SYNTHESIS AND PROPERTIES OF 4-MERCAPTO-2,3,5,6-TETRABROMOPYRIDINE

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2,3,5,6-Tetrabromopyridines with 4-mercapto, 4-chlorosulfenyl, and 4-chlorosulfonyl groupings were synthesized, and some of their reactions were studied.

In contrast to pentafluoro(chloro)pyridines, pentabromopyridine (I) has not been adequately studied. Reactions only with alkoxides and amines and reactions involving reduction and oxidation are known for it [1, 2]. We have modified [4] the method for the preparation of pentabromopyridine [3], as a result of which it has become accessible.

In order to synthesize 4-mercapto-2,3,5,6-tetrabromopyridine (II) and some other 4-sulfur-containing derivatives we studied the reaction of I with potassium hydrosulfide. The attack by the mercaptide ion in ethanol was directed exclusively to the 4 position to give II. The introduction of a mercapto group in the pyridine ring deactivates the remaining bromine atoms. We were unable to replace the bromine atom in the 2 position by a mercapto group even in dimethylformamide (DMF) at 150°C.

On the basis of the IR spectra (ν_{SH} 2560 cm^{-1}) it may be assumed that II, in contrast to 4-thiopyridone [5], exists in the thiol form in the solid state and in CCl_4.

Compound II is readily acetylated by acetic anhydride to give 2,3,5,6-tetrabromo-4-pyridyl acetyl sulfide (III). 2,3,5,6-Tetrabromo-4-pyridyl methyl, ethyl, and β-hydroxyethyl sulfides (IV-VI), respectively, were obtained by the action of dimethyl sulfate, ethyl bromide, and ethylene chlorohydrin on the sodium salt of mercaptan II. Without prior purification III and IV do not contain isomeric impurities, according to the PMR data (from the presence of only one singlet at 2.94 and 2.87 ppm, respectively).

Since sulfide molecule IV contains two nucleophilic centers — the sulfur and the nitrogen atoms — it seemed of interest to study the oxidation of sulfide IV. The reaction with nitric acid gives 2,3,5,6-tetrabromo-4-pyridyl methyl sulfoxide (VII), and hydrogen peroxide in acetic acid leads to 2,3,5,6-tetrabromo-4-pyridyl methyl sulfone (VIII). An absorption band at 1082 cm^{-1} (SO group) is observed in the IR spectra of product VII, while bands at 1160 and 1340 cm^{-1} (SO_2 group) are observed in the spectrum of VIII. Thus in all cases attack by oxygen is directed at the sulfur atom rather than at the nitrogen atom. The previously described [1] 4-amino-2,3,5,6-tetrabromopyridine (IX) was obtained by the action of ammonia on sulfone VIII.

Bis(2,3,5,6-tetrabromo-4-pyridyl) disulfide (X) was obtained in low yield in the oxidation of mercaptan II with bromine in acetic acid. Disulfide X is obtained in quantitative yield when acetic acid is replaced by aqueous alkali. The action of nitric acid or hydrogen peroxide in acetic acid on II leads to 2,3,5,6-tetrabromopyridine-4-sulfonic acid (XI).

Chlorination of thiol II with chlorine in CCl_4 leads to the formation of the stable 2,3,5,6-tetrabromopyridine-4-sulfenyl chloride (XII). The reaction of the latter with acetone or aniline gave, respectively, 2,3,5,6-tetrabromo-4-pyridylmercaptoacetone (XIII) and 2,3,5,6-tetrabromopyridine-4-sulfenic acid anilide (XIV). We were unable to obtain tetrabromopyridinesulfenic acid esters. The principal product of the reaction of sulfenyl chloride XII with alcohols is disulfide X, the formation of which evidently proceeds via a radical mechanism [6]. Disulfide X is also formed by the action of moisture on sulfenyl chloride XII.

