

# FLUORINATED HETEROCYCLIC COMPOUNDS

## Methylpyridines

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**D**ERIVATIVES of benzene containing one or more trifluoromethyl groups are exceptionally stable compounds and therefore have many potential uses. The heterocyclic picolines and lutidines, as well as  $\gamma$ -collidine, resemble methylbenzenes in respect to the methyl groups, which are in each instance attached to carbon atoms of six-membered rings containing conjugated double bonds. It would be expected that (trifluoromethyl)pyridines might possess enhanced stability similar to that of the (trifluoromethyl)benzenes. The present investigation was undertaken in an attempt to gain information as to the validity of this assumption.

A few ring-chlorinated (trichloromethyl)pyridines are known (1-5). In the present work (trifluoromethyl)pyridines were prepared by the liquid-phase chlorination of methylpyridines in the presence of water, and fluorination of the (chloromethyl)pyridines thus produced.

The starting materials for this investigation are: 2,4,6-trimethylpyridine technical without purification; 2,6-dimethylpyridine, minimum purity 98%; 2,4-dimethylpyridine, 90% distilled within 2.0° C.; 2-methylpyridine, minimum purity of 95%.

### CHLORINATION

The chlorination apparatus consisted of a vertical Pyrex tube, 75 mm. in diameter and 120 cm. long, sealed at one end and closed at the top with a rubber stopper. Two 8-mm. Pyrex tubes led to two 20-mm. extra-coarse gas-dispersion disks at the lower end of the tube. A 200° C. thermometer was supported with the bulb just beneath the surface of liquid to be chlorinated, and a 250-ml. dropping funnel extended through the stopper for addition of water as required. A 10-mm. glass delivery tube passed up through the stopper and was connected to a vertical condenser, the condensate being collected in a trap while gases escaped through an exit line. During early stages of chlorination, the tube was heated by an electric heater placed around the bottom of the tube. Illumination by two banks of three 200-watt incandescent bulbs was found to have no effect on the results. The methods involved in the chlorination of these compounds may best be illustrated by three examples.

A sufficient quantity of water (20 ml.) was introduced into the tube to cover the gas-dispersion disk, the flow of chlorine was started, and 214.2 grams (2 moles) of 2,6-dimethylpyridine were added. The temperature was held below 50° C. for 3.5 hours by an ice bath. The chlorination tube was then heated, water slowly evaporating. The temperature rose to 150° C. during a period of 2 hours, was held at this level for 19 hours, and was then raised to 180° C. for 6 hours. The chlorinated mixture was aerated and poured into a beaker, where the product crystallized. The weight of product was 572.7 grams; the weight of 2 moles of 2,6-bis(trichloromethyl)pyridine is 627.5 grams. Vacuum filtration of the

**A METHOD for the chlorination of methylpyridines in the presence of water was developed. Photochemical chlorination was employed to give the corresponding (trichloromethyl)pyridine. In some instances ring chlorination occurred. Fluorination of the chloro derivatives with hydrogen fluoride under autogenous pressure gave substituted (trifluoromethyl)pyridines. Physical constants are reported.**

product gave 281 grams of crude 2,6-bis(trichloromethyl)pyridine. This was recrystallized from 100 ml. of 95% ethyl alcohol, and pure 2,6-bis(trichloromethyl)pyridine (237 grams) obtained; the yield was 37.8% of theory.

2-Methylpyridine was chlorinated photochemically, light being supplied by two banks of three 200-watt bulbs. Forty milliliters of water were added to the tube with 279.2 grams (3 moles) of 2-methylpyridine, and chlorine was passed into the tube until the mixture was saturated with chlorine. The reaction product (716.9 grams) was treated as in the preceding experiment and rectified. The boiling points (at 15 mm.) of the fractions obtained were: (I) 122-125° C., containing mostly 2-(trichloromethyl)pyridine; (II) 147-155° C., containing mostly 5-chloro-2-(trichloromethyl)pyridine; (III) 182-185° C., containing mostly 3,5-dichloro-2-(trichloromethyl)pyridine; (IV) 201-205° C., containing mostly 3,4,5-trichloro-2-(trichloromethyl)pyridine. Structure of the compounds of fractions II, III, and IV was proved by hydrolysis to 5-chloropyridine-2-carboxylic acid (1), 3,5-dichloropyridine-2-carboxylic acid (2), and 3,4,5-trichloropyridine-2-carboxylic acid (3), respectively.

2,4-Dimethylpyridine and 20 ml. of water were poured into the tube, the flow of chlorine was started, and 2,4-dimethylpyridine (107.1 grams, 1.0 mole) added. The temperature of the mixture was held below 50° C. for 3 hours, raised to 150° C. during 4 hours, and maintained at this level for 6 hours. Water was added dropwise to prevent precipitation of any hydrochloride during chlorination. When the mixture was saturated with chlorine, it was blown with air to drive out remaining gases. Crystals of 2,4-bis(trichloromethyl)pyridine which separated on standing were removed by filtration and weighed 106 grams, a yield and conversion of 33.9%. On recrystallization from 100 ml. of 95% ethyl alcohol, dark-colored crystals were obtained. These were decolorized with activated charcoal and recrystallized from dilute alcohol. Analysis: calculated for  $C_7H_4Cl_2N$ , 67.8% Cl; found, 67.4% Cl.

