CHLORINATION AND OXIDATION OF SOME SULFUR-CONTAINING TETRACHLOROPYRIDINE DERIVATIVES

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In the chlorination of 4-methyl- and 4-chloroformylmethylenethiotetrachloropyridines, the chlorine atom enters the methyl or methylene group. In the case of the 4-(p-chlorobenzyl)-thio derivative, the molecule is cleaved to give tetrachloropyridine-4-sulfenyl chloride. Hydrogen peroxide oxidizes substituted benzyl- and ethoxycarbonylmethylenethiotetrachloropyridines to the corresponding sulfones, while nitric acid gives a mixture of tetrachloropyridinesulfonic acid and the corresponding benzoic acid.

The chlorination of dialkyl and aryl alkyl sulfides usually gives chloro-substituted sulfides [1,2]. However, as with other α- or γ-alkylthio derivatives of nitrogen heterocyclic compounds [4], in the chlorination of 2-methylthiopyridine [3] the alkylthio group is split out to form α- or γ-chloro-substituted heterocycles.

The aim of the present investigation was a study of the chlorination and oxidation of 4-methylthio-2,3,5,6-tetrachloropyridine (IIa) and other sulfides in which a hydrogen atom in the methyl group is replaced by aryl and carboxyl groups. The starting material for the preparation of the indicated compounds was 4-mercapto-2,3,5,6-tetrachloropyridine (I) [5,6], which is converted to the corresponding sulfides (IIa-f, Table 1) on reaction with methyl iodide, benzyl halides, and haloacetic acids. In the chlorination of IIa in refluxing carbon tetrachloride, one hydrogen atom of the methyl group is replaced by chlorine to give 4-chloromethylthio-2,3,5,6-tetrachloropyridine (III). In contrast to the methylthio derivatives, 4-(p-chlorobenzylthio)-2,3,5,6-tetrachloropyridine readily splits out a benzyl residue under the influence of chlorine or sulfuryl chloride, even at room temperature, to give 2,3,5,6-tetrachloropyridine-4-sulfenyl chloride (IV). A difficult-to-separate mixture of chlorination products and starting material is obtained in the case of 2,3,5,6-tetrachloro-4-pyridylthioglycolic acid (IIf). In this connection, IIf was converted, by treatment with thionyl chloride, to 2,3,5,6-tetrachloro-4-pyridylthioglycolic acid chloride (V), which on chlorination for 3 h with gaseous chlorine in thionyl chloride, gives 2,3,5,6-tetrachloropyridylchlorothioglycolic acid chloride (VIII), which is readily hydrolyzed to 2,3,5,6-tetrachloro-4-pyridylchlorothioglycolic acid (IX). Both acid chlorides (V and VIII) are converted by ammonia and aniline to the amides and anilides (VI, VII, X, and XI) of the corresponding thioglycolic acids (IIf and IX).

We investigated the oxidation of sulfides IIb-f with hydrogen peroxide in acetic acid, trifluoroacetic acid, nitric acid, and chromic anhydride in sulfuric and acetic acids. Oxidation with hydrogen peroxide in glacial acetic acid usually leads to the corresponding sulfones. Their structures were confirmed by the presence of characteristic absorption bands in the IR spectra at 1150 and 1325 cm^{-1}, which are characteristic for the symmetrical and asymmetrical vibrations of the SO_2 group [7]. However, IIf forms 4-hydroxy-2,3,5,6-tetrachloropyridine (XIII) under the same conditions. The same compound (XIII) was obtained by the action on IIe of 90% hydrogen peroxide in trifluoroacetic acid. The reaction of IIe with chromic anhydride in sulfuric acid at 100° proceeds similarly. A sulfone (XIIe) could be obtained in the reaction of chromic anhydride in acetic acid and 30% hydrogen peroxide in trifluoroacetic acid. The oxidation of sulfides IIb-e with 30% hydrogen peroxide in trifluoroacetic acids gives the corresponding sulfones (XIIb-e) in quantitative yields (Table 2).

