SOME REACTIONS OF DIETHYL 2,3,5,6-TETRACHLOROPYRIDIN-4-YLMALONATE

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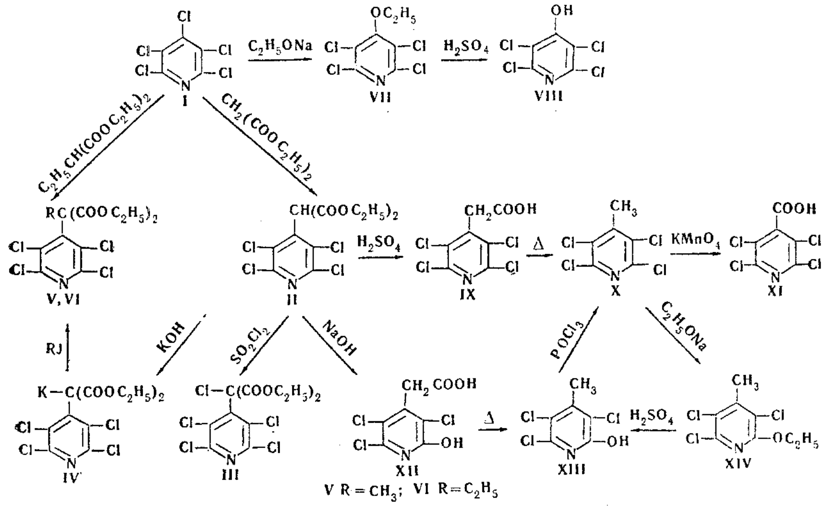
The acid and alkaline hydrolysis of diethyl 2,3,5,6-tetrachloropyridin-4-ylmalonate has been studied. A method has been developed for obtaining diethyl (2,3,5,6-tetrachloropyridin-4-yl)alkylmalonates.

Continuing investigations begun previously [1] on the chemistry of pentachloropyridine (I), we have studied some reactions of diethyl 2,3,5,6-tetrachloropyridin-4-ylmalonate (II) [2] (see scheme).



The reaction of I with the sodium derivative of diethyl ethylmalonate in absolute ethanol gave an 84% yield of 2,3,5,6-tetrachloro-4-ethoxypyridine (VII), also synthesized directly from I and sodium ethoxide in absolute ethanol. This direction of the reaction is probably explained by the fact that because of steric hindrance I reacts more readily with sodium ethoxide than with sodiomalonic ester. To prove its structure, VII was saponified with 80% sulfuric acid to give the known [3] 2,3,5,6-tetrachloropyridin-4-ol (VIII).

The hydrolysis of the ester II with 80% sulfuric acid formed 2,3,5,6-tetrachloropyridin-4-ylacetic acid (IX). Its pK_a value was found by the potentiometric titration of a 0.001 M aqueous solution at 25°C, $pK_a = 3.23$. The induction parameter of the tetrachloropyridinyl residue calculated from Taft's equation is 2.31.

When II was subjected to alkaline hydrolysis, in addition the saponification of the ethoxycarbonyl group, the chlorine atom in position 2 was replaced by a hydroxy group with the formation of 3,5,6-trichloro-

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2-hydroxypyridin-4-ylacetic acid (XII), the esterification of which in methanol or ethanol in the presence of sulfuric acid gave the corresponding esters, while its decarboxylation led to 3,5,6-trichloro-2-hydroxy-4-methylpyridine (XIII). On being heated with $POCl_3$ in a sealed tube at 190°C, the latter was converted into the 4-methyltetrachloropyridine X. The action of sodium ethoxide on X in ethanol formed 3,5,6-trichloro-2-ethoxy-4-methylpyridine (XIV), the saponification of which 80% sulfuric acid gave XIII.

EXPERIMENTAL

Potassium Derivative of Diethyl 2,3,5,6-Tetrachloropyridin-4-ylmalonate (IV). With heating, 3.7 g (0.01 mole) of II was dissolved in 100 ml of water containing 0.6 g of potassium hydroxide. After the complete dissolution of II, the water was distilled off in vacuum to dryness, and the residue was dissolved in ether and was precipitated with petroleum ether. Yield 95%, mp 310-312°C. Found, %: Cl 34.18; N 9.33. $C_{12}H_{10}Cl_4KNO_4$. Calculated, %: Cl 33.89; N 9.30.

Diethyl Chloro(2,3,5,6-tetrachloropyridin-4-yl)malonate (III). A sodium of 3.7 g (0.01 mole) of II in 50 ml of chloroform was treated with 1.6 ml of sulfuryl chloride, and the mixture was boiled for 5 h. After cooling, it was treated with a cold aqueous solution of sodium bicarbonate and was then washed with water. The chloroform solution was separated off, dried, filtered, and evaporated. Yield 4 g (97%), mp 134-135°C (from ethanol). Found, %: Cl 42.85; N 3.39. $C_{12}H_{10}Cl_5NO_4$. Calculated, %: Cl 43.34; N 3.41.

