and methanol. The yield was 900 mg. (91%). After two crystallizations from 80% acetic acid the product formed pale yellow needles melting at 211–212°, slightly soluble in water, acetone, and alcohol, soluble in acetic acid and very soluble in pyridine (XIV).

Anal. Calcd. for $C_7H_4I_2N_2$: N, 7.53. Found[10]: N, 7.50.

Nitration of Ethyl 6-Methyl-4-hydroxy-2-pyridone-3-carboxylate (I).—A solution of 2 g. of I in 4 cc. of concentrated sulfuric acid was cooled in ice and treated with 2 cc. of fuming nitric acid (d. 1.5). The temperature of the reaction mixture, which was removed from the ice-bath, slowly rose above room temperature. When it was again at room temperature, the solution was added to 30 g. of ice. The yellow product which precipitated was collected on a filter and washed with water. The ethyl 6-methyl-5-nitro-4-hydroxy-2-pyridone-3-carboxylate (III) weighed 2.1 g. (86%) and melted at 253° with decomposition after recrystallization from alcohol.

Anal. Calcd. for $C_9H_{10}N_2O_6$: C, 44.61; H, 4.16; N, 11.57. Found[10]: C, 44.95; H, 3.94; N, 11.46.

The reduction of this substance and its conversion to a product resembling pyriplastin has not yet been completed.

Summary

A series of pyridones derived from *n*-amyl 6-methyl-4-hydroxy-2-pyridone-3-carboxylate has been prepared. Nitration of the ester and conversion of the nitro derivative to an amide gave a product containing both the amide group and two replaceable hydroxyl groups or their equivalent. Treatment with phosphorus oxychloride affected the amide group first. The intermediate cyano pyridone was isolated and characterized. Further treatment with phosphorus oxychloride replaced the hydroxyls by chlorine. The amine-ester, *n*-amyl 6-methyl-5-amino-4-hydroxy-2-pyridone-3-carboxylate, gave on heating a polycondensation to a polyamide, pyriplastin. Conversion of the dichloro compounds to di-iodo compounds and reduction of the nitro group by hydriodic acid preserved with hypophosphorous acid has been found convenient and rapid. Conversion of the dihalogenated compounds to substances more closely related to pyridoxin has not been successful.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Preparation and Reactions of Some Polysubstituted Pyridines. 2-Methyl-3-hydroxy-5-hydroxymethylpyridine (4-Deshydroxymethylpyridoxin)

BY L. A. PEREZ-MEDINA,[1] R. P. MARIELLA[2] AND S. M. MCELVAIN

The well-known reactivity of 2- and 4-halogen substituents in the pyridine nucleus prompted a study of the replacement of one or both of the halogens of 2-methyl-3-nitro-4,6-dichloro-5-cyanopyridine[3] (VI) and of the corresponding amino compound (IX) by the cyano group. Although attempts to bring about such a replacement using a variety of conditions and reagents were uniformly unsuccessful, the behaviors of these and other halogenated pyridines in certain reactions seem of sufficient interest to report. In connection with this work a related series of tetrasubstituted pyridine derivatives, prepared from the cyanopyridone (I), was developed. The transformations and interrelationships of the various pyridine derivatives that are the subject of this paper are illustrated in the accompanying flow sheet.

The reduction of the nitro group of VI over Adams platinum oxide catalyst or with stannous chloride produced IX, but reduction of this nitro group with zinc and sulfuric acid simultaneously removed the 4-chloro substituent to yield X, which was also obtained from VII. Both IX and X, as would be expected, were converted by hydrogenation over a palladium catalyst to the diamine XIII, which was isolated as the dihydrochloride.

It was not possible to replace any of the halogen substituents of VI, IX or XV by the cyano group using either sodium, cuprous, mercuric or silver cyanide in a variety of solvents and at reaction temperatures of 80–200°. In most cases the halogen compound was recovered unchanged, but when a solution of IX and sodium cyanide in 80% methanol was refluxed for forty-eight hours one of the chlorine substituents was replaced by a methoxyl group. The fact that the corresponding 4-bromo compound (XV) yielded the same product, establishes XII as the structure of this methoxy compound. The preferential replacement of the 4-halogen substituents of IX and XV by a methoxyl instead of the cyano group in an alcoholic solution of sodium cyanide was quite unexpected and remains difficult to rationalize.[4]

A noteworthy difference in behavior was observed with the amines IX and X. Both of these amines were readily diazotized and the diazonium chloride of the former was hydrolyzed to the corresponding 2-methyl-3-hydroxy-4,6-dichloro-5-cyanopyridine. However, a similar attempt to convert the diazonium chloride prepared from X