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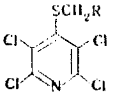
TABLE 1



Comp.	R	mp, °C	Empirical formula	Found, %		Calc., %		Yield, %
				Cl	S	Cl	S	
IIa	H	64—66 [a]	$C_6H_3Cl_4NS$	53,7	—	53,9	—	92,0
IIb	p-$NO_2C_6H_4$	140—142 [b]	$C_{12}H_6Cl_4N_2O_2$	37,2	8,2	37,0	8,3	85,0
IIc	p-ClC_6H_4	78—79 [b]	$C_{12}H_6Cl_5NS$	47,4	8,6	47,4	8,6	97,0
IId	p-$CF_3C_6H_4$	105—106 [b]	$C_{13}H_6Cl_4F_3NS$	35,0	8,2	34,9	7,9	98,0
IIe	$COOC_2H_5$	48—49a	$C_9H_7Cl_4NO_2S$	42,4	9,5	42,4	9,5	98,0

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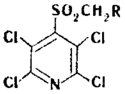
[a] From aqueous ethanol.
[b] From ethanol.

TABLE 2



Comp.	R	mp, °C	Empirical formula	Found, %		Calc., %		Yield, %
				Cl	S	Cl	S	
XIIa	p-$NO_2C_6H_4$	196—197 [a]	$C_{12}H_6Cl_4N_2O_4S$	33,9	8,1	34,1	7,7	92
XIIb	p-ClC_6H_4	181—182 [b]	$C_{12}H_6Cl_5NO_2S$	44,0	—	43,8	—	96
XIIa	p-$CF_3C_6H_4$	148—149 [a]	$C_{13}H_6Cl_4F_3NO_2$	32,2	7,8	32,3	7,3	91
XII a	$COOC_2H_5$	114—116 [a]	$C_9H_7Cl_4NO_4S$	39,3	9,0	38,7	8,7	95

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[a] From heptane.
[b] From methanol.

The oxidation of alkylthiotetrachloropyridines with nitric acid gives sulfoxides [8]. However, in the reaction of nitric acid (sp. gr. 1.42) with the analogous sulfides with benzyl residues (IIb-d), the molecule is cleaved to give 2,3,5,6-tetrachloropyridine-4-sulfonic acid (XIV) and the corresponding benzoic acid. Acid XIV has not been reported, and we therefore attempted to obtain it by oxidation of I with nitric acid. When this was done, about 20% 4-nitro-2,3,5,6-tetrachloropyridine was formed along with XIV. The oxidation of I with 30% hydrogen peroxide in trifluoroacetic acid gave XIV in quantitative yield. The reaction of XIV with PCl_5 gave 2,3,5,6-tetrachloropyridine-4-sulfonyl chloride (XV), which was recently obtained by oxidative chlorination of I [9]. In contrast to pyridine-2- and -4-sulfonyl chlorides, which decompose to 2- or 4-chloropyridines and SO_2 at room temperature, the formation of stable XV is apparently explained by the steric effect of two chlorine atoms, which prevent replacement of the SO_2Cl group by chlorine via an S_Ni mechanism. The action of ammonia in XV gave amide XVI, which gives 2,3,5,6-tetrachloropyridine-4-sulfonic acid N,N-dichloroamide (XVII) on chlorination in alkali.

EXPERIMENTAL

2,3,5,6-Tetrachloro-4-pyridylthioglycolic Acid (IIf). A 2.5-g (0.01 mole) sample of I was dissolved in a solution of 0.4 g (0.01 mole) of NaOH in 100 ml of water, 1.16 g (0.01 mole) of sodium monochloroacetate was added, and the mixture was refluxed for 1 h and acidified to give 3 g (98%) of a product with mp 175-176° (from aqueous ethanol). Found: Cl 46.1; S 10.5%. $C_7H_3Cl_4NO_2S$. Calculated: Cl 42.2; S 10.4%.

Ethyl 2,3,5,6-Tetrachloro-4-pyridylthioglycolate (IIe). A 2.5-g (0.01 mole) sample of I was dissolved in an alcoholic solution of sodium ethoxide (0.23 g-atom of sodium in 25 ml of absolute ethanol), 1.23 g (0.01 mole) of ethyl chloroacetate in 25 ml of absolute ethanol was added, and the mixture was refluxed for 1 h. The ethanol was removed by distillation to give 3.3 g (98%) of product. Compounds IIa-d were similarly obtained (Table 1).

