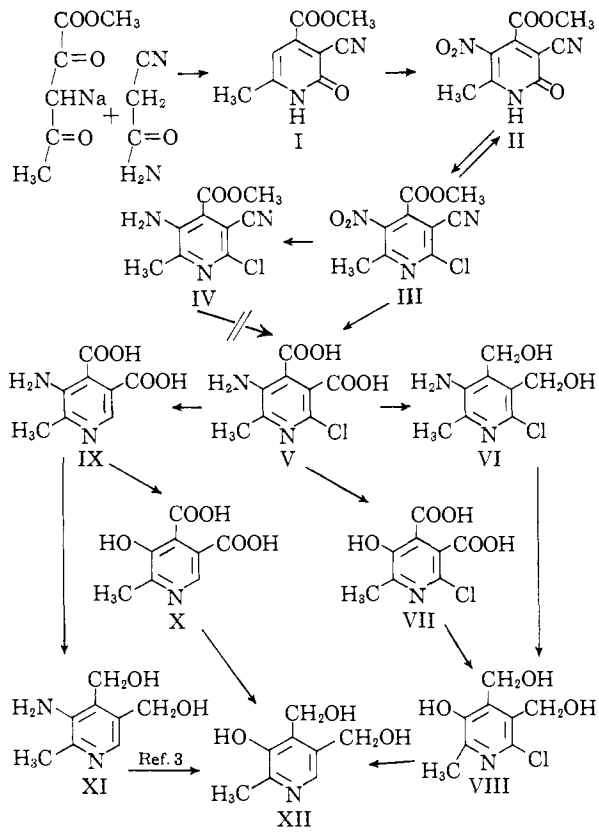
(2) L. Velluz and G. Amiard, *Bull. soc. chim., France*, 136 (1947).

(3) R. G. Jones and E. C. Kornfeld, THIS JOURNAL, **73**, 107 (1951).

(4) Intermediates in which groups in the 4-position and 5-position are chemically bonded (*e.g.*, lactones, lactams, anhydrides, etc.) were not overlooked as possibilities. In any event, the basic transformations would remain essentially as outlined above.

(5) S. A. Harris and K. Folkers, THIS JOURNAL, **61**, 1245 (1939).

(6) J. H. Mowat, F. J. Pilgrim and G. H. Carlson, *ibid.*, **65**, 954 (1943).



removal of the chlorine, a group subject to ready hydrogenolysis or nucleophilic displacement.

Our first approach to the conversion of III to VIII involved, as a first step, the iron in acetic acid reduction of the nitro group to an amino group. The product of this reduction, 2-methyl-3-amino-4-carbomethoxy-5-cyano-6-chloropyridine (IV), is an interesting compound in its own right. Although it contains two "basic" nitrogen atoms, it is almost devoid of any solubility in even hot concentrated aqueous hydrochloric acid. Furthermore, even in methanol solution there is no tendency for this compound to form a hydrochloride as evidenced by the identical ultraviolet spectra obtained in the presence of either excess hydrochloric acid or excess sodium hydroxide. Finally, this unusual diamine was not titratable with perchloric acid in acetic acid. It is concluded that the several electron withdrawing groups are particularly efficient in this molecule.[7] As might be anticipated from these data, we were unable to hydrolyze IV to the desired amino chlorodiacid V. Even after three hours of reflux in concentrated hydrochloric acid, two-thirds of the amine IV remained out of solution and unchanged. We were unable to separate the material which had dissolved and reacted (aptly described as an "untidy mixture") into any pure components.

A second approach to the synthesis of 6-chloropyridoxine from the nitrochlorocyanoester III was no more fruitful than the first one. It was hoped to hydrolyze the latter compound to the corresponding nitrochlorodiacid with subsequent reduction of the nitro group to form V. The only compound we were able to isolate from III under hydrolytic conditions was its synthetic precursor II.

A third and rather different route to 6-chloropyridoxine from our "starting material" III was then considered: the possible simultaneous catalytic reduction of the nitro and nitrile groups, while leaving the chloro group intact. In one of the attempts to carry out such a reduction—a run in *ca.* 20% hydrochloric acid with platinum oxide as catalyst—three moles of hydrogen was taken up rapidly and cleanly, at which time uptake essentially stopped. Since this is the theoretical amount of hydrogen required to reduce the nitro group, the expected product, especially in view of the hydrolytic studies above, would be the aminochlorocyanoester IV or possibly the corresponding pyridone. To our surprise a completely unexpected compound was formed in very high yield. This product was shown to be 2-methyl-3-amino-6-chloropyridine-4,5-dicarboxylic acid (V), the very intermediate we had failed to prepare *via* separate reduction and hydrolysis steps. It was characterized by analysis, titration studies, formation of a cyclic anhydride on sublimation and finally by catalytic hydrogenolysis to known 2-methyl-3-amino-pyridine-4,5-dicarboxylic acid.[1] The same product was formed in somewhat lower yield when palladium-on-carbon was substituted for platinum oxide or when the known ethyl ester[1] was substituted for the methyl ester. The mechanism of this hydrolysis remains obscure, although it does not seem likely that the catalyst plays a direct role.