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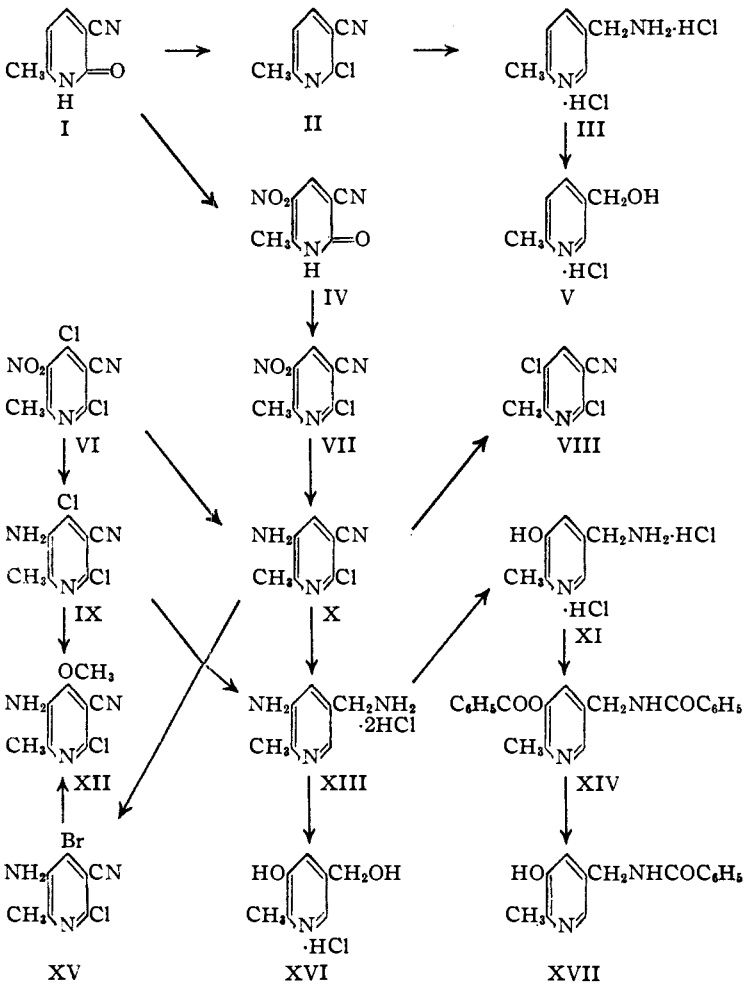
(3) Bruce and Perez-Medina, THIS JOURNAL, **69**, 2571 (1947).

(4) A similar but not exactly analogous inertness of halogen to replacement by a cyano group is shown by bromoacetal, which reacts very slowly (forty hours) and incompletely (14%) with a refluxing solution of sodium cyanide and catalytic amounts of sodium iodide in ethyl alcohol to form cyanoacetal (Uhle and Jacobs, *J. Org. Chem.*, **10**, 81 (1945)). However, the halogen of either chloro-, bromo- or iodoacetal is readily replaced by a hydroxyl group in an alcoholic solution of sodium hydroxide (Beyerstedt and McElvain, THIS JOURNAL, **58**, 529 (1936)).

FLOW SHEET



to the corresponding 3-hydroxy compound yielded only the dichloro compound, VIII. Indeed this latter compound was obtained in small yield when the diazonium *sulfate* from X was hydrolyzed; presumably the necessary chloride ions for this transformation were furnished by hydrolysis of the 6-chloro substituent of a portion of the material. It would appear from these results that the introduction of a 3-chloro substituent, rather than the hydroxyl group, is the preferred reaction if the 4-position of the pyridine nucleus is unsubstituted, but the presence of the 4-chloro substituent in IX prevents the introduction of a halogen in the adjacent position just as the 5-cyano group prevents the introduction of a cyano group in the place of the 4-halogen substituent of IX and XV.

Treatment of the diprimary amine (XIII) with two equivalents of nitrous acid served only to diazotize one of the primary amino groups; subsequent hydrolysis produced a mono-hydroxy compound. The structure XI is assigned to this product because of the characteristic enol coloration it shows with ferric chloride; both XVI and XVII show a similar coloration, whereas III, V and XIV show no color with this reagent.

Six equivalents of nitrous acid converted the diprimary amine (XIII) to the dihydroxy compound XVI, which was isolated both as the hydrochloride and as the free base. As may be seen from its structure, XVI differs from pyridoxin only in the absence of the 4-CH_2OH group. A number of attempts were made to convert XVI to pyridoxin by the action of formaldehyde, and to pyridoxal by the Reimer–Tiemann reaction. All of these attempts were unsuccessful; as examples, XVI was recovered after heating the sodium salt of the free base of XVI for six hours at 200° in a 40% aqueous formaldehyde solution, or after heating the free base at 100° with trioxane. The inertness of XVI toward formaldehyde is in marked contrast to the recently reported facile reaction of 3-hydroxypyridine with formaldehyde to form 2-hydroxymethyl-3-hydroxypyridine.[5]

Similarly XVI failed to react with diethylamine and formaldehyde after several hours at 100°; 70% of the original XVI was recovered from this reaction. This result is of particular interest in view of the recent report that 2-methyl-3-hydroxypyridine[6] readily forms the corresponding 4-diethylaminomethyl derivative with these reagents.