2,3,5,6-Tetrachloro-4-pyridyl Chloromethyl Sulfide (III). A 2.6-g (0.01 mole) sample of IIa was dissolved in 15 ml of dry CCl_4, and dry chlorine was passed through the refluxing mixture for 12 h. The solvent was removed in vacuo to give 2.4 g (93%) of a product with mp 109-111° (from ethanol). Found: Cl 60.1; S 11.1%. $C_6H_2Cl_5NS$. Calculated: Cl 59.7; S 10.8%.

2,3,5,6-Tetrachloropyridine-4-sulfenyl Chloride (IV). A. A 3.7-g (0.01 mole) sample of IIc was dissolved in 50 ml of dry CCl_4, and dry chlorine was passed through the mixture at 20° for 2 h. The solvent was removed in vacuo to dryness to give 2.5 g (88%) of a product with mp 64-65° (from heptane) (mp 64-66° [10]). Found: Cl 62.6%. C_5Cl_5NS. Calculated: Cl 62.7%.

B. A 3.7-g (0.01 mole) sample of IIc was dissolved in 25 ml of sulfuryl chloride, and the mixture was held at room temperature for 12 h. The sulfuryl chloride was removed in vacuo to dryness to give 2.7 g (95%) of a product with mp 65-66° (from heptane).

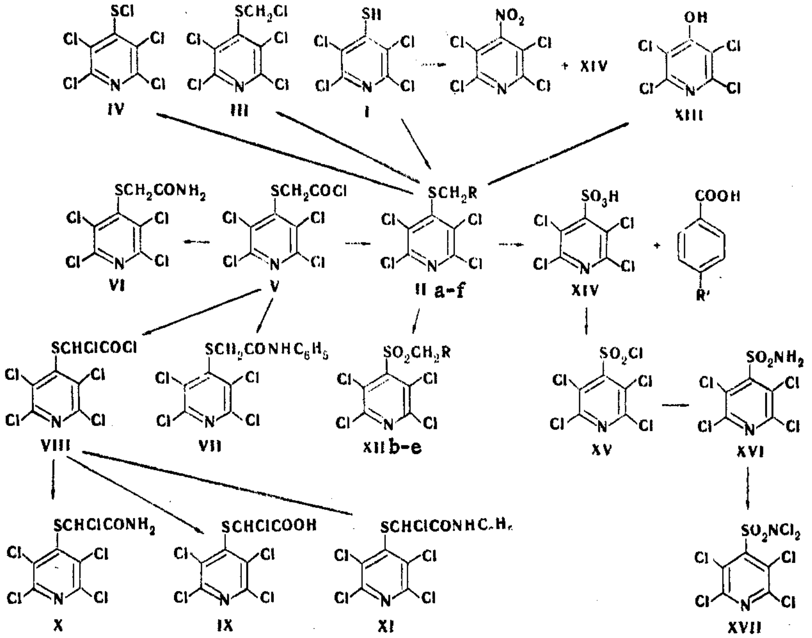
2,3,5,6-Tetrachloro-4-pyridylthioglycolic Acid Chloride (V). A 1.5-g (5 mmole) sample of IIf was dissolved in 10 ml of thionyl chloride, and the mixture was refluxed for 1 h. The thionyl chloride was removed in vacuo to dryness to give 1.5 g (93%) of a product with mp 72-74° (from petroleum ether). Found: Cl 54.2; S 10.1%. $C_7H_2Cl_5NOS$. Calculated: Cl 54.5; S 9.8%.

2,3,5,6-Tetrachloro-4-pyridylthioglycolic Acid Amide (VI). This compound was obtained in 85% yield from V and gaseous ammonia in benzene and had mp 208-209° (from methanol). Found: Cl 46.7%. $C_7H_4Cl_4N_2OS$. Calculated: Cl 46.4%.

2,3,5,6-Tetrachloro-4-pyridylthioglycolic Acid Anilide (VII). This compound was obtained in 80% yield from V and aniline in benzene and had mp 182-183° (from aqueous ethanol). Found: Cl 37.3; S 8.3%. $C_{13}H_8Cl_4N_2OS$. Calculated: Cl 37.2; S 8.4%.