With the key intermediate V in hand, the synthesis of 6-chloropyridoxine was a relatively straightforward matter—either diazotization of V to 2-methyl-3-hydroxy-6-chloropyridine-4,5-dicarboxylic acid (VII)[8] followed by reduction with sodium borohydride–aluminum chloride in diglyme, or alternatively hydride reduction (V → VI)—with diazotization (VI → VIII) as a final step. 6-Chloropyridoxine was characterized by analysis, similarity of its ultraviolet spectrum to those of pyridoxine and its ready catalytic hydrogenolysis to pyridoxine. It showed no pyridoxine activity in a pyridoxine bioassay[9] and no properties which would characterize this material as a pyridoxine antagonist in various biological tests.[10]

Returning to the key intermediate V used for the synthesis of chloropyridoxine, it was of some interest to consider the six interrelated routes to pyridoxine XII conceived by the permutations of

(7) Analogous results were obtained with the corresponding ethyl ester, 2-methyl-3-amino-4-carbethoxy-5-cyano-6-chloropyridine, prepared by the method of Itiba and Emoto (ref. 1). With the cyano and ester groups hydrolyzed (compound V), this behavior was no longer as pronounced. However, the hydrate hydrochloride of V was readily hydrolyzed by warming in water and V itself remained nontitratable with perchloric acid in acetic acid.

(8) This was the only pyridinedicarboxylic acid of the four studied here (V, VII, IX, XI) that showed an appreciable solubility in ether, a property utilized in its isolation. It is likely that this diacid does not exist as a zwitterion, whereas the other three, each containing at least one relatively more basic nitrogen atom, probably do exist as zwitterions.

(9) We are indebted to Dr. D. B. Seeley and his associates for a pyridoxine bioassay employing a strain of *Streptococcus faecalis* (A.T.C.C. 8043).

(10) We are indebted to Dr. B. A. Sobin and his associates for this testing.

the three necessary chemical steps—diazotization, hydrogenolysis and hydride reduction. These six routes involve a total of six intermediates (VI to XI) and all six were prepared in the course of this work. The three intermediates which lack chlorine are known from previous work[1,3] while those containing chlorine are new pyridoxine intermediates. The catalytic hydrogenolysis and diazotization reactions are not worthy of special comment, except to say that the diazotizations of the aminodiacids (V and IX) were best carried out by adding a little more than the theoretical amount of sodium nitrite in aqueous solution to a heated aqueous slurry of the aminodiacid *without the agency of an added mineral acid*. All of the hydride reductions carried out in this work employed sodium borohydride–aluminum chloride in diethylene glycol dimethyl ether. These are discussed fully in the section below.

The Hydride Reduction of Pyridinedicarboxylic Acids.—Although the lithium aluminum hydride reduction of pyridinedicarboxylic acid esters has been studied in detail,[3,11] we have found no reports in the literature of the hydride reduction of the corresponding pyridinedicarboxylic acids. Since these esters are often difficult to prepare in high yields,[3,12] a method for direct reduction of pyridinediacids seemed desirable. The use of lithium aluminum hydride for the reduction of diacids in general has been reviewed recently.[13] The procedure employed for diacids with low solubility in the ether used as solvent is generally a very prolonged one, with a Soxhlet extractor employed for the addition of the diacid.[14] A second complication in the reduction of polyfunctional organic molecules, especially phenolic acids, is the possibility that highly insoluble incompletely reduced complexes will precipitate in the reaction mixture.[15] No exhaustive work on the lithium aluminum hydride reduction of pyridinecarboxylic acids was carried out in the course of this study. However, preliminary work on the lithium aluminum hydride reduction of 2-methyl-3-hydroxypyridine-4,5-dicarboxylic acid (X) in either diethyl ether or tetrahydrofuran suggested that both complicating factors were probably operating.

More recently, Brown and Subba Rao have reported an entirely new hydride reducing system for carboxylic acids.[16] These workers reduced a wide variety of monocarboxylic acids with sodium borohydride–aluminum chloride in diethylene glycol dimethyl ether (diglyme). The only two dicarboxylic acids (succinic and adipic) which they surveyed were only partially reduced in this new hydride system. Pyridine itself was indicated to be partially reduced, probably to a dihydro compound. In view of these prior results, we were gratified to find the sodium borohydride–aluminum chloride system applicable to the reduction of pyridinedicarboxylic acids to bis-(hydroxymethyl)-pyridines.

