Synthesis of 1,4-Dioxino[2,3-*b*:5,6-*b*']dipyridine

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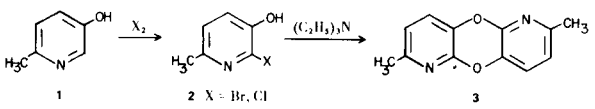
The halogenation of 2-methyl-5-hydroxypyridine (**1**) (1) by bromine or iodine in pyridine solution is reported to yield the 2-bromo- and 2-iodopyridines (**2**, X = Br, I), respectively (2). The preparation of the analogous 2-chloro compound (**2**, X = Cl), however, has not been mentioned. It could be obtained by chlorination of a solution of **1** in concentrated hydrochloric acid with chlorine. The 2-bromo compound was prepared by an analogous procedure using bromine in hydrobromic acid and proved to be identical with a specimen obtained in the above mentioned reaction with pyridine as solvent.

The nmr spectrum of **2** (X = Cl) correlated with the known data (2) for the 2-bromo- and 2-iodopyridines (**2**-iodopyridines (**2**, X = Br, I).

Nucleophilic substitutions of the bromo- and iodo compounds have been the subject of several publications (3). This note reports the unexpectedly different course which resulted in the attempt to replace the halogen substituents of compounds **2** (X = Br, Cl) by an amino or by an hydroxyl group.

Heating a suspension of **2** (X = Cl) in a mixture of equal parts of water and a tertiary amine such as triethyl- or tributylamine in an autoclave to 160° furnished the dioxinodipyridine derivative **3** in 59% yield. The structure of the product was confirmed by its nmr spectrum. The

SCHEME I



formation of **3** occurred also in the presence of 1 *N* sodium hydroxide solution or aqueous ammonia and further by changing the solvent and using either dimethylformamide, ethanol or 1-butanol instead of water, although the yields obtained were always considerably lower (9-18%). There were no by-products formed, only unreacted starting material was recovered. Similarly, the bromo analogue (**2**, X = Br) reacted to yield **3**, but extensive decomposition occurred during the reaction, and the dioxinodipyridine was obtained in only 12% yield.

This method provided an easy access to a dimethyl derivative of the 1,4-dioxino[2,3-*b*:5,6-*b*']dipyridine system, the unsubstituted parent compound (**4**) having been prepared earlier by a rather cumbersome multiple step reaction (4). Thermal decarboxylation of the dicarboxylic acid **12** afforded another alternative for the preparation of this heterocycle. All attempts, however, failed to synthesize **4** starting from the 2-chloro- or from the 2-bromo-3-hydroxypyridine and applying the experimental conditions used above.

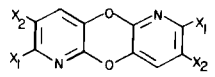
The structural relationship of **3** with the dibenzo-1,4-dioxine led us to prepare some halogenated derivatives of **3** and to compare their toxicity with that of the known 2,3,7,8-tetrachloro-1,4-dibenzodioxine.

The results of the reactions carried out with **3** are compiled in Table I and show the products obtained by halogenating either the pyridine nucleus or the methylsubstituents and their various other transformations.

Nuclear chlorination or bromination of **3** occurred at 25° in dimethylformamide solution. The nmr spectra of the products **5** and **6** showed that ring substitution had occurred in the position ortho to the methyl groups. No other products could be isolated from the reaction mixture. Nitration of **3** followed the same substitution pattern affording **7**.

Selective chlorination of the methyl groups were readily achieved, since known methods could be applied. Chlori-

Table I



	X_1	X_2	Yield (%)
3	CH_3	H	59
4	H	H	69
5	CH_3	Cl	88.3
6	CH_3	Br	42.4
7	CH_3	NO_2	30.6
8	CH_2Cl	H	54.5
9	CCl_3	H	92.8
10	CCl_3	Cl	71.9
11	Cl	Cl	75.4
12	COOH	H	99.5
13	COOH	Cl	52.8

nation of **3** in refluxing chlorobenzene yielded the bis-chloromethyl compound **8** as the only product but under the influence of ultraviolet radiation the bis-trichloromethyl derivative **9** was formed. Chlorination of **5** under the same reaction conditions yielded likewise **10**.