2,3,5,6-Tetrachloro-4-pyridylchlorothioglycolic Acid Chloride (VIII). A 1.5-g (5 mmole) sample of IIf was dissolved in 10 ml of thionyl chloride, and the mixture was refluxed for 1 h. Without isolating V, the mixture was chlorinated with dry chlorine for 3 h at the reflux point. The thionyl chloride was removed in vacuo to give 1.5 g (83%) of a product with bp 149-151° (0.1 mm). Found: Cl 60.0; S 8.6%. C_7HCl_6NOS. Calculated: Cl 59.2; S 8.9%.

2,3,5,6-Tetrachloro-4-pyridylchlorothioglycolic Acid (IX). A 0.9-g (2.5 mmole) sample of VIII was treated with 5 ml of water, and the mixture was allowed to stand at 20° for 2 h. Workup gave 0.7 g (82%) of IX with mp 151-152° (from heptane). Found: Cl 52.4%. $C_7H_2Cl_5NO_2S$. Calculated: Cl 52.0%.



IIa-f R = H, p-$NO_2C_6H_4$, p-ClC_6H_4, p-$CF_3C_6H_4$, $CO_2C_2H_5$, COOH; R' = NO_2, Cl, CF_3

2,3,5,6-Tetrachloro-4-pyridylchlorothioglycolic Acid Amide (X). This compound was obtained in 90% yield from VIII and dry ammonia and had mp 194-196° (from aqueous methanol). Found: Cl 52.0; N 8.3%. $C_7H_3Cl_5N_2OS$. Calculated: Cl 52.1; N 8.2%.

2,3,5,6-Tetrachloro-4-pyridylchlorothioglycolic Acid Anilide (XI). This compound was obtained in 90% yield from VIII and aniline in dry benzene and had mp 186-187° (from methanol). Found: Cl 42.8; N 6.9%. $C_{13}H_7Cl_5N_2OS$. Calculated: Cl 42.6; N 6.7%.

2,3,5,6-Tetrachloro-4-pyridyl p-Nitrobenzyl Sulfone (XIIb). A. A 3.8-g (0.01 mole) sample of IIb was dissolved in 20 ml of trifluoroacetic acid, 5 ml of 30% H_2O_2 was added, and the mixture was heated to 60°, after which the reaction proceeded vigorously without heating. A large portion of the solvent was removed by distillation, and the residue was poured into water. Workup gave 3.8 g (92%) of XIIb. Compounds XIIc-e (Table 2) were similarly obtained.

B. A 3.8-g (0.01 mole) sample of IIb was dissolved in 40 ml of glacial acetic acid, 5 ml of 30% H_2O_2 was added, and the mixture was allowed to stand at 20° for 24 h and was then refluxed for 2 h. The mixture was worked up as in method A to give 2.5 g (61%) of a product with mp 195-196° (from heptane). Found: Cl 34.2%. $C_{12}H_6Cl_4N_2O_4S$. Calculated: Cl 34.1%.

Ethyl 2,3,5,6-Tetrachloro-4-pyridylsulfonyl acetate (XIIe). A 1.5-g (15 mmole) sample of chromic anhydride was dissolved in 10 ml of glacial acetic acid, 1.7 g (5 mmole) of IIe was added, the mixture was stirred at 80° for 1 h, 1.5 ml of water was added, and the resulting mixture was refluxed for 30 min. A portion of the acid was removed by vacuum distillation, and the residue was poured over ice to give 0.9 g (50%) of a product with mp 113-115° (from heptane). Found: S 8.9%. $C_9H_7Cl_4NO_4S$. Calculated: S 8.7%.

4-Hydroxy-2,3,5,6-tetrachloropyridine (XIII). A. A 1.5-g (5 mmole) sample of IIf was dissolved in 40 ml of glacial acetic acid, 3 ml of 30% H_2O_2 was added, and the mixture was held at 20° for 24 h. It was then refluxed for 2 h, a large portion of the solvent was removed by distillation, and the residue was poured over water to give 0.75 g (65%) of a product with mp 228-229° (from heptane) (mp 232-233° [11]). Found: Cl 60.3%. C_5HCl_4NO. Calculated: Cl 60.7%.