Four pyridinedicarboxylic acids (V, VII, IX and X) were reduced satisfactorily with sodium borohydride–aluminum chloride in diglyme in the course of this study. Because of relative ease of isolation and because a bioassay method was available[9] for preliminary determination of the conversion to pyridoxine, 2-methyl-3-hydroxypyridine-4,5-dicarboxylic acid was chosen for a detailed study of the conditions for this reaction. Twice the theoretical quantity of sodium borohydride was required for high conversion to pyridoxine. The quantity of aluminum chloride required was not nearly so critical. The results of experiments in which the quantities of sodium borohydride and aluminum chloride were varied are shown in Table I. The yield and conversion also were dependent on the order of addition of reagents. Thus, we employed a procedure in which an aluminum chloride solution was the final reagent added. Use of the previously described "normal" addition procedure[16] (organic compound added last) gave 10–15% lower yields and conversions, while use of the "reverse" addition procedure[16] (sodium borohydride added last) gave 25–30% lower yields and conversions.

TABLE I

SODIUM BOROHYDRIDE AND ALUMINUM CHLORIDE REQUIREMENTS FOR THE REDUCTION OF 2-METHYL-3-HYDROXYPYRIDINE-4,5-DICARBOXYLIC ACID

Moles of $NaBH_4$ per moles of hydroxydiacid	Moles of $AlCl_3$ per mole of $NaBH_4$	Isolated yield, %	Approx. conversion, %[a]
1.75[b]	0.33	0	low
1.97	.33	12	52
2.61	.33	58	72
3.50	.33	73	81
4.38	.33	74	83
7.00	.33	68	77
2.61	.67	50	71
3.50	.18	64	78
3.50	0	0	0

[a] Estimated from ultraviolet spectra of reaction mixtures after removal of boron and from bioassay data. [b] Theoretical quantity for reaction with three active hydrogens and complete reduction to a dialcohol.

The best procedure as developed for the sodium borohydride–aluminum chloride reduction of 2-methyl-3-hydroxypyridine-4,5-dicarboxylic acid was applied successfully to the reduction of 2-methyl-3-aminopyridine-4,5-dicarboxylic acid (IX) to the already known[3] 2-methyl-3-amino-4,5-bis-(hydroxymethyl)-pyridine (XI), 2-methyl-3-amino-

(11) A. Cohen, J. W. Haworth and E. G. Hughes, *J. Chem. Soc.*, 4374 (1952).

(12) We would like to mention here our experiences with the synthesis of dimethyl 2-methyl-3-hydroxypyridine-4,5-dicarboxylate *via* a procedure similar to that used by Jones and Kornfeld (ref. 3). The highest yield of diester we were able to obtain was 8%. Attempts to recover the unchanged diacid by the method of Jones and Kornfeld gave instead a very high yield of one of the monomethyl esters. Although this material has very similar melting point, ultraviolet spectra in acid and solubility characteristics to the starting diacid it has an ultraviolet spectra in base and an infrared spectra distinctly different from that of the parent compound. The half-ester was characterized by elemental analysis and titration studies and by its hydride reduction to pyridoxine. No attempt was made to determine which carboxylic acid group was esterified.

(13) V. M. Micovic and M. L. Mihailovic, "Lithium Aluminum Hydride in Organic Chemistry," Monographs of the Serbian Academy of Sciences, Vol. CCXXXVII, 1955.

(14) See for example, R. F. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 2548 (1947).

(15) See for examples, E. G. Peppiatt and R. J. Wicker, *Chemistry & Industry*, 932 (1954).

(16) H. C. Brown and B. C. Subba Rao, THIS JOURNAL, **77**, 3164 (1955); **78**, 2582 (1956).

6-chloropyridine-4,5-dicarboxylic acid (V) to 2-methyl-3-amino-4,5-bis-(hydroxymethyl)-6-chloropyridine (VI), 2-methyl-3-hydroxy-6-chloropyridine-4,5-dicarboxylic acid (VII) to 6-chloro-pyridoxine (VIII), and the monomethyl ester of 2-methyl-3-hydroxypyridine-4,5-dicarboxylic acid[12] to pyridoxine (XII). There was no tendency for loss of chlorine *via* reduction as evidenced by total lack of any pyridoxine activity[9] among the products of the reduction of the hydroxychlorodiacid VII. There was no evidence that the presence of the chlorine atom further increased the amount of hydride required for complete reduction as might be anticipated from previous studies[17] in which, in the absence of a large excess of reducing agent, the lithium aluminum hydride reduction of 3-chlorophthalic acid gave 7-chlorophthalide as product.[18]

Experimental

All melting points are uncorrected. All ultraviolet spectra were *ca.* 0.001% in methanol solution, either 0.01 *N* in sodium hydroxide (base) or 0.01 *N* in hydrochloric acid (acid).

The sodium salt of methyl acetopyruvate was prepared according to the procedure of Royals[19] except that the sodium salt was isolated by filtration directly from the reaction mixture (*i.e.*, without acidification) and used without further purification in the subsequent step. The sodium salt had an ultraviolet spectrum in either acidic or basic methanol identical with that of methyl acetopyruvate isolated and purified in the usual manner,[19] λ_{max} (acid) 285 mμ, log ϵ 3.78, and λ_{max} (base) 317 mμ, log ϵ 4.15.