Replacement of the trichloromethyl groups of **5** by chloro substituents could be successfully carried out by chlorinating a solution of **5** in hexachlorobutadiene at 180-185° under ultraviolet radiation, the symmetrical tetrachloro compound **11** being obtained in 75% yield. The chlorolysis of **10** was also carried out either in nitrobenzene or in refluxing p-dichlorobenzene **11** being formed in 32% yield. However, its separation from a large number of by-products proved to be unattractive.

The chlorolysis of the 2,7-bis-trichloromethyl groups of **9** by chlorine failed when carried out under these conditions and starting material was recovered.

The trichloromethyl groups of **9** and **10** were hydrolyzed with water in a solution of 95% sulfuric acid to yield the corresponding dicarboxylic acids **12** and **13**, respectively.

The dicarboxylic acid **12** decarboxylated upon heating and yielded **4** which was found to be identical with the product prepared according to the literature method (4).

The *dosis lethalis* (LD_{50}) of the symmetrical tetrachloro compound **11** is 300 mg./kg. (as tested on rats) and therefore it is by far less toxic than the structural analogue 2,3,7,8-tetrachloro-1,4-dibenzodioxine which has a corresponding value for the *dosis lethalis* of 0.022-0.045 mg./kg. (5).

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded in potassium bromide discs, nmr spectra were recorded at 100 MHZ in deuteriosulfuric acid with hexamethyldisiloxane (HMDS) as external standard, unless otherwise stated.

2-Chloro-3-hydroxy-6-methylpyridine (**2**, X = Cl).

Into a solution of 492 g. (4.5 mole) of 2-methyl-5-hydroxypyridine in 3.7 l. of concentrated hydrochloric acid were introduced 1040 g. (14.67 moles) of chlorine at 70° over a period of 8 hours. The solution was allowed to stand for 24 hours, the solvent was allowed to stand for 24 hours, the solvent was distilled off ***in vacuo*** until a heavy suspension was formed. Filtration and successive washing with acetone yielded 564 g. (69.6%) of the hydrochloric acid salt of **2**, X = Cl; m. p. 205° dec. The crude salt could not be recrystallized without partial dissociation into the free base but it was sufficiently pure to meet the analytical specification.

Anal. Calcd. for $C_6H_7Cl_2NO$: Cl, 39.38. Found: Cl, 39.61.

The hydrochloric acid salt of **2**, X = Cl (564 g., 3.13 moles) was suspended in 1 liter of water and the solution neutralized by addition of powdered sodium bicarbonate. The product was filtered from the solution and washed with water, yielding 416 g. (93%) of almost pure product, m. p. 188-190°. Recrystallization from methanol-water (1:1) yielded white crystals, m. p. 190-191°; nmr (deuteriochloroform): δ = 1.95 (s, CH_3), 5.69 H(5), 5.92 H(4).

Anal. Calcd. for C_6H_6ClNO: C, 50.19; H, 4.21; Cl, 24.69; N, 9.76. Found: C, 49.89; H, 4.15; Cl, 25.09; N, 9.75.

2-Bromo-3-hydroxy-6-methylpyridine (**2**, X = Br).

To a solution of 32.7 g. (0.3 mole) of 2-methyl-5-hydroxypyridine in 250 ml. of concentrated hydrobromic acid was added with stirring 144 g. (0.9 mole) of bromine at 70° over a period of 1 hour. The temperature was maintained and stirring continued for an additional 5 hours. Then nitrogen was passed through the solution for 1 hour and the solution evaporated under vacuum to a volume of about 50 ml. Cooling and filtration yielded 46.7 g. (58.2%) of crystals, which were washed with 150 ml. of acetone, m. p. 225 dec. The HBr-salt of **2**, X = Br could not be recrystallized without decomposing into the free base and hydrogen bromide. Analysis approximately fitted the required data.