Diethyl (2,3,5,6-Tetrachloropyridin-4-yl)ethylmalonate (VI). A. 15 g of anhydrous potassium carbonate and 20.8 g (0.11 mole) of diethyl ethylmalonate were added to 25 g (0.1 mole) of I in 100 ml of dry dimethylformamide and the mixture was heated at 140-150°C with continuous stirring for 3 h, after which it was poured into cold water and the product was extracted with ether. Acidification of the aqueous solution gave 2,3,5,6-tetrachloropyridin-4-ol (VIII). Yield 25%, mp 229-230°C (from aqueous methanol). According to the literature [3], mp 232-233°C. Found, %: Cl 60.63. Calculated for C_5HCl_4NO, %: Cl 60.94. The ethereal solution was dried with sodium sulfate, and the VI was isolated by vacuum distillation. Yield 10 g (24%), bp 140°C (0.06 mm), mp 126-128°C (from aqueous ethanol). Found, %: Cl 34.96; N 3.26. $C_{14}H_{15}Cl_4NO_4$. Calculated, %: Cl 35.23; N 3.40.

B. A solution of 4.1 g (0.01 mole) of IV in 100 ml of dry tetrahydrofuran was treated with 3.1 g (0.02 mole) of ethyl iodide. The mixture was boiled for 7 h, the solvent was distilled off, the residue was diluted with water, and the VI was filtered off. Yield 3.2 g (80%), mp 127-128°C, identified by a mixed melting point.

Diethyl (2,3,5,6-Tetrachloropyridin-4-yl)methylmalonate (V). This was obtained in a similar manner to VI by method B. Yield 50%, mp 134-136°C (from aqueous methanol). Found, %: Cl 36.28; N 3.55. $C_{13}H_{13}Cl_4NO_4$. Calculated, %: Cl 36.50; N 3.60.

2,3,5,6-Tetrachloro-5-ethoxypyridine (VII). A. Five grams (0.02 mole) of I was added to an ethanolic solution of sodium ethoxide (0.5 g of sodium in 40 ml of ethanol) and the mixture was boiled for 1 h; then the ethanol was distilled off in vacuum, water was added to the residue, and, after cooling, the crystals that deposited were filtered off. Yield 3.3 g (60%), mp 58-59°C (from ethanol). Found, %: Cl 54.32; N 5.21. $C_7H_5Cl_4NO$. Calculated, %: Cl 54.40; N 5.36.

B. Diethyl ethylmalonate was slowly added to a solution of 2.3 g (0.1 g-atom) of sodium in 150 ml of absolute ethanol, and then 25 g (0.1 mole) of I was added and the mixture was boiled with stirring for 2 h. The ethanol was distilled off and the residue was treated with water and with ether. The ethereal layer was separated off and dried, the ether was evaporated off, and the residue was distilled in vacuum. Yield 2.2 g (85%), bp 140°C (6 mm); mp 58-59°C. Found, %: Cl 54.27; N 5.18. $C_7H_5Cl_4NO$. Calculated, %: Cl 54.40; N 5.36.

2,3,5,6-Tetrachloropyridin-4-ol (VIII). A mixture of 2.6 g (0.01 mole) of VII and 10 ml of 80% sulfuric acid was heated at 155°C for 4-5 h and was then poured onto ice, and the precipitate was filtered off. Yield 2.3 g (100%), mp 229-230°C (from aqueous methanol). Found, %: Cl 60.53; N 5.96. C_5HCl_4NO. Calculated, %: Cl 60.94; N 6.01.

2,3,5,6-Tetrachloropyridin-4-ylacetic Acid (IX). With continuous stirring, 3.7 g (0.01 mole) of II in 20 ml of 80% sulfuric acid was heated at 140-150°C for 30 min. The reaction mixture was poured onto ice and the resulting crystals were filtered off and dissolved in aqueous sodium carbonate solution and separated from the starting material by filtration. Acidification of the filtrate with dilute hydrochloric acid precipitated the IX. Yield 2.4 g (90%), mp 183-184°C (from water). According to the literature [5], mp 170-180°C. Found, %: Cl 51.80; N 5.26. $C_7H_3Cl_4NO_2$. Calculated, %: Cl 51.63; N 5.09.