3-Cyano-4-carbomethoxy-6-methyl-2-pyridone (I).—To a 1-liter flask equipped with a stirrer and reflux condenser there was added in the following order: 450 ml. of methanol (analytical reagent grade), 50 g. (0.30 mole) of the sodium salt of methyl acetopyruvate and 27.8 g. (0.33 mole) of cyanacetamide. The stirred mixture was refluxed for 2 hours. After cooling to room temperature, 60 ml. of concentrated hydrochloric acid made up to 450 ml. with ice and water was added slowly with stirring. Following a stirring period of 30 minutes in an ice-bath the product was recovered by filtration with two 50-ml. washes with ice-water. Yield of high purity dried 3-cyano-4-carbomethoxy-6-methyl-2-pyridone (I) was 42 g. (73%), m.p. 229–233° dec.

An analytical sample was prepared by recrystallization from dioxane and then from methanol. The ultraviolet spectrum in acidic methanol has λ_{max} 364 mμ, log ϵ 3.91, and λ_{max} *ca.* 222 mμ. In basic methanol the peaks are shifted to λ_{max} 364, log ϵ 3.84, and λ_{max} 229, log ϵ 4.09.

Anal. Calcd. for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58; neut. equiv., 192.2. Found: C, 56.25; H, 4.15; N, 14.1; neut. equiv., 189.

3-Cyano-4-carbomethoxy-5-nitro-6-methyl-2-pyridone (II) was prepared in 60–65% yields *via* the fuming nitric acid in glacial acetic acid procedure previously reported for the synthesis of the corresponding ethyl ester,[1] m.p. 213 to 214° dec., neut. equiv. calcd. for $C_9H_7N_3O_5$ 237.2, found 241. The ultraviolet spectrum in acid methanol had λ_{max} 332 mμ, log ϵ 4.08. In base the peak was shifted to λ_{max} 353 mμ, log ϵ 4.12.

2-Methyl-3-nitro-4-carbomethoxy-5-cyano-6-chloropyridine (III) was prepared by a procedure closely analogous to that used by Itiba and Emoto[1] in the synthesis of the corresponding ethyl ester. The crude product was recrystallized from isopropyl alcohol before use in subsequent reactions, m.p. 86.5–88°. An analytical sample was prepared by recrystallization from hexane–benzene. The ultraviolet spectrum in acid–methanol had λ_{max} 298 mμ, log ϵ 3.63. In base–methanol (unstable on standing), the peaks were λ_{max} 306 mμ, log ϵ 3.90, and λ_{max} 277 mμ, log ϵ 3.76.

Anal. Calcd. for $C_9H_6N_3O_4Cl$: C, 42.30; H, 2.37; N, 16.45. Found: C, 42.84; H, 2.35; N, 16.73.

Hydrolysis of 2-Methyl-3-nitro-4-carbomethoxy-5-cyano-6-chloropyridine.—2-Methyl-3-nitro-4-carbomethoxy-5-cyano-6-chloropyridine (12.8 g., 0.05 mole) was stirred with 100 ml. of water and 100 ml. of concentrated hydrochloric acid for *ca.* 16 hours. The reaction mixture was taken to dryness. The residue was warmed with 50 ml. of acetonitrile and a substance which was water soluble removed by filtration. The filtrate was warmed with decolorizing charcoal and then filtered. After standing overnight 2.3 g. (20%) of crystalline product was recovered by filtration. This material was identical in all respects with *bona fide* 3-cyano-4-carbomethoxy-5-nitro-6-methyl-2-pyridone (II).

2-Methyl-3-amino-4-carbomethoxy-5-cyano-6-chloropyridine (IV).—A mixture of 25 g. of 2-methyl-3-nitro-4-carbomethoxy-5-cyano-6-chloropyridine (III), 25 g. of iron filings (*ca.* 40 mesh) and 300 ml. of glacial acetic acid was heated 1.5 hours on the steam-bath. The mixture was filtered hot and the filter cake washed with hot glacial acetic acid (a total of 200 ml. in portions). Water (500 ml.) was added to the filtrate. After chilling thoroughly, 17.7 g. (81%) of 2-methyl-3-amino-4-carbomethoxy-5-cyano-6-methylpyridine was recovered by filtration, m.p. 170–171.5°. An analytical sample was prepared for analysis by recrystallization from 95% ethanol, m.p. 173.6–174°. The ultraviolet spectrum in either acid–methanol or base–methanol has λ_{max} 377 mμ, log ϵ 3.84, and λ_{max} 271 mμ, log ϵ 3.98.

Anal. Calcd. for $C_9H_8N_3O_2Cl$: C, 47.91; H, 3.57; N, 18.62. Found: C, 47.93; H, 3.37; N, 18.30.