Anal. Calcd. for $C_6H_7Br_2NO$: Br, 59.4. Found: Br, 58.6.

The hydrobromic acid salt of **2**, X = Br (26.7 g., 0.099 mole) was dissolved in 500 ml. of boiling water followed by addition of an aqueous solution of 1 *N* sodium bicarbonate to *p*H 8. Filtration of the cold solution yielded 15.8 g. (84.8%) of white crystals, m. p. 191-192° (from water-methanol) (2,3).

2,7-Dimethyl-1,4-dioxino[2,3-*b*:5,6-*b*']dipyridine (**3**).

1) A suspension of 300 g. (2.09 mole) of **2**, X = Cl in a mixture of 700 g. of triethylamine and 700 ml. of water was placed in a 2.5 liter autoclave with an enamel lining and heated to 160° for a period of 86 hours. The crystals formed were filtered form the dark colored solution, suspended in 100 ml. of water, stirred for 1 hour and filtered (132 g., 59%). Twenty-four g. of the crude product was recrystallized from 200 ml. of dimethylformamide and yielded 21 g. of white crystals, m. p. 225-227°; ir cm^{-1} (potassium bromide): 1592, 1449, 1404, 1253, 840, 775, 734; nmr: 8.02 (H 3); 8.64 (H 4) $J_{3,4}$ = 8 Hz; 3.18 (s) CH_3.

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.24; H, 4.81; N, 13.10.

2) The reaction was carried out as described above with 5.6 g. (0.03 mole) of **2**, X = Br, 10 ml. of triethylamine and 10 ml. of water. The mixture was heated to 160° for 24 hours. Isolation of the product yielded 0.4 g. (12.2%) of **3**, m. p. 226-228°. The ir spectrum was superimposable with that of a sample obtained from **2** (X = Cl).

1,4-Dioxino[2,3-*b*:5,6-*b*']dipyridine (**4**).

On heating 9.18 g. (0.03 mole) of **12** above its decomposition point carbon dioxide evolution started. The partially sublimed product was combined with the distillate (4.3 g., 69%) and recrystallized from ethanol, m. p. 174-176°. The ir spectrum of the specimen prepared according to (4) and that of **4** were superimposable.

2,7-Dimethyl-3,8-dichloro-1,4-dioxino[2,3-*b*:5,6-*b*']dipyridine (**5**).

Into a solution of 42.8 g. (0.2 mole) of **3** in 5 l. of dimethylformamide were introduced 150 g. (2.11 mole) of chlorine at 25° over a period of 30 minutes. The yellow suspension was allowed to stand for 5 hours at room temperature, then the crystalline precipitate was filtered and washed with ether to yield 50.6-51.8 g. (88.3-91.6%). For recrystallization 1 g. of the product was dissolved in 25 ml. of boiling dimethylformamide and 0.95 g. were recovered on cooling, m.p. 284-286°; ir cm^{-1}: 3021, 1575, 1429, 1330, 1248, 1016, 991, 893, 799, 726; nmr: δ = 3.25 (s, CH_3); 8.79 (s, H(4)).

Anal. Calcd. for $C_{12}H_8Cl_2N_2O_2$: C, 50.90; H, 2.85; Cl, 25.05; N, 9.90. Found: C, 51.13; H, 2.76; Cl, 24.79; N, 10.03.

2,7-Dimethyl-3,8-dibromo-1,4-dioxino[2,3-*b*:5,6-*b'*]dipyridine (**6**).

To a solution of 21.4 g. (0.1 mole) of **3** in 3 l. of dimethylformamide 160 g. (1 mole) of bromine was added and the resulting solution allowed to stand for 24 hours. Crystals (15.8 g., 42.4%) were filtered from the cold solution and recrystallized form dimethylformamide, m. p. 306°; ir cm^{-1} (potassium bromide): 1565, 1428, 1325, 1245, 883; nmr: δ = 2.65 (s, CH_3); 7.25 (s, H(4)).