The bromination of XVI was attempted under a variety of conditions, but in no case could a definite nuclear bromination product be isolated. In contrast to this behavior is the facile bromination of the aminopyridine X to produce XV. In such solvents as chloroform and acetic acid, the free base of XVI gave a characteristic red perbromide which, on further heating to promote nuclear bromination, changed to a useless tar; similarly, this free base failed to decolorize a solution of pyridine perbromide in acetic acid at 100°. Attempts to brominate XVI in alkaline hypobromite solutions gave colored gums that appeared to be oxidation products of the original

(5) Urbanski, *J. Chem. Soc.*, 1104 (1946).

(6) Brown and Miller, *J. Org. Chem.*, **11**, 388 (1946). These authors accept the 3-orientation suggested by Wulff (U. S. Patents 1,880,645–6 (1932)) for the sulfonic acid obtained from the sulfonation of α-picoline. Since this acid has been shown to be 2-methyl-5-pyridinesulfonic acid (McElvain and Goese, THIS JOURNAL, **65**, 2233 (1943); *cf.* also Parker and Shive, *ibid.*, **69**, 63 (1947)), it appears that the pyridol used by Brown and Miller in the Mannich reaction was 2-methyl-5-hydroxypyridine, in which case the 6-orientation of the diethylaminomethyl group is not excluded.

material. The amidopyridol (XVII) showed a similar behavior.

It seems likely that the marked difference in the reactivities of X and XVI toward bromination is related to the difference in basicities of the two compounds. The amine X is non-basic (it does not form a salt with hydrochloric acid) and consequently does not form a perbromide, while the free base of XVI readily forms a perbromide. The temperature required to convert this perbromide to a nuclear bromination product[7] undoubtedly promotes attack of the perbromide bromine on the vulnerable side chains of XVI in addition to, or to the exclusion of, nuclear bromination.

Experimental

3-Cyano-6-methyl-2-pyridone[8] (I).—Sodium formylacetone was prepared in the following manner: To 46 g. of sodium wire in 1 liter of anhydrous ether was added, over a period of two and one-half hours, a mixture of 116 g. (2 moles) acetone and 148 g. (2 moles) ethyl formate. During the addition of the acetone–formate mixture the ether was stirred mechanically and the temperature kept below 10°. When the addition was complete the reaction mixture was allowed to stand at room temperature for two hours, filtered, the sodium formylacetone washed with ether and placed immediately in the desiccator over calcium chloride. The dry product weighed 178 g. (82%).

To a solution of 75 g. of sodium formylacetone and 60 g. of cyanoacetamide in 300 ml. of water was added a solution of piperidine acetate (8 ml. of glacial acetic acid in 20 ml. of water and sufficient piperidine to produce a basic reaction). The resulting solution was refluxed for two hours, after which time 250 ml. of water and sufficient acetic acid to render the reaction mixture acidic were added. After standing in an ice-bath for two hours, the precipitated pyridone was filtered off, washed with ice water and dried. The yield was 63 g. (68%); a sample recrystallized from 50% alcohol melted at 294–296° dec.

2-Methyl-5-cyano-6-chloropyridine[9] (II).—A mixture of 10 g. of I and 70 g. of phosphorus pentachloride was heated to gentle reflux for an hour. The resulting solution then was poured onto ice and the aqueous layer neutralized with sodium bicarbonate. The brown solid which separated was filtered off and dried; it weighed 11 g. (97%) and melted at 95–100°. Recrystallization from petroleum ether gave light tan needles, m. p. 114–115°. Vacuum sublimation gave white needles with essentially the same melting point.

2-Methyl-5-aminomethylpyridine Dihydrochloride (III).—To a solution of 2.1 g. of the cyanopyridine (II) in 150 ml. of absolute alcohol were added a solution of 200 mg. of palladium chloride in 1 ml. of concentrated hydrochloric acid, 12 ml. of a 15% solution of hydrogen chloride in absolute alcohol, and 3 g. of Norit. The resulting suspension was shaken with hydrogen under 30 pounds pressure at room temperature. The absorption of hydrogen ceased after three hours, after which time another solution of 200 mg. of palladium chloride in 1 ml. of concentrated hydrochloric acid was added and the hydrogenation resumed. After another eight hours the hydrogen absorption had stopped. The catalyst and support were filtered, washed with water, and the filtrate concentrated to 2 ml. Addition of 50 ml. of absolute alcohol caused the precipitation of 2.0 g. (75%) of 2-methyl-5-methylaminopyridine dihydrochloride as voluminous white crystals, m. p. 278–280°. Recrystallization from a mixture of concentrated hydrochloric acid and alcohol gave a product melting at 279–280°.[10] This compound showed no coloration with ferric chloride.

Anal. Calcd. for $C_7H_{12}Cl_2N_2$: Cl, 36.3. Found: Cl, 36.4.