Hydrolysis of 2-Methyl-3-amino-4-carbomethoxy-5-cyano-6-chloropyridine (IV).—A mixture of 24 g. (0.10 mole) of IV was refluxed for a total of three hours with 200 ml. of concentrated hydrochloric acid. Pure starting material was recovered directly in 63% yield (15 g.) by filtration of the reaction mixture. No material could be caused to precipitate by gradual change in *p*H of the filtrate through a range which should have precipitated the desired pyridine diacid (V, see below). Evaporating the filtrate to low volume and subsequent operations with various organic solvents did not lead to the isolation of any pure products.

2-Methyl-3-amino-6-chloropyridine-4,5-dicarboxylic Acid (V).—These various reagents were mixed in a 3-liter round bottom flask: 127.8 g. (0.50 mole) of IV, 1 liter of water, 1 liter of concentrated hydrochloric acid and 5.5 g. of platinum oxide catalyst. The mixture was hydrogenated in a low pressure hydrogenation apparatus with rocker agitation. The temperature was maintained from 40 to 60° by external heating. Approximately 37 liters of hydrogen was taken up during *ca.* 4 hours at which time uptake practically stopped. The slurry was agitated another hour. The flask was disconnected and the slurry heated to 95° before filtering with suction. On cooling, 124.6 g. (87%) of the hydrate hydrochloride of V crystallized from the filtrate, m.p. 208–211°. A sample was prepared for analysis by drying at 100° at 2 mm.

Anal. Calcd. for $C_8H_{10}N_2O_5Cl_2$: C, 33.70; H, 3.54; N, 9.83; Cl^-, 12.4; H_2O, 6.32; neut. equiv., 95.0. Found: C, 33.16; H, 3.60; N, 9.44; Cl^-, 12.3; H_2O, 6.63; neut. equiv., 96.5.

(17) R. F. Bird and E. E. Turner, *J. Chem. Soc.*, 5050 (1952).

(18) (a) We did obtain some spectral evidence that lactones were among the products when close to the theoretical quantity of sodium hydride–aluminum chloride was employed in the cases studied here. No attempt was made to purify or fully characterize these products. (b) Since the completion of this work, the reduction of pyridinecarboxylic esters with sodium borohydride and aluminum chloride has been reported (J. A. Bigot, Th. J. deBoer and F. L. J. Sixma, *Rec. trav. chim.*, **76**, 996 (1957)). These workers isolated a complex formed between borine (BH_3) and ethyl isonicotinate when the latter was treated with sodium borohydride in diglyme. This greatly increased the hydride requirement for reduction of the ester group. Although we have not attempted isolation, formation of a similar complex, in the case of the pyridine diacids studied here, could well account for the high hydride requirement for complete reduction. Two alternative explanations present themselves: (1) With close to the theoretical quantity of sodium borohydride there is formed, *via* interaction with the acid functions (at oxygen or at nitrogen), an insoluble complex. Thus sticky complexes were indeed obtained under such conditions prior to the addition of the aluminum chloride; with large excesses of sodium borohydride a soluble complex is formed as evidenced by the resultant clear solutions, provided that the reaction mixtures were not heated prior to addition of the aluminum chloride (*cf.* footnote 21). (2) Only two or three of the four hydride "ions" originally present in the sodium borohydride are effective reducing agents for the substrates studied here.

(19) E. E. Royals, THIS JOURNAL, **67**, 1508 (1945).

The hydrate hydrochloride was converted to the anhydrous free base by the following procedure: 100 g. (0.35 mole) of the hydrate hydrochloride was slurried in 500 ml. of water, boiled for 15 minutes and chilled. The free base was filtered off and dried over caustic at reduced pressure. Recovery was 77.5 g. (96%), m.p. 217.8–218.2 dec. This material has an ultraviolet spectrum in acid–methanol with λ_{max} 359 mμ, log ε 3.78; λ_{max} 253 mμ, log ε 3.96; and λ_{max} 227 mμ, log ε 4.06. In base–methanol the peaks are λ_{max} 332 mμ, log ε 3.67, and λ_{max} 228 mμ, log ε 4.13.

Anal. Calcd. for $C_8H_7N_2O_4Cl$: C, 41.66; H, 3.06; N, 12.15; neut. equiv., 115.3. Found: C, 41.35; H, 2.90; N, 11.91; neut. equiv., 116.

The free base V was converted by sublimation to an anhydride having characteristic infrared bands at 5.41 and 5.67 μ.

Catalytic reduction–hydrolysis of 2-methyl-3-nitro-4-carbethoxy-5-cyano-6-chloropyridine, prepared by the method of Itiba and Emoto,[1] under identical conditions gave somewhat lower yields of the same aminochlorodiacid as product V.

The hydrochloride of 2-methyl-3-amino-4,5-bis-(hydroxymethyl)-6-chloropyridine (VI) was prepared *via* a hydride reduction (sodium borohydride and aluminum chloride in diglyme) of the aminochlorodiacid V using reaction conditions and an isolation procedure identical to those for the preparation of pyridoxine from the hydroxydiacid X. The yield was 44% of theoretical. An ultraviolet spectrum of the diglyme mother liquor indicated *ca.* 33% of the product was lost in this way. An analytical sample was prepared by recrystallization from 95% ethanol, m.p. 270°. The ultraviolet spectrum in acid–methanol has λ_{max} 340 mμ, log ε 3.68; λ_{max} 265 mμ, log ε 3.73; and 232 mμ, log ε 4.10. The ultraviolet spectrum in base–methanol has λ_{max} 313 mμ, log ε 3.71, and λ_{max} 250 mμ, log ε 3.98.