Anal. Calcd. for $C_{12}H_8Br_2N_2O_2$: C, 38.74; H, 2.17; Br, 42.96; N, 7.53. Found: C, 39.02; H, 2.21; Br, 42.76; N, 7.61.

2,7-Dimethyl-3,8-dinitro-1,4-dioxino-2,3-*b*:5,6-*b'*]dipyridine (**7**).

To a mixture of 50 ml. of glacial acetic acid and 100 ml. of nitric acid (100%, d = 1.52) 21.4 g. (0.1 mole) of **3** were added at 25-30° over a period of 8 minutes with external cooling. Heating was continued at 60° for 24 hours. The cold solution was swept with nitrogen for 10 minutes and stored for 15 hours at 0°. Crystals precipitated which were filtered and washed with water to give 9.3 g. (30.6%), m. p. 288-290° (from acetonitrile); ir cm^{-1}: 1587, 1529, 1428, 1333, 797; nmr: δ = 9.26 (s, H(4)); 3.43 (s, CH_3).

Anal. Calcd. for $C_{12}H_8N_4O_6$: C, 47.37; H, 2.65; N, 18.42. Found: C, 47.09; H, 2.62; N, 18.38.

2,7-Bis(chloromethyl)-1,4-dioxino[2,3-*b*:5,6-*b'*]dipyridine (**8**).

Chlorine (250 g., 3.52 moles) was passed into a stirred, refluxing solution of 26.7 g. (0.125 mole) of **3** in 450 ml. of chlorobenzene over a period of 4.5 hours. Then nitrogen was passed through the solution for 10 minutes. Filtration of the cold solution yielded crystals (19.3 g., 54.5%) which were washed with a few ml. of chlorobenzene and ether. Recrystallization from dimethylformamide gave white crystals (15 g.), m. p. 239-241°; ir cm^{-1}: 3030, 1592, 1466, 838, 787, 714; nmr: δ = 4.39 (CH_2); 6.50 H(5); 7.24 H(4).

Anal. Calcd. for $C_{12}H_8Cl_2N_2O_2$: C, 50.90; H, 2.85; Cl, 25.05; N, 9.90. Found: C, 50.86; H, 2.86; Cl, 25.15; N, 10.01.

2,7-Bis(trichloromethyl-1,4-dioxino[2,3-*b*:5,6-*b'*]dipyridine (**9**).

A solution of 26.7 g. (0.125 mole) of **3** in 250 ml. of hexachlorobutadiene was irradiated with an ultraviolet source and maintained at a temperature of 185-195° while chlorine (150 g., g., 2.11 mole) was introduced over a period of 2 hours. The solution was then cooled to 20°, the product filtered and washed with carbon tetrachloride, 48.9 g. (92.8%). Recrystallization from benzene yielded white crystals, m. p. 272-273°; ir cm^{-1}: 1579, 1449, 1626, 801, 774, 735; nmr: δ = 7.62-7.86, AB-system, J = 8.

Anal. Calcd. for $C_{12}H_4Cl_6N_2O_2$: C, 34.24; H, 0.95; Cl, 50.54; N, 6.66. Found: C, 34.18; H, 1.01; Cl, 50.32; N, 6.65.

2,7-Bis(trichloromethyl)-3,8-dichloro-1,4-dioxino[2,3-*b*:5,6-*b'*]-dipyridine (**10**).

A solution of 28.3 g. (0.1 mole) of **5** in 500 ml. of chlorobenzene was irradiated with an ultraviolet lamp and maintained at reflux temperature while chlorine (150 g., 2.11 moles) was introduced over a period of 2.5 hours. After adding 100 ml. of pentane the crystals were filtered from the solution and discarded. The filtrate was evaporated to dryness, 500 ml. of pentane added to the remaining oil, and the crude crystalline product (35.2 g., 71.9%) was filtered after standing for 5 hours, m. p. 170-190°. Recrystallization from methanol yielded white crystals (26 g., 53.1%), m. p. 199-202°; ir cm^{-1}: 1550, 1429, 1310, 1269, 836, 813, 784, 724.