2-Methyl-5-hydroxymethylpyridine Hydrochloride (V).—A solution of 2 g. of the dihydrochloride (III) in 10 ml. of water was treated successively with a mixture of 40 ml. of concentrated hydrochloric acid and 80 ml. of water, which had been heated to 95°, and a solution of 4.5 g. of sodium nitrite in 10 ml. of water. The resulting solution was kept at 95–100° until the evolution of gas ceased. The solution then was evaporated to dryness and the white crystalline residue extracted with three 20-ml. portions of boiling absolute alcohol. After filtration, the combined extracts were concentrated to approximately 5 ml., treated with dioxane until crystals began to appear, and then allowed to crystallize. The yield of 2-methyl-5-hydroxymethyl hydrochloride which separated amounted to 0.7 g. (43%), m. p. 112–115°. After several recrystallizations from an alcohol–dioxane mixture an analytical sample that melted at 119–120°[11] was obtained. This compound showed no coloration with ferric chloride.

Anal. Calcd. for $C_7H_{10}ClNO$: Cl, 22.22; N, 8.78. Found: Cl, 22.10; N, 8.76.

3-Cyano-5-nitro-6-methyl-2-pyridone (IV).—A suspension of 13.4 g. of the cyanopyridone (I) in 50 ml. of acetic anhydride was cooled in an ice–salt bath to −5°. Separately 13 ml. of acetic anhydride containing a few mg. of urea was cooled below 0° and mixed with 7 ml. of fuming nitric acid. This nitrating mixture was added to the pyridone suspension at 0°. When the addition was complete the reaction mixture was removed from the cooling bath and shaken. The rise in temperature was slow until it reached about 25° and then became very rapid. When the temperature of the reaction mixture reached 35° the flask was immersed in the ice-bath for a short time to check the vigorous reaction. This cooling was repeated at 45° and the temperature finally allowed to reach 55–60°. The proper control of the temperature is very important; if it is kept too low (45°) the nitration is incomplete; on the other hand if the heat evolution is not checked as indicated complete oxidation of the pyridone occurs. When no further evolution of heat was noticeable the reaction mixture was cooled to 10° and poured onto 250 g. of crushed ice. Then it was filtered, the nitro compound washed several times with ice water, and finally with cold 50% alcohol. The yield of the nitropyridone was 9.1 g. (51%); the recrystallized product (from glacial acetic acid) melted at 253–254° d.

Anal. Calcd. for $C_7H_3N_3O_3$: N, 23.47. Found: N, 23.69.

2-Methyl-3-nitro-5-cyano-6-chloropyridine (VII).—A suspension of 10 g. of the nitropyridone IV and 14 g. of phosphorus pentachloride in 50 ml. of phosphorus oxychloride was refluxed for thirty minutes. Solution was attained during the first twenty-twenty-five minutes. The solvent was removed, as completely as possible under reduced pressure, the residue cooled in ice and carefully treated with 20 ml. of 50% alcohol. When the evolution of hydrogen chloride had ceased, the mixture was heated on the steam-bath for five minutes, then cooled in ice and filtered. The crude product so obtained weighed 10 g. Recrystallization from methanol with charcoal gave 8.2 g. (74.5%) of pure product, m. p. 98–99°.

Anal. Calcd. for $C_7H_4ClN_3O_2$: Cl, 17.95; N, 21.28. Found: Cl, 17.96; N, 21.62.

(7) *Cf.* the pyrolysis of pyridine perbromides, Englert and McElvain, THIS JOURNAL, **51**, 863 (1929); McElvain and Goese, *ibid.*, **65**, 2227 (1943).

(8) This pyridone has been reported by Dornow, *Ber.*, **73**, 153 (1940), who prepared it in 35% yield by condensing β-ethoxycrotonaldehyde diethylacetal with cyanoacetamide.

(9) This pyridone has been prepared previously by Reider and Elderfield, *J. Org. Chem.*, **7**, 286 (1942), by the decarboxylation of 2-methyl-4-carboxy-5-cyano-6-chloropyridine.

(10) This compound has been reported by Graf, *J. prakt. Chem.*, **136**, 88 (1936), as melting at 247°; it was prepared in 53% yield by the reduction of 2-methyl-5-cyanopyridine with chromous acetate.

(11) Graf (ref. 10) reported this compound to melt at 102°.

2-Methyl-3-amino-5-cyano-6-chloropyridine (X).—A suspension of 3 g. of the pure nitro compound (VII) in 15 ml. of ether was treated slowly with a filtered solution of 50 g. of stannous chloride in 50 ml. of concentrated hydrochloric acid. Sufficient heat was evolved so that by the end of the reaction the ether had evaporated and a clear, slightly colored solution remained. After standing until the temperature dropped to 25°, the reaction mixture was diluted with 60 ml. of cold water to precipitate the amine, cooled in ice for half an hour, and then filtered. The precipitate was washed with cold water containing a small amount of hydrochloric acid. The yield of the amine (X) was 2.3 g. (90%); a sample recrystallized from methanol melted 224–225°.

Anal. Calcd. for $C_7H_6ClN_3$: Cl, 21.16; N, 25.08. Found: Cl, 21.31; N, 24.78.

The N-acetyl derivative of X was prepared by dissolving the base in acetic anhydride, concentrating by boiling to a small volume and decomposing the excess anhydride with water. When this solution was neutralized with ammonia, a crystalline precipitate of 2-methyl-3-acetamino-5-cyano-6-chloropyridine separated; m. p. 183–185°.