In contrast to tetrachloropyridine-4-sulfenyl chloride [7], the reaction of sulfenyl chloride XII with triethyl phosphite does not lead to the formation of sulfide V but rather gives the product of Arbuzov rearrangement — O,O-diethyl-S-(2,3,5,6-tetrabromo-4-pyridyl)

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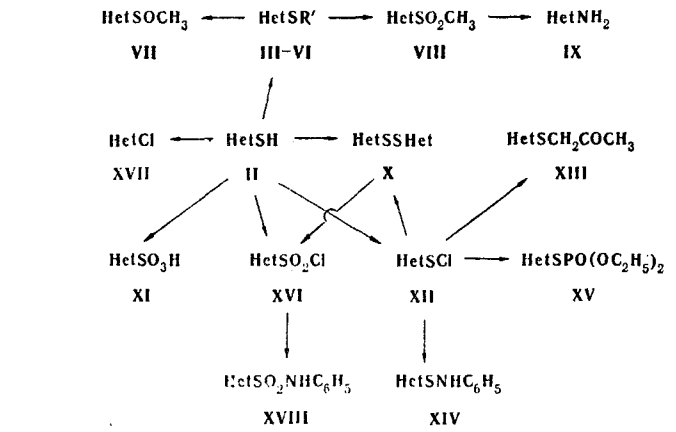
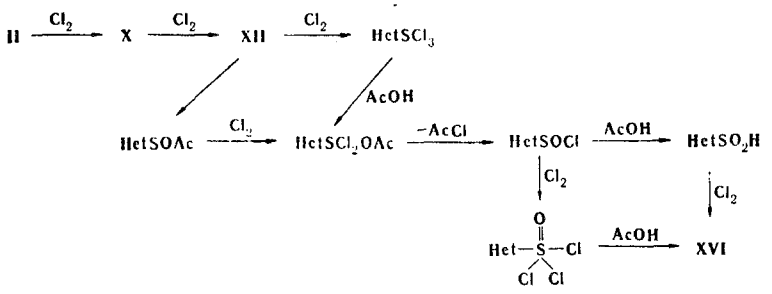
thiophosphate (XV). The S—Cl bond in XII is less polarized than in tetrachloropyridine-4-sulfenyl chloride and, with respect to its degree of polarity, approaches the S—Cl bond in pentachlorobenzenesulfenyl chloride, which also reacts with triethyl phosphite via the scheme of the Arbuzov rearrangement [8]. Phosphate XV was also obtained by reaction of sulfenyl chloride XII with diethyl phosphite.



Het- 2,3,5,6-tetrabromo-4-pyridyl; III $R'=COCH_3$; IV $R'=CH_3$; V $R'=C_2H_5$; VI $R'=(CH_2)_2OH$

The stable 2,3,5,6-tetrabromopyridine-4-sulfonyl chloride (XVI) was obtained by oxidation chlorination of mercaptan II with chlorine in glacial acetic acid, whereas 2,3,5,6-tetrabromo-4-chloropyridine (XVII) is formed in aqueous acetic acid. It is known [9] that conjugated imino chlorides of sulfonic acids with the general formula $-N{=}C[-C{=}C-]_nSO_2Cl$ are unstable compounds and decompose via an S_Ni mechanism with the evolution of sulfur dioxide and the formation of the corresponding chloro derivatives (XVII in this case). The formation of stable sulfonyl chloride XVI is evidently explained not only by the steric effect of the two bromine atoms in the 3 and 5 positions, which hinder replacement of the SO_2Cl group by chlorine, but also by the impossibility of the formation of a positive charge on the nitrogen atom because of drawing away of the electron pair toward the bromine atoms and the SO_2Cl group.

The mechanism of the conversion of II to sulfonyl chloride XVI can be represented by the scheme



The first two steps include oxidation of thiol II by chlorine to disulfide X, Which is subsequently cleaved to sulfenyl chloride XII. In conformation of this we also obtained sulfonyl chloride XVI by the action of chlorine in acetic acid on disulfide X and sulfenyl chloride XII; sulfonyl chloride XVI is formed much more rapidly from X and XII than from II. Two parallel mechanisms are possible for the conversion of sulfenyl chloride XII initially to the sulfenyl chloride [10], which can be subsequently converted to sulfonyl chloride XVI also via two pathways.

2,3,5,6-Tetrabromopyridine-4-sulfonic acid anilide (XVIII) was obtained by the action of aniline on sulfonyl chloride XVI. All of the described transformations give the products in close to quantitative yields.