Anal. Calcd. for $C_{12}H_2Cl_8N_2O_2$: C, 29.42; H, 0.41; Cl, 57.91; N, 5.72. Found: C, 29.61; H, 0.58; Cl, 57.38; N, 5.88.

2,3,7,8-Tetrachloro-1,4-dioxino[2,3-*b*:5,6-*b'*]dipyridine (**11**).

1) A suspension of 14.1 g. (0.05 mole) of **5** in 100 ml. of hexachlorobutadiene was irradiated with an ultraviolet source and chlorine introduced at an initial temperature of 80°. The temperature rose to 140° over a period of 5 minutes and after 10 minutes had reached 180-185°. Carbon tetrachloride was distilled off during the rise in temperature. After 2 hours a total of 200 g. of chlorine had been introduced. The product (12.4 g., 75.4%) was filtered from the cold solution and recrystallized from chlorobenzene, m. p. 303-304° (white crystals) 3 g. were dissolved in 65 ml. of boiling chlorobenzene and 2.5 g. were recovered on cooling; ir cm^{-1}: 1555, 1416, 1379, 1248, 1205, 1147, 903, 894.

Anal. Calcd. for $C_{10}H_2Cl_4N_2O_2$: C, 37.07; H, 0.62; Cl, 43.78; N, 8.65. Found: C, 37.25; H, 0.71; Cl, 43.59; N, 8.64.

2) A suspension of 3.5 g. (0.002 mole) of **10** in 30 ml. of *o*-dichlorobenzene was irradiated with an ultraviolet light source and heated to reflux. Chlorine was passed through the solution for a period of 3 hours. Filtration of the cold solution gave 9.3 g. of crystals, from which 8.1 g. of hexachlorobenzene was sublimed off at 140°/0.5 torr, and the residue (0.75 g., 32.6%) recrystallized from chlorobenzene, m. p. 306. The ir spectrum was found to be superimposable with that of the product obtained under 1).

1,4-Dioxino[2,3-*b*:5,6-*b'*]dipyridine-2,7-dicarboxylic Acid (**12**).

A stirred suspension of 84 g. (0.2 mole) of **9** in 500 g. of concentrated sulfuric acid was heated to 100° (bath temperature) for a period of 30 minutes and then 60 ml. of water was added dropwise over the same period of time. Stirring was continued for an additional 10 minutes followed by the dropwise addition of 500 ml. of water at 100-120°. The suspension formed was cooled to room temperature, filtered through a glass fritted funnel and washed with water, 54.6 g. (99.5%), m. p. slow dec. above 310°. Small samples can be recrystallized from a large volume of dimethylformamide.

Anal. Calcd. for $C_{12}H_6N_2O_6$: C, 52.56; H, 2.20; N, 10.22. Found: C, 52.41; H, 2.45; N, 10.24.

3,8-Dichloro-1,4-dioxino[2,3-*b*:5,6-*b'*]dipyridine-2,7-dicarboxylic Acid (**13**).

A stirred suspension of 9.8 g. (0.02 mole) of **10** in 60 g. of concentrated sulfuric acid was heated to 100° (bath temperature). When the evolution of hydrogen chloride had ceased (after about 20 minutes), 10 ml. of sulfuric acid was added and heating continued for an additional 30 minutes. The suspension was poured onto ice, filtered over a glass fritted funnel and washed with water. The crude product (7.5 g.) was dissolved in 50 ml. of 1 *N* aqueous sodium hydroxide and filtered from the undissolved residue. The hot filtrate was acidified with concentrated hydrochloric acid, and the resulting crystals filtered and washed with water to yield 3.6 g. (52.8%). The acid meets analytical specifications without further purification, however, small samples could be recrystallized from a large volume of water, m. p. 266° dec., ir cm^{-1}: 1709 (COOH).

Anal. Calcd. for $C_{12}H_4Cl_2N_6O_6$: C, 42.00; H, 1.17; Cl, 20.67; N, 8.16. Found: C, 42.31; H, 1.25; Cl, 20.48; N, 8.14.

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