Anal. Calcd. for $C_9H_8ClN_3O$: C, 51.54; H, 3.85. Found: C, 51.42; H, 3.70.

The monochloropyridine X also was formed when 2-methyl-3-nitro-4,6-dichloro-5-cyanopyridine (VI) was reduced as follows: Four grams of VI and 6 g. of granulated zinc were refluxed with 100 ml. of a solution prepared by mixing 170 ml. of 50% methanol and 10 ml. of concentrated sulfuric acid. Complete solution of VI took place in about forty minutes. Refluxing was continued for another hour. The solution then was decanted from the excess zinc, diluted with 50 ml. of water, and cooled in ice for two hours before filtration. The yield of X was 1.4 g. (50%). A sample recrystallized from methanol melted at 224–226° and did not depress the melting point of a sample of X prepared from VII as described above. Similarly a mixture of the acetyl derivatives of samples of X, prepared from VI and VII, showed no depression of the melting point.

2-Methyl-3-amino-4,6-dichloro-5-cyanopyridine[3] (IX).—The nitro compound VI[3] (5 g.) was reduced in ether suspension with 25 ml. of stannous chloride solution as described above in the preparation of X. The corresponding amino compound IX, m. p. 179–180°, was obtained in quantitative yield.

2-Methyl-3-amino-4-bromo-5-cyano-6-chloropyridine (XV).—A solution of 2.3 g. of the amine X in 40 ml. of glacial acetic acid at 70° was treated with 1.4 ml. of bromine in 3 ml. of acetic acid. A thick precipitate formed at once. When the temperature dropped to 40° the reaction mixture was diluted with 150 ml. of water, cooled in ice and finally filtered. The yield of XV was 3.72 g. (80%). A sample recrystallized from 50% alcohol melted at 185–186°.

Anal. Calcd. for $C_7H_5BrClN_3$: C, 34.09; H, 2.04; N, 17.05. Found: C, 34.23; H, 2.05; N, 17.52.

The following reagents and reaction conditions were used in unsuccessful attempts to replace a halogen of VI, IX and XV by a cyano group: (a) an alcoholic solution of VI was refluxed with cuprous or mercuric cyanide for twenty-four hours, after which VI was recovered unchanged; (b) a pyridine solution of IX or XV was boiled with cuprous cyanide for sixteen hours, after which about 40% of either starting material was recovered; the remainder in each case was an intractable tar; (c) an alcoholic solution of the bromo compound, XV, was refluxed overnight with mercuric or silver cyanide, after which it was quantitatively recovered; (d) a solution of IX and sodium cyanide in 80% dioxane was heated twenty-four hours at 200° with no evidence of reactions; (e) see the preparation of XII below for the reaction of IX and XV with sodium cyanide in 80% methanol.

2-Methyl-3-amino-4-methoxy-5-cyano-6-chloropyridine (XII).—This compound was best prepared by the following procedure: A solution of 1 g. of XV and 0.3 g. of potassium methoxide in 20 ml. of absolute methanol was refluxed for 24 hours, after which time it was evaporated to dryness. The remaining yellow solid was extracted with anhydrous ether and the insoluble potassium bromide filtered off. Evaporation of the ether left 0.7 g. (87%) of XII, m. p. 124–127°. After recrystallization from water the product melted at 130–131°.

Anal. Calcd. for $C_8H_8ClN_3O$: Cl, 17.95; N, 21.25. Found: Cl, 18.35; N, 21.14.

The methoxypyridine XII was isolated in 32 and 41% yields, respectively, when either IX or XV was heated for forty-eight hours in refluxing 80% methanol containing two equivalents of sodium cyanide. The yield from IX could be raised to 50% if potassium iodide (20 mg. per 1 g. of IX) was added to the alcoholic solution of sodium cyanide.

2-Methyl-3-hydroxy-4,6-dichloro-5-cyanopyridine.—A solution of 0.5 g. of the amine IX in 20 ml. of hot hydrochloric acid (2 volumes concentrated hydrochloric acid and 1 volume water) was cooled in ice (whereupon it partially crystallized) and treated with 0.23 g. of sodium nitrite in 2 ml. of water, which caused the precipitated amine to dissolve; a sample of the resulting yellow solution coupled with an alkaline solution of β-naphthol. Decomposition of the diazonium salt, with the evolution of gas, could only be effected by adding this solution to 20 ml. of cupric sulfate solution (one part of sulfate in 2 parts of water) at the boiling point. When the resulting solution was diluted with 20 ml. of water and cooled in ice, a crystalline solid separated which was collected and recrystallized from methanol. The yield was 0.22 g. (44%) of 2-methyl-3-hydroxy-4,6-dichloro-3-cyanopyridine, m. p. 287–289° dec. This compound did not dissolve in 10% aqueous sodium hydroxide.

Anal. Calcd. for $C_7H_4Cl_2N_2O$: C, 41.39; H, 1.99; Cl, 34.94; N, 13.80. Found: C, 41.52; H, 2.01; Cl, 34.95; N, 14.01.