Anal. Calcd. for $C_8H_{12}N_2O_2Cl_2$: N, 11.72; Cl^-, 14.83. Found: N, 11.65; Cl^-, 14.59.

2-Methyl-3-hydroxy-6-chloropyridine-4,5-dicarboxylic Acid (VII).—A slurry consisting of 57.5 g. of the aminochlorodiacid (V, free base) and 400 ml. of water was heated to 70°. While maintaining the temperature at 70–75°, 22 g. of sodium nitrite in 150 ml. of water was added dropwise as fast as possible, but slowly enough to avoid undue foaming. The mixture was cooled almost immediately in an ice-bath and simultaneously acidified with 80 ml. of concentrated hydrochloric acid. The aqueous solution was extracted with ether (six 250-ml. portions). The combined extracts were dried over anhydrous sodium sulfate, filtered and taken to dryness. The residue was refluxed with 140 ml. of acetonitrile to remove by-products and, after chilling, the product recovered by filtration; yield 30 g. (52%) of good quality product. An analytical sample was prepared by recrystallization from methanol–benzene, m.p. 215–216 dec. The ultraviolet spectrum in acid–methanol has λ_{max} 327 mμ, log ε 3.74 and in base–methanol λ_{max} 320 mμ, log ε 3.77.

Anal. Calcd. for $C_8H_6NO_5Cl$: C, 41.50; H, 2.61; N, 6.07; neut. equiv., 116. Found: C, 41.53; H, 2.72; N, 6.14; neut. equiv., 118.

This material gave an anhydride on sublimation which had characteristic infrared bands at 5.41 and 5.64 μ.

6-Chloropyridoxine (VIII).—A. By Hydride Reduction.—The hydroxychlorodiacid VII was reduced to 6-chloropyridoxine under conditions identical to those employed for the reduction of the hydroxydiacid X to pyridoxine. However, recovery of the product was considerably complicated by the fact that the product did not crystallize from the diglyme residue after removal of boron (as methyl borate) and methanol. The mixture of aluminum salts and chloropyridoxine in diglyme was taken to dryness, dissolved in water, made slightly basic and continuously extracted with ether. The crystalline product was removed by filtration of the ether extraction after first reducing the volume. The yield was 31% of theoretical. An analytical sample was prepared by recrystallization from methanol–benzene, m.p. 192.5–193° dec. The ultraviolet spectrum in acid–methanol has λ_{max} 297 mμ, log ε 3.77; in base–methanol, λ_{max} 318 mμ, log ε 3.80, and λ_{max} 253 mμ, log ε 3.98.

Anal. Calcd. for $C_8H_{10}NO_3Cl$: C, 47.19; H, 4.95; N, 6.88; Cl, 17.4. Found: C, 47.45; H, 4.93; N, 6.79; Cl, 17.1.

B. By Diazotization.—The aminochlorodialcohol (VI, hydrochloride, 0.75 g.) was heated in a steam-bath with 15 ml. of water. An aqueous solution of sodium nitrite (0.7 g. in 5 ml. of water) was added dropwise. A total of 0.15 g. of chloropyridoxine was isolated by filtration of the chilled reaction mixture and ether extraction of the filtrate.

The Monohydrate of 2-Methyl-3-aminopyridine-4,5-dicarboxylic Acid (IX).—The following reagents were shaken in a Parr low-pressure hydrogenation apparatus at 56–58° external temperature: 11.8 g. of the aminochlorodiacid (V, free base), 150 ml. of 1.024 *N* aqueous sodium hydroxide and *ca.* 1 teaspoonful of Raney nickel. Hydrogenation was carried out for *ca.* 3.5 hours by which time the pressure had dropped to a constant value. After cooling, the catalyst was removed by filtration, the filtrate was made acidic with 10 ml. of concentrated hydrochloric acid. The product was recovered by filtration of the chilled mixture; yield 10 g. (93%), m.p. 247.8° dec., literature[1] m.p. 241–242° dec. The ultraviolet spectrum of IX in acid–methanol has λ_{max} 350 mμ, log ε 3.79. In base–methanol it has λ_{max} 312 mμ, log ε 3.68.

An identical product was prepared by two steps from the pyridine derivative IV with procedures already described in the literature for the corresponding ethyl ester derivatives (catalytic dechlorination[1,2] and hydrolysis with concentrated hydrochloric acid.[1] The intermediate 2-methyl-3-amino-4-carbomethoxy-5-cyanopyridine had m.p. 165.6–166.8°. This intermediate has an ultraviolet spectrum in acid–methanol with λ_{max} 369 mμ, log ε 3.86; λ_{max} 264 mμ, log ε 3.76; and λ_{max} 235, log ε 4.08. In base–methanol it has λ_{max} 364 mμ, log ε 3.88; λ_{max} 263 mμ, log ε 3.77; and λ_{max} 230 mμ, log ε 4.10.