Ethyl 2,3,5,6-Tetrachloropyridin-4-ylacetate (XV). A few drops of sulfuric acid (d 1.84) was added to a solution of 2.7 g (0.01 mole) of IX in 50 ml of ethanol, the mixture was boiled for 2 h, the ethanol was eliminated in vacuum, and the residue was treated with ether and with 2% aqueous bicarbonate solution. The ethereal layer was separated off, dried with calcium chloride, and evaporated. Yield 2.7 g (90%), mp 68°C (from aqueous ethanol). Found, %: Cl 46.78; N 4.61. $C_9H_7Cl_4NO_2$. Calculated, %: Cl 46.86; N 4.62.

3,5,6-Trichloro-2-hydroxypyridin-4-ylacetic Acid (XII). 7.5 g (0.02 mole) of II was dissolved in 300 ml of water, containing 4 g (0.1 mole) of NaOH. As the II dissolved with heating, the solution acquired a light yellow color. The mixture was boiled for 6-7 h until it had become decolorized. After cooling, the XII was precipitated by acidification with hydrochloric acid. Yield 4.7 g (92%), mp 227-228°C (from water). Found, %: Cl 41.55; N 5.66. $C_7H_4Cl_3NO_3$. Calculated, %: Cl 41.51; N 5.44.

Methyl 3,5,6-Trichloro-2-hydroxypyridin-4-ylacetate (XVI). A solution of 2.5 g (0.01 mole) of XII in 50 ml of methanol with a few drops of sulfuric acid (d 1.84) was heated for 1-2 h, the methanol was distilled off in vacuum, the mixture was diluted with water, and the ester XVI was filtered off. Yield 2.6 g (95%), mp 190-191°C (benzene + petroleum ether). Found, %: Cl 39.64; N 5.16. $C_8H_6Cl_3NO_3$. Calculated, %: Cl 39.37; N 5.17.

Ethyl 3,5,6-Trichloro-2-hydroxypyridin-4-ylacetate (XVII). This was obtained in a similar manner to XVI. Yield 95%, mp 154-156°C (from heptane). Found, %: Cl 37.38; N 5.31. $C_9H_8Cl_3NO_3$. Calculated, %: Cl 37.43; N 4.92.

3,5,6-Trichloro-2-hydroxy-4-methylpyridine (XIII). A. With constant stirring, 2.5 g (0.01 mole) of XII was heated in an oil bath with the temperature being raised gradually to 240°C over 20 min. Yield 1.9 g (90%), mp 214-215°C (from aqueous ethanol). Found, %: Cl 49.76; N 6.57. $C_6H_4Cl_3NO$. Calculated, %: Cl 50.11; N 6.58.

B. A solution of 2.4 g (0.01 mole) of XIV in 5-7 ml of 80% sulfuric acid was heated at 140-150°C for 20 min. The reaction mixture was poured into ice water, and the crystals that deposited were filtered off. Yield 1.9 g (90%). Identification by mixed melting point.

2,3,5,6-Tetrachloro-4-methylpyridine (X). A. 2.75 g (0.01 mole) of IX was heated in an oil bath at 200°C for 1 h. Yield 2.2 g (95%), mp 89-90°C (from aqueous ethanol). Found, %: Cl 61.29; N 6.42. $C_6H_3Cl_4N$. Calculated, %: Cl 61.47; N 6.06.

B. A mixture of 2.1 g (0.01 mole) of XIII and 15 ml of phosphorus oxychloride was heated in a tube at 180-190°C for 4 h. Then the contents of the tube were transferred to a flask containing crushed ice. The crystals that deposited were filtered off. Yield 2.3 g (100%), mp 90°C (from aqueous ethanol). Identification by mixed melting point.

2,3,5,6-Tetrachloroisonicotinic Acid (XI). Over 3 h, with stirring, 1.5 g of potassium permanganate was added to 1.15 g (0.005 mole) of X in 30 ml of water at 80-90°C. The excess of potassium permanganate was destroyed by the addition of 5 ml of methanol. The hot solution was filtered from the manganese dioxide and evaporated to 1/3 of its original volume. The concentrated solution was acidified with dilute (1:1) hydrochloric acid, giving a precipitate of 0.2 g (15%) of XI, mp 220-222°C (from water). According to the literature [6], mp 224-225°C. Found, %: Cl 54.36; N 5.38. $C_6HCl_4NO_2$. Calculated, %: Cl 54.40; N 5.36.

3,5,6-Trichloro-2-ethoxy-4-methylpyridine (XIV). To a solution 0.23 g (0.01 g-atom) of sodium in 50 ml of absolute ethanol was added 2.3 g (0.01 mole) of X, and the mixture was boiled for 20-30 min. The ethanol was distilled off in vacuum, and the residue was diluted with water. The oil that separated out crystallized on cooling. Yield 2.4 g (100%), mp 48-50°C (from aqueous ethanol). Found, %: Cl 43.93; N 5.83. $C_8H_8Cl_3NO$. Calculated, %: Cl 44.28; N 5.82.

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