EXPERIMENTAL

The IR spectra of KBr pellets and solutions of the compounds in CCl_4 were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in $CHCl_3$ were recorded

TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C	Found, %		Empirical formula	Calc., %	
		Br	S		Br	S
II	189—190[a]	75,1	7,5	C_5HBr_4NS	74,9	7,5
III	131—133[b]	68,4	6,9	$C_7H_3Br_4NOS$	68,2	6,8
IV	137—138[a]	72,5	7,5	$C_6H_3Br_4NS$	72,5	7,3
V	116—117[c]	70,1	3,3	$C_7H_5Br_4NS$	70,3	3,1
VI	160—162[c]	67,5	6,8	$C_7H_5Br_4NOS$	67,9	6,8
VII	201—202[b]	69,9	7,1	$C_6H_3Br_4NOS$	70,0	7,0
VIII	192—194[c]	68,0	6,8	$C_6H_3Br_4NO_2S$	67,6	6,8
X	172—173[b]	74,9	7,4	$C_{10}Br_8N_2S_2$	75,1	7,5
XI	223 (dec.)	64,8	6,5	$C_5HBr_4NO_3S \cdot H_2O$	64,9	6,5
XII	101—102[b]			C_5Br_4ClNS[d]		
XIII	109—110[c]	65,5	6,4	$C_8H_5Br_4NOS$	66,2	6,6
XIV	136—138[b]	61,8	—	$C_{11}H_6Br_4N_2S$	61,7	—
XV	131—133[b]	56,8	—	$C_9H_{10}Br_4NO_3PS$[e]	56,8	—
XVI	97—99[b]	4Br+1Cl 72,0	6,6	$C_5Br_4ClNO_2S$	4Br+1Cl 72,0	6,5
XVII	159—161[b]	4Br+1Cl 83,3	—	C_5Br_4ClN	4Br+1Cl 82,7	—
XVIII	159—160[c]	59,0	5,8	$C_{11}H_6Br_4N_2O_2S$	58,1	5,8

a) From propanol. b) From heptane. c) From aqueous ethanol. d) Found: 4Br + 1Cl 77.0; N 3.3%. Calculated: 4Br + 1Cl 77.0; N 3.0%. e) Found: P 5.6%. Calculated: P 5.5%.

at room temperature with a Tesla BS-487B spectrometer (80 MHz) with hexamethyldisiloxane as the external standard. The results of analysis and the melting points of the synthesized compounds are presented in Table 1.

4-Mercapto-2,3,5,6-tetrabromopyridine (II). A 3.6-g (64 mmole) sample of KOH was dissolved in a mixture of 150 ml of ethanol and 5 ml of water, and the solution was saturated with H_2S at −5°C for 30 min. A 15-g (32 mmole) sample of pentabromopyridine was added, and the mixture was heated at 70°C for 2.5 h as the passage of hydrogen sulfide into it was continued. The mixture was then poured into water, and the aqueous mixture was acidified with HCl and worked up to give 13.1 g of II. IR spectrum: 2560 cm^{-1} (SH).

2,3,5,6-Tetrabromo-4-pyridyl Acetyl Sulfide (III). A 2.13-g (5 mmole) of II was refluxed in 20 ml of acetic anhydride for 30 min, after which the solvent was removed by vacuum distillation, and the residue was treated with 2% KOH. The yield was 2.33 g. IR spectrum: 1700 cm^{-1} (C=O). PMR spectrum: 2.94 ppm (s, CH_3).

2,3,5,6-Tetrabromo-4-pyridyl Methyl Sulfide (IV). An 8.52-g (0.02 mole) sample of II and 2.24 g (0.04 mole) of KOH were dissolved in 100 ml of water, and 5.04 g (0.04 mole) of dimethyl sulfate was added dropwise with vigorous stirring at 20°C. The mixture was then allowed to stand for 30 min, after which it was worked up to give 8.47 g of the product. IR spectrum: 1428, 2930, and 3010 cm^{-1} (C—H). PMR spectrum: 2.87 ppm (s, CH_3).

2,3,5,6-Tetrabromo-4-pyridyl Ethyl Sulfide (V). A 0.1-g (0.64 mmole) sample of ethyl bromide was added to a solution of 0.2 g (0.44 mmole) of the sodium salt of II in 10 ml of ethanol, and the mixture was refluxed for 1.5 h. The yield was 0.19 g.

2,3,5,6-Tetrabromo-4-pyridyl β-Hydroxyethyl Sulfide (VI). This compound was similarly obtained from the sodium salt of II and ethylene chlorohydrin.