Anal. Calcd. for $C_9H_9N_3O_7$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.26; H, 4.52; N, 21.73.

2-Methyl-3-hydroxypyridine-4,5-dicarboxylic Acid (X).—In our hands the procedure to be described gave much better yields of 2-methyl-3-hydroxypyridine-4,5-dicarboxylic acid than that previously reported by Itiba and Emoto.[1] To a slurry of 10 g. of 2-methyl-3-aminopyridine-4,5-dicarboxylic acid monohydrate in 70 ml. of water maintained at 70–75° there was added portionwise over a few minutes a solution of 4.1 g. of sodium nitrite in 14 ml. of water. Finally 0.5 g. of urea was added and then 15 ml. of concentrated hydrochloric acid (considerable gas evolution). The mixture was cooled in an ice-bath before recovery of 8.0 g. (87%) of 2-methyl-3-hydroxypyridine-4,5-dicarboxylic acid by filtration with washes by water, methanol and finally ether; m.p. 255–258° dec., literature m.p. 258–259° dec. A sample purified by dissolution in excess aqueous sodium hydroxide and reprecipitation with *excess* acid[20] had an ultraviolet spectrum in acid–methanol with λ_{max} 303 mμ, log ε 3.91; and in base–methanol with λ_{max} 312 mμ, log ε 3.82.

2-Methyl-3-amino-4,5-bis-(hydroxymethyl)-pyridine (XI).—This reduction was carried out under essentially identical conditions to those employed for the reduction of the hydroxydiacid X to pyridoxine (*vide post*). The isolation was also identical except that the product did not crystallize directly from the diglyme after the distillative removal of methyl borate and methanolic hydrochloric acid. At this stage, an equal volume of absolute alcohol was added, and the mixture heated and filtered hot to remove inorganic salts. The monohydrochloride of 2-methyl-3-amino-4,5-bis-(hydroxymethyl)-pyridine crystallized from the filtrate on standing overnight in the refrigerator in 41% of the theoretical yield. A second crop (30% of theoretical) was obtained by distilling the mother liquor to dryness and recrystallizing the residue from 95% ethanol. The dihydrochloride and the free base of this compound have been reported previously.[3] An analytical sample was prepared by recrystallization from 95% ethanol, m.p. 197.0–199.0°. This material had an ultraviolet spectrum in acid–methanol with λ_{max} 325 mμ, log ε 3.85, and λ_{max} 254 mμ, log ε 3.64. In base–methanol it had λ_{max} 304 mμ, log ε 3.75, and λ_{max} 241 mμ, log ε 3.84.

Anal. Calcd. for $C_8H_{13}N_2O_2Cl$: C, 46.95; H, 6.40; N, 13.69; Cl^-, 17.33. Found: C, 46.96; H, 6.48; N, 13.72; Cl^-, 17.35.

The Monomethyl Ester of 2-Methyl-3-hydroxypyridine-4,5-dicarboxylic Acid.—The procedure used was that re-

(20) The monosodium salt will precipitate if the amount of acid is insufficient.

ported[3] for the formation of the dimethyl ester except for use of lower temperature of reaction (25–30°) and longer reaction time (8 days). The yield of dimethyl ester was 8%. The process for recovery of the starting hydroxydiacid X gave instead a 70% yield of a monomethyl ester of X. This material had an ultraviolet spectrum in acid–methanol with λ_{max} 305 mμ, log ε 3.87. In base–methanol it had λ_{max} 316 mμ, log ε 3.68, and λ_{max} 270 mμ, log ε 3.45.

Anal. Calcd. for $C_9H_9NO_5$: C, 51.16; H, 4.30; N, 6.63; neut. equiv., 211.2. Found: C, 51.13; H, 4.15; N, 6.40; neut. equiv., 211.