2-Methyl-3,6-dichloro-5-cyanopyridine (VIII).—A solution of 0.9 g. of the amine X in 30 ml. of 1:1 hydrochloric acid was cooled to 0–3° and treated with a solution of 0.45 g. of sodium nitrite in 3 ml. of water. After fifteen minutes a solution of 0.5 g. of urea in 2 ml. of water was added and the diazo solution then poured into 60 ml. of a boiling saturated solution of cupric sulfate. A vigorous evolution of gas occurred and a crystalline precipitate formed. The solution was cooled in ice, the precipitate filtered off and recrystallized from 50% methanol. The yield of VIII, m. p. 103–104°, was 0.3 g. (27%).

Anal. Calcd. for $C_7H_4Cl_2N_2$: C, 44.93; H, 2.16; Cl, 37.93; N, 14.98. Found: C, 44.94; H, 2.07; Cl, 37.89; N, 14.94.

A sample of VIII depressed the melting point of the isomeric 2-methyl-4,6-dichloro-5-cyanopyridine,[12] m. p. 100–101°, approximately 25°.

After the preceding experiment was completed, it was found later that VIII is very volatile with steam; consequently it is quite likely that the yield obtained in the above experiment would have been greater if the following procedure, used with the diazonium sulfate, had been employed. One gram of the amine X was placed in a wide test-tube and covered with 4 ml. of cold concentrated sulfuric acid. To this ice cold suspension was added a solution of 0.5 g. of sodium nitrite in 3 ml. of concentrated sulfuric acid. The reaction mixture was kept in ice and shaken until solution was attained, which took about one hour. A coupling test with alkaline β-naphthol produced an abundant red precipitate. Ice was added to the diazo solution to make the final volume about 20 ml. and then 0.1 g. of urea was added. The resulting solution then was added to 60 ml. of boiling saturated cupric sulfate solution, contained in a flask arranged for steam distillation. During the addition of the diazo solution steam was passed through the cupric sulfate solution. White crystals of VIII immediately appeared in the condenser. They were collected and dried: the yield amounted to 0.12 g.

(12) Späth and Koller, *Ber.*, **58**, 2124 (1925).

2-Methyl-3-amino-5-aminomethylpyridine Dihydrochloride (XIII).—To 2 g. of X in 150 ml. of hot absolute alcohol were added: (a) 200 mg. of palladium chloride in 1 ml. of concentrated hydrochloric acid, (b) 10 ml. of alcoholic hydrochloric acid (15% hydrogen chloride in absolute alcohol), and (c) 3 g. of Norit. This mixture was shaken with hydrogen at room temperature and 30 pounds pressure. After two hours the hydrogenation was discontinued and an additional 200 mg. of palladium chloride in 1 ml. of concentrated hydrochloric acid added. After an additional five hours, the absorption of hydrogen had practically stopped. The precipitated hydrochloride was collected, together with the catalyst, and washed with absolute alcohol. Then 30 ml. of water was passed through the filter to dissolve the salt. The aqueous filtrate was concentrated until the first crystals appeared, then diluted with 50 ml. of absolute alcohol, cooled and filtered. The yield of XIII averaged 85% of the theoretical for approximately fifty such reductions. A sample purified by dissolving the reduction product in a minimum of concentrated hydrochloric acid and pouring this solution into an excess of absolute alcohol, melted at 295–297° dec.

Anal. Calcd. for $C_7H_{13}Cl_2N_3$: C, 39.99; H, 6.24; Cl, 33.76; N, 20.01. Found: C, 39.61; H, 6.18; Cl, 33.30; N, 20.03.

This salt (XIII) was obtained in similar yields when the above hydrogenation procedure was applied to the dichloropyridine IX.

The amine XIII was converted to its dibenzoyl derivative by shaking it with a 1.5 fold excess of benzoyl chloride in the presence of aqueous sodium bicarbonate solution. The 2-methyl-3-benzoylamino-5-benzoylaminomethylpyridine, after several recrystallizations from an alcohol-water mixture, melted at 204–205°.

Anal. Calcd. for $C_{21}H_{19}N_3O_2$: C, 73.02; H, 5.56; N, 12.16. Found: C, 73.25; H, 5.54; N, 12.29.

2-Methyl-3-hydroxy-5-aminomethylpyridine Dihydrochloride (XI).—A solution of 2.5 g. (0.12 mole) of the dihydrochloride (XIII) in 15 ml. of water and 10 ml. of 2 *N* hydrochloric acid was treated at 0–3° with a solution of 1.7 g. (0.25 mole) of sodium nitrite in 5 ml. of water. The resulting faint yellow solution was slowly added to 25 ml. of 2 *N* hydrochloric acid at the boiling point. When the gas evolution ceased the solution was concentrated almost to dryness under reduced pressure and the residue extracted 3 times with 15-ml. portions of hot absolute alcohol. Evaporation of the alcoholic extract under diminished pressure produced an oil which was dissolved in 20 ml. of absolute alcohol and again filtered in order to separate a small amount of sodium chloride present. After removal of the alcohol, the remaining oil was kept overnight in a desiccator over sulfuric acid when it partially crystallized. Digestion with acetone, filtration and evaporation produced 1.3 g. of a hygroscopic product, which was purified by dissolving in hot alcohol containing some charcoal and then filtering the resulting alcoholic solution into hot dioxane and allowing the salt to crystallize. The hydrochloride (XI) so obtained was not so hygroscopic and melted at 268–270° dec.; yield, 0.64 g. (31%).