2,3,5,6-Tetrabromo-4-pyridyl Methyl Sulfoxide (VII). A 0.44-g (1 mmole) sample of sulfide IV was refluxed in 10 ml of nitric acid (sp. gr. 1.42) for 5 min, after which the mixture was poured over ice. The yield was 0.45 g. IR spectrum: 1082 cm^{-1} (S=O).

2,3,5,6-Tetrabromo-4-pyridyl Methyl Sulfone (VIII). A 10-ml sample of 30% H_2O_2 was added dropwise at 20°C to a solution of 4.4 g (0.01 mole) of sulfide IV in 50 ml of acetic acid, and the mixture was refluxed for 3 h. It was then cooled and worked up to give 3.32 g of VII. IR spectrum: 1160, 1340 (SO_2); 2930, 3010 cm^{-1} (C—H).

4-Amino-2,3,5,6-tetrabromopyridine (IX). Dry ammonia gas was passed into a solution of 0.21 g (0.44 mole) of sulfone VII in 10 ml of absolute ethanol at 20°C for 2 h, after which the solvent was removed by vacuum distillation, and the residue was treated with water. The yield of product with mp 236-238°C (dec., from methanol) [mp 237-239°C (dec.) [1]] was 0.18 g (88%).

Bis(2,3,5,6-tetrabromo-4-pyridyl) Disulfide (X). A) Bromine water was added in small portions with stirring to a solution of 4.26 g (0.01 mole) of II and 0.56 g (0.01 mole) of potassium hydroxide in 50 ml of water until the reaction mixture no longer decolorized the bromine. The development of a persistent brown coloration constituted evidence that the reaction was complete. The mixture was then allowed to stand for 2 h. The yield was 4.15 g.

B) A 0.23-g (0.5 mmole) sample of sulfenyl chloride XII was stirred in 10 ml of absolute ethanol at 20°C for 8 h. The yield of disulfide X was 0.21 g.

2,3,5,6-Tetrabromopyridine-4-sulfonic Acid (XI). A) A 5-ml sample of 90% H_2O_2 was added dropwise to a solution of 2.13 g (5 mmole) of II in 25 ml of chloroform and 50 ml of trifluoroacetic acid, and the mixture was maintained at 20°C for 3 h. The yield was 1.7 g. Acid XI was characterized in the form of the benzylthiuronium salt. A 0.5-g (1 mmole) sample of the monohydrate of acid XI was dissolved in 5 ml of water, and 0.27 g (1.1 mmole) of benzylthiuronium bromide was added. Workup gave 0.52 g (83%) of a product with mp 207-208°C (from aqueous methanol). Found: Br 49.2; S 10.0%. $C_{13}H_{11}Br_4N_3O_3S_2$. Calculated: Br 49.9; S 10.0%.

B) A 2-g (4.7 mmole) sample of II was refluxed in 20 ml of nitric acid (sp. gr. 1.42) for 5 h, after which the mixture was cooled and filtered, and the filtrate was vacuum evaporated to half its original volume. The yield was 0.58 g (26%).

2,3,5,6-Tetrabromopyridine-4-sulfenyl Chloride (XII). Dry chlorine was passed at 20°C into a suspension of 2.13 g (5 mmole) of II in 50 ml of dry CCl_4 for 3 h, after which the solvent was removed by vacuum distillation. The yield was 2.28 g.

2,3,5,6-Tetrabromo-4-pyridylthioacetone (XIII). A 0.23-g (0.5 mmole) sample of sulfenyl chloride XII was dissolved in 5 ml of acetone, and the mixture was allowed to stand for 5 min. The solvent was removed by vacuum distillation to give the product (0.24 g). IR spectrum: 1700 cm^{-1} (C=O).

2,3,5,6-Tetrabromopyridine-4-sulfenic Acid Anilide (XIV). A 0.19-g (2 mmole) sample of freshly distilled aniline was added to a solution of 0.46 g (1 mmole) of sulfenyl chloride XII in 10 ml of dry benzene, and the mixture was maintained at 20°C for 1 h. The solvent was then removed by vacuum distillation, and the residue was treated with 1% HCl. The yield was 0.47 g. IR spectrum: 3354 cm^{-1} (NH).