Pyridoxine Hydrochloride (XII). General Hydride Reduction Procedure.—A 1-liter round-bottom flask was equipped with gas inlet (positive pressure of nitrogen maintained throughout the reaction), a gas outlet at the top of a condenser (no water), stirrer, addition funnel and thermometer. Commercial diglyme, 120 ml. (0.07% water by modified Karl Fischer, 0.04–0.05% –OH by acetylation) and 8 g. of sodium borohydride (98% by manufacture's assay) were added to the flask and stirred to dissolve the solid. Powdered 2-methyl-3-hydroxypyridine-4,5-dicarboxylic acid (11.8 g., 0.06 mole) was added portionwise over 20 minutes. The internal temperature rose to 45°[21] and a dark orange solution resulted. There was then added 9.3 g. of aluminum chloride (anhydrous reagent, sublimed, small lump[22]) dissolved in 70 ml. of diglyme. The latter addition required 10 minutes with internal temperature rising to 68°. At one point the bright yellow reaction mixture set up, but thinned out readily on the addition of further aluminum chloride solution. The stirred mixture then was heated to 135° for 15 minutes. By the time 115° was reached, the mixture had changed from bright yellow to white and reaction was undoubtedly nearly complete by this stage.[23] The reaction mixture was cooled and unreacted hydride destroyed by the dropwise addition of 250 ml. of methanolic HCl (saturated at *ca.* 50°). Methyl borate was removed by the fractional distillation through a 1" × 18" column packed with 3/16" glass helices. To obtain a negative flame test, 75 ml. of distillate was required. Sodium chloride was removed from the distillation residue by a hot filtration with 2 × 50 ml. of wash with hot methanol. The methanol was distilled out of the filtrate at atmospheric pressure from a steam-bath. By this time the flask contained a crystalline solid and two liquid layers. Cooling and the addition of 15 ml. of methanolic HCl brought the lower and somewhat viscous layer back into solution. After storing in the refrigerator for 2.5 days, the product was filtered off with a minimum of wash with cold methanol. The yield of crude pyridoxine hydrochloride was 10.1 g., m.p. 196–199°, purity determined by the ultraviolet spectrum was 90%. The crude was recrystallized from 95% ethanol to yield 9.0 g. (73% of theoretical), m.p. 204–206° dec., literature[24] m.p. 205–212° dec. This material had an ultraviolet spectrum identical with that of purified commercial pyridoxine hydrochloride; in acid–methanol it has λ_{max} 292 mμ, log ε 3.96, and in base–methanol λ_{max} 307 mμ, log ε 3.84, and λ_{max} 246 mμ, log ε 3.85.

Anal. Calcd. for $C_8H_{12}NO_3Cl$: C, 46.72; H, 5.88; N, 6.81; Cl^-, 17.24. Found: C, 46.67; H, 5.83; N, 6.78; Cl^-, 17.31.

Pyridoxine hydrochloride also was obtained by the reduction of the monomethyl ester[12] of 2-methyl-3-hydroxypyridine-4,5-dicarboxylic acid. The yield (with 3.0 moles of sodium borohydride per mole of substrate) was 71%.

Finally, pyridoxine was prepared by the catalytic dechlorination of 6-chloropyridoxine. A slurry of 2.7 g. of 6-chloropyridoxine, 150 ml. of 95% ethanol and 2 g. of 5% palladium-on-calcium carbonate was shaken in a Parr low pressure hydrogenation apparatus (40 to 30 p.s.i.; temperature, 20–40°). The catalyst was removed by filtration and an excess of concentrated hydrochloric acid was added to the filtrate. Evaporation to dryness and then recrystallization from 95% ethanol gave 1.6 g. (58%) of pyridoxine hydrochloride.

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(21) The temperature should be kept in the range of 30 to 45°. If over-cooled the hydroxydiacid will not react immediately, but will build up in the mixture and suddenly react with much foaming. If over-heated, a sticky complex will fall out of solution and conversion will be cut considerably.

(22) Powdered aluminum chloride will react with the diglyme too vigorously and may even ignite from the heat.

(23) Lower temperatures, *e.g.*, 95° for 1 hour or 45° for 18 hours, are equally satisfactory.

(24) "The Merck Index," 6th edition, Merck and Co., Inc., Rahway, N. J., 1952.

GROTON, CONN.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF KANSAS]

Studies on the Formation and Reactions of 1-Pyrroline[1]

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1-Pyrroline is formed by partial dehydrogenation of pyrrolidine and by partial hydrogenation of pyrrole. It can be synthesized by dehydrohalogenation of N-chloropyrrolidine, or by periodate degradation of 3-hydroxypiperidine. 1-Pyrroline undergoes condensation with pyrrole and alkylated pyrroles to form a new series of compounds, the pyrrolidylpyrroles. The major isomer formed by condensation of 1-pyrroline with pyrrole is 2-(2-pyrrolidyl)-pyrrole. 1-Piperideine undergoes a similar condensation with pyrrole.

Introduction

Theoretically, partial hydrogenation of pyrrole or partial dehydrogenation of pyrrolidine can result in the formation of any combination of three isomers, 1-pyrroline (I), 2-pyrroline (II) and 3-pyrroline (III).

Catalytic hydrogenation has been reported for pyrrole[3–5] and several substituted pyrroles.[6,7]

(1) This investigation was performed as a part of American Petroleum Institute Research Project 52 on "Nitrogen Constituents of Petroleum," which is conducted at the University of Kansas in Lawrence, Kan., and at the Bureau of Mines Experiment Stations at Laramie, Wyo., and Bartlesville, Okla.

(2) From the dissertation submitted by Donald W. Fuhlhage to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Degree of Doctor of Philosophy.

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(7) J. L. Rainey and H. Adkins, *ibid.*, **61**, 1104 (1939).