An aqueous solution of XI gives a deep red coloration when treated with ferric chloride solution.

Anal. Calcd. for $C_7H_{12}Cl_2N_2O$: C, 39.82; H, 5.73; Cl, 33.59; N, 13.27. Found: C, 39.52; H, 5.74; Cl, 33.25; N, 12.78.

2-Methyl-3-benzoyloxy-5-benzoylmethylaminopyridine (XIV).—A mixture of 0.50 g. of the dihydrochloride XI, 1.5 equivalents of benzoyl chloride and 20 ml. of a 10% solution of sodium bicarbonate was shaken until the odor of the benzoyl chloride disappeared. The solid (XIV), which separated as fine white needles, was filtered off and recrystallized from dilute alcohol; it weighed 0.55 g. (61%) and melted at 141–142°.

Anal. Calcd. for $C_{21}H_{18}N_2O_3$: C, 72.81; H, 5.23; N, 8.09. Found: C, 72.55; H, 4.98; N, 8.34.

2-Methyl-3-hydroxy-5-benzoylaminomethylpyridine (XVII).—A suspension of 0.42 g. of XIV in 25 ml. of 0.12 *N* sodium hydroxide was boiled until solution was obtained (*ca.* half an hour). After cooling, the alkaline solution was acidified with dilute hydrochloric acid and then treated with an excess of solid sodium bicarbonate. A flocculent precipitate of XVII separated. After filtering and drying, it weighed 0.24 g. (81%) and melted at 242–243°. This compound, in dilute alcohol solution, gave a deep red color with ferric chloride solution.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83. Found: C, 68.98; H, 5.16.

2-Methyl-3-hydroxy-5-hydroxymethylpyridine Hydrochloride (XVI).—To a hot (90–95°) solution of 2.1 g. (0.01 mole) of XIII and 40 ml. of concentrated hydrochloric acid in 90 ml. of water was added a solution of 4.4 g. (0.06 mole) of sodium nitrite in 10 ml. of water. The solution was kept at 95° until the evolution of gas ceased. Then the water was removed under diminished pressure and the remaining crystalline solid extracted three times with 20-ml. portions of boiling absolute alcohol. The alcohol solution, after filtration, was concentrated to about 5 ml. and treated with dioxane to precipitate a white fluffy solid. This material was somewhat tacky, but after one recrystallization from alcohol–dioxane, 0.8 g. (46%) of the hydrochloride (XVI), m. p. 162–165°, was obtained.

This product did not give the correct analytical results so it was converted to the diacetate by refluxing for an hour with acetyl chloride. After evaporation to dryness the remaining crystalline solid was recrystallized from an alcohol–ether mixture. The 2-methyl-3-acetoxy-5-acetoxymethylpyridine hydrochloride so obtained melted at 125–126°.

Anal. Calcd. for $C_{11}H_{14}ClNO_4$: N, 5.40. Found: N, 5.62.

This diacetate was saponified by refluxing for an hour with 0.1 *N* sodium hydroxide. After acidification with dilute hydrochloric acid and evaporation to dryness, the crystalline residue was extracted with absolute alcohol. Concentration of the alcoholic solution and the addition of ether caused the 2-methyl-3-hydroxy-5-hydroxymethylpyridine hydrochloride (XVI) to crystallize. This product melted at 168–170° and gave the characteristic red color with ferric chloride.

Anal. Calcd. for $C_7H_{10}ClNO_2$: C, 47.87; H, 5.74; N, 7.98. Found: C, 47.56; H, 5.74; N, 8.18.

The free base was prepared from the hydrochloride XVI by dissolving 2 g. of the latter compound and 0.97 g. of sodium bicarbonate in 10 ml. of water and evaporating this solution to dryness. The solid residue was extracted with three 15-ml. portions of boiling absolute alcohol. After filtration, the alcoholic solution was evaporated to dryness and the residue (1.4 g., m. p. 165–170°) was sublimed under 0.2 mm. pressure and at 180–190°; 1 g. (63%) of glistening white prisms of 2-methyl-3-hydroxy-5-hydroxymethylpyridine, m. p. 173–174°, was obtained; recrystallization of this product from ethyl acetate gave an analytical sample, m. p. 174–175°.

Anal. Calcd. for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.80; H, 6.77; N, 10.31.