O,O-Diethyl-S-(2,3,5,6-tetrabromo-4-pyridyl) Thiophosphate (XV). A) A solution of 0.67 g (1.45 mmole) of sulfenyl chloride XII in 10 ml of dry benzene was added dropwise at 40°C to a solution of 0.25 g (1.5 mmole) of triethyl phosphite in 10 ml of dry benzene, and the mixture was stirred for 2 h. The solvent was then removed by vacuum distillation. The yield was 0.7 g.

B) A solution of 0.3 g (2.2 mmole) of diethyl phosphite in 5 ml of dry CCl_4 was added dropwise at 0°C to a solution of 0.92 g (2 mmole) of sulfenyl chloride XII, and the mixture was maintained at this temperature for 1.5 h. It was then treated with water and extracted with CCl_4. The extract was dried over calcium chloride and worked up to give 1.05 g (93%) of product.

2,3,5,6-Tetrabromopyridine-4-sulfonyl Chloride (XVI). A) Dry chlorine was passed into a suspension of 2.13 g (5 mmole) of II in 70 ml of glacial acetic acid at 20°C for 7 h, after which the mixture was poured over ice. The yield was 2.36 g. IR spectrum: 1170 and 1390 cm^{-1} (SO_2).

B) This compound was similarly obtained in quantitative yield from disulfide X after 4.5 h.

C) This compound was similarly obtained in quantitative yield from sulfenyl chloride XII after 2.5 h.

2,3,5,6-Tetrabromo-4-chloropyridine (XVII). Chlorine was passed into a suspension of 0.5 g (1.17 mmole) of II in 40 ml of 98% acetic acid at 20°C for 3 h, after which the mixture was poured over ice. The yield was 0.45 g.

2,3,5,6-Tetrabromopyridine-4-sulfonic Acid Anilide (XVIII). A 0.17-g (1.8 mmole) sample of aniline was added to a solution of 0.3 g (0.6 mmole) of sulfonyl chloride XVI in 10 ml of dry benzene, and the mixture was maintained at 20°C for 24 h. The solvent was then removed

by vacuum distillation, and the residue was washed with 1% HCl. The yield was 0.3 g. IR spectrum: 1170, 1360 (SO_2); 3342 cm^{-1} (NH).

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SUBSTITUTION REACTIONS INVOLVING THE 2,6-METHYL GROUPS OF 1,4-DIHYDROPYRIDINES

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4,4-Disubstituted 1,4-dihydropyridines (I) are brominated with bromine in chloroform to give 2,6-bis(bromomethyl)-4,4-disubstituted 1,4-dihydropyridines (II), whereas 2,6-bis(dibromomethyl)-4,4-disubstituted 1,4-dihydropyridines (III) are obtained in the case of bromination of I in acetic acid. The bromine atoms in II and III are labile and readily undergo nucleophilic substitution.

Prior to our previous studies [1-3] substitution reactions involving the 2,6-methyl groups of 1,4-dihydropyridines were unknown. A communication regarding the possibility of nitration of the 2,6-methyl groups in polysubstituted 1,4-dihydropyridines was published recently [4].

We have investigated the bromination of 4,4-dialkyl-1,4-dihydropyridines. It is known [7] that 1,4-dihydropyridines undergo oxidation when they are treated with bromine. The bromination of 1,4-dihydropyridinecarboxylic acid esters leads to the formation of tetrabromo derivatives, the structures of which have not been proved [5, 6].

The 4-C—C=O bond undergoes cleavage to give 8-[10',12'-dioxodiindeno[1,2-b:2',1'-e)-11'-pyridyl]-1-naphthoic acid in the reaction of dioxane dibromide with spiro[2-oxoacenaphthene-1,11'-10',12'-dioxo-5',11'-dihydrodiindeno(1,2-b:2',1'-e)pyridine] [8].

We have shown that the 2,6-methyl groups to give dibromo derivatives Ia-d are brominated selectively in the bromination of 2,6-dimethyl-3,5-dicyano-4,4-dialkyl-1,4-dihydropyridines with bromine in chloroform [1, 3] or with dioxane dibromide in dioxane. (See scheme at top of next page).

Tetrabromo derivatives IIa-c were obtained by the action of excess bromine or 1,4-dihydropyridines in glacial acetic acid; we were able to obtain tetrabromo derivatives in chloroform only for 1,4-dihydropyridines with spiro rings in the 4 position. In all of these

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