B. A 1.7-g (5 mmole) sample of IIe was dissolved in 20 ml of trifluoroacetic acid, and the solution was cooled and treated with 3 ml of 90% H_2O_2. As the temperature increased, an exothermic reaction began, at the end of which a portion of the solvent was removed by vacuum distillation. The residue was poured into water to give 0.5 g (45%) of product.

C. A 1.7-g (5 mmole) sample of IIe was dissolved in 5 ml of concentrated H_2SO_4, and a solution of 1.5 g (15 mmole) of chromic anhydride in 5 ml of water was added dropwise with stirring. The mixture was heated at 100° for 2 h and poured into water to give 0.8 g (73%) of product.

2,3,5,6-Tetrachloropyridine-4-sulfonic Acid (XIV). A. A 2.5-mmole sample of IIb, IIc, or IId was dissolved in 15 ml of nitric acid (sp. gr. 1.42), and the mixture was refluxed for 1.5 h, cooled, and poured into water. The corresponding precipitated benzoic acid was removed by filtration, and the filtrate was evaporated to dryness in vacuo to give 95-98% XIV. Compound XIV was characterized as the o-toluidine salt. A 1.5-g (5 mmole) sample of XIV was dissolved in 50 ml of water containing 0.28 g (5 mmole) of KOH, 0.72 g (5 mmole) of o-toluidine hydrochloride in 10 ml of water was added, and the precipitated toluidine salt of XIV was removed by filtration to give 2 g (100%) of a product with mp > 300° (from water). Found: Cl 35.4; N 6.9%. $C_{12}H_{10}Cl_4N_2O_3S$. Calculated: Cl 35.2; N 6.9%.

B. A 2.5-g (0.01 mole) sample of I was dissolved in 25 ml of nitric acid (sp. gr. 1.42), and the mixture was heated at 75° for 5 h. The mixture was then cooled and poured into water, and the resulting precipitated 4-nitro-2,3,5,6-tetrachloropyridine was removed by filtration to give 0.5 g (20%) of a product with mp 72-73° (from methanol) (mp 70.5° [12]). Found: Cl 54.2; N 10.7%. $C_5Cl_4N_2O_2$. Calculated: Cl 54.2; N 10.7%. Evaporation of the filtrate to dryness gave 80% XIV.

C. A 2.5-g (0.01 mole) sample of I was dissolved in 100 ml of trifluoroacetic acid, and 5 ml of 30% H_2O_2 was added to the cooled solution. The mixture was then heated to 60°, after which the reaction proceeded vigorously without heating. The solvent was removed in vacuo to dryness to give 2.8 g (93%) of XIV.

2,3,5,6-Tetrachloropyridine-4-sulfonic Acid (XV). A 1.5-g (5 mmole) sample of XIV was dissolved in 100 ml of dry benzene, 2.1 g (10 mmole) of PCl_5 was added, and the solution was refluxed for 30 min. It was then cooled, and dry gaseous SO_2 was passed through it. The solvent and liquid reaction products were removed in vacuo to give 0.8 g (50%) of XV with mp 53° (from heptane) (mp 53-54° [9]). Found: Cl 56.5; S 10.1%. $C_5Cl_5NO_2S$. Calculated: Cl 56.3; S 10.2%.

2,3,5,6-Tetrachloropyridine-4-sulfonamide (XVI). This compound was obtained in 90% yield from XV and gaseous ammonia in benzene and had mp 195-196° (from acetone and heptane) (mp 196-197° [9]). Found: Cl 47.9; N 9.5%. $C_5H_2Cl_4N_2O_2S$. Calculated: Cl 47.9; N 9.6%.

2,3,5,6-Tetrachloropyridine-4-sulfonic Acid N,N-Dichloroamide (XVIII). A 0.3-g (1 mmole) sample of XVII was dissolved in 10 ml of aqueous sodium hydroxide (0.8 g of NaOH in 100 ml of water), and gaseous chlorine was passed through the solution for 10 min. The resulting precipitate was removed by filtration, washed with water, and air dried to give 0.35 g (95%) of a product with mp 118-120° (from CCl_4). Found: Cl 57.6; N 7.4%. $C_5Cl_6N_2O_2S$. Calculated: Cl 58.4; N 7.7%.

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