The following unsuccessful attempts were made to introduce a 4-CH_2OH into XVI: (a) 0.1 g. of the hydrochloride (XVI) in 2 ml. of water containing sodium hydroxide just sufficient to form the sodium salt of the free base and 1 ml. of 40% formalin were heated at temperatures from 25–200° for six to twenty-four hours. After cooling and acidification with hydrochloric acid, evaporation of the solvent and extraction of the residue with alcohol returned 60–100% of the original hydrochloride (XVI) in each case; (b) a similar experiment at 250° gave a 20% recovery of XVI with the remainder as an uncrystallizable oil; (c) 0.1 g. of the free base from XVI was heated with 1 g. of trioxane in a sealed tube at 100° for twelve hours after which 70% of the hydrochloride (XVI) was recovered; (d) repetition of (a) with a two-fold excess of diethylamine present in the reaction mixture at 100° produced no reaction with XVI.

Similarly, after a mixture of 0.1 g. of the hydrochloride of XV, 10 ml. of 50% alcohol, 1 g. of sodium hydroxide and 3 ml. of chloroform was refluxed for three hours, 70% of the original hydrochloride could be recovered.

Summary

The preparations, properties and inter-relationships of some tri-, tetra- and pentasubstituted pyridine derivatives are described.

4-Deshydroxymethylpyridoxin has been prepared and is shown to be singularly unreactive toward substitution in the 4-position.

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[CONTRIBUTION FROM THE UNIVERSITY OF CALIFORNIA, CITRUS EXPERIMENT STATION]

Mechanisms of Insecticidal Action. I. Dithienyltrichloroethanes

BY ROBERT L. METCALF AND FRANCIS A. GUNTHER

The pharmacological effects of the replacement of phenyl groups by thienyl groups in biologically active molecules have been studied by numerous investigators.[1] As might be predicted from certain similarities in the physical properties of thiophene and benzene, and the close approximation in molecular size of the two groups,[2] thienyl isosters have, in some cases, inhibited normal biological processes and in others have retained at least a portion of the activity of the parent compound.

It was therefore of interest in connection with our studies of the mode of action of DDT to prepare certain dithienyltrichloroethanes and to compare their insecticidal activities with those of the corresponding DDT derivatives. Insecticidal evaluations were performed with two laboratory test insects, the greenhouse thrips, *Heliothrips haemorrhoidalis* (Bouché), and the fly, *Drosophila melanogaster* Meig.

Results and Discussion

Dithienyltrichloroethane has been described by Peter[3] and by Prill, *et al.*,[4] who found it insecticidally inactive against the housefly.

Because of the possible significance of alkaline dehydrohalogenation in the mode of toxic action of compounds of the DDT type,[5] the molar per cent. dehydrohalogenation of the compounds described in this paper was measured by the method of Müller.[5]

As is indicated in Table I, none of the thienyltrichloroethanes showed any appreciable insecticidal activity to the two test insects. Supplementary tests with compounds II, IV and VI applied externally to the german cockroach, *Blatella germanica* (L.), and in the food of the confused flour beetle, *Tribolium confusum* Duv., also failed to give any appreciable indication of insecticidal activity, but compound II appeared to be slightly toxic to the honey bee *Apis mellifera* L. The data obtained on molar per cent. dehydrohalogenation agree well with that of Müller[5] for compounds I, III, V and VII. The corresponding thienyl isosters are fully as responsive to alkaline dehydrohalogenation, and it therefore seems improbable that failure of this mechanism is responsible for the non-activity of compounds II, IV, VI, VIII and IX. It was hoped that the properties of compounds VIII and IX would yield information as to whether 2-substituted-thienyl- or 3-substituted-thienyl-trichloroethane was more similar spatially to *p,p'*-DDT and its analogs: but the results were inconclusive.

TABLE I

AROMATIC AND PSEUDOAROMATIC DISUBSTITUTED TRICHLOROETHANES

$(R)_2CHCCl_3$

Compound	R =	M. p., °C.	Mole % HCl released in 1 *N* KOH	Approximate relative toxicity[a] at LD_{50} to *D. melanogaster*	Approximate relative toxicity[a] at LD_{50} to *H. haemorroidalis*
I	*p*-ClC_6H_4—	109–110	1.06	1	1
II	5-ClC_4H_2S—	65–66	0.99	>1000	100
III	*p*-BrC_6H_4—	136–137	1.10	1000	5
IV	5-BrC_4H_2S—	94.0–94.7	1.07	>1000	>100
V	C_6H_5—	64–65	0.54	1000	100
VI	C_4H_3S—2—	78.4–79.2	1.08	>1000	100
VII	*p*-$CH_3C_6H_4$—	86–87	0.22	10	3
VIII	5-$CH_3C_4H_2S$—	70–71	1.06	>1000	>100
IX	4-$CH_3C_4H_2S$—	124–125	0.59	>1000	>100

[a] Figures represent the relative amounts of materials necessary to give equivalent mortalities when *p,p'*-DDT = 1.

The failure of compounds II, IV, VIII and IX to give the indophenin reaction indicates that either the 2-5 or the 2-3 positions are blocked in all these compounds.[6] Steric considerations, however, make it seem probable that the 2,5 positions are the ones actually filled. That the condensation takes place in the 2- position was indicated by the alkaline dehydrohalogenation of the parent compound 2,2-bis-(thienyl-2)-1,1,1-trichloroethane (VI) to the corresponding ethylene, followed by oxidation to the known ketone 2,2'-

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