### FLUORINATION

(Chloromethyl)pyridines were fluorinated in a 1.5-liter steel autoclave lined with nickel and cold-tested at 5000 pounds per square inch. The autoclave was equipped with a safety disk, valve, and thermowell. The temperature was measured by a thermocouple and potentiometer. The autoclave was heated by a removable electric heater; the temperature was controlled by a variable transformer. The methods involved in the fluorination of chloro derivatives of the methylpyridines are illustrated also by specific examples.

2,6-Bis(trichloromethyl)pyridine (122 grams) and anhydrous hydrogen fluoride (320 grams) were heated in a 1.5-liter autoclave for 30 hours at a maximum temperature of 300° C. The reaction product, a dark liquid, became solid upon addition of water, and was steam-distilled to obtain a white solid. This white solid was

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TABLE I. HALOMETHYLPYRIDINES

Compound	Empirical Formula	% Cl		% F		Mol. Wt.		B.P., ° C. (Mm.)	M.P., ° C.	$n_D^{25}$	$d_4^{25}$
		Calcd.	Found	Calcd.	Found	Calcd.	Found				
2,4,6-Tris(trichloromethyl)-pyridine	C <sub>7</sub> H <sub>2</sub> Cl <sub>9</sub> N	73.9	74.8	...	...	...	...	.....	166-168	....	....
2,6-Bis(trichloromethyl)-pyridine	C <sub>7</sub> H <sub>3</sub> Cl <sub>6</sub> N	67.8	67.8	...	...	...	...	.....	83.5-84.5	....	....
Chloro-2,6-bis(trichloromethyl)-pyridine	C <sub>7</sub> H <sub>2</sub> Cl <sub>7</sub> N	71.3	71.3	...	...	...	...	180-185 (9)	86.5-87.5	....	....
2,6-Bis(trifluoromethyl)-pyridine	C <sub>7</sub> H <sub>3</sub> F <sub>6</sub> N	..	..	53.2	53.2	215.0	215	149-150 (748.3)	56.6-57.5	....	....
Chloro-2,6-bis(trifluoromethyl)-pyridine	C <sub>7</sub> H <sub>2</sub> ClF <sub>5</sub> N	14.2	14.1	45.8	45.4	248.5	245	164.6-165.0 (748.2)	1.6-2.0	1.4140	1.5644
2,4-Bis(trichloromethyl)-pyridine	C <sub>7</sub> H <sub>3</sub> Cl <sub>6</sub> N	67.8	67.4	..	..	...	..	.....	86.5-87.5	....	....
2,4-Bis(trifluoromethyl)-pyridine	C <sub>7</sub> H <sub>3</sub> F <sub>6</sub> N	..	..	53.2	49.5	215.0	216	126.0-127.0 (746.2)	Did not crystallize	1.3833	1.4701
Chloro-2,4-bis(trifluoromethyl)-pyridine	C <sub>7</sub> H <sub>2</sub> ClF <sub>5</sub> N	14.2	13.8	45.8	43.1	248.5	250	144.5-145.5 (746.2)	Did not crystallize	1.4113	1.5426
2-(Trichloromethyl)pyridine	C <sub>6</sub> H <sub>4</sub> Cl <sub>3</sub> N	54.1	54.6	...	...	...	...	125.0-126.0 (25)	-10	1.5596	1.4526
5-Chloro-2-(trichloromethyl)-pyridine	C <sub>6</sub> H <sub>3</sub> Cl <sub>4</sub> N	61.4	61.7	...	...	...	...	139.0-142.0 (25)	45.5-46.5	....	....
3,5-Dichloro-2-(trichloromethyl)pyridine	C <sub>6</sub> H <sub>2</sub> Cl <sub>5</sub> N	66.8	66.8	...	...	...	...	161.0-162.0 (25)	35.5-36.5	....	....
3,4,5-Trichloro-2-(trichloromethyl)pyridine	C <sub>6</sub> HCl <sub>6</sub> N	71.0	71.0	...	...	...	...	172.0-175.0 (25)	99.0-100.0	....	....
5-Chloro-2-(trifluoromethyl)-pyridine	C <sub>6</sub> H <sub>3</sub> ClF <sub>5</sub> N	19.5	19.4	31.4	30.8	181.5	182	151.0-152.0 (744.6)	37.5-38.0	....	....
3,5-Dichloro-2-(trifluoromethyl)pyridine	C <sub>6</sub> H <sub>2</sub> Cl <sub>2</sub> F <sub>3</sub> N	32.8	32.6	26.4	24.3	215.9	216	177.0-178.0 (747.4)	15	1.4780	1.5122

recrystallized from 95% ethyl alcohol and found to be 2,6-bis(trifluoromethyl)pyridine. Physical constants and analyses are reported in Table I.

Chlorinated 2-methylpyridine (523.7 grams) was placed in a 1.5-liter autoclave and heated with anhydrous hydrogen fluoride (600 grams) for 28 hours at a maximum temperature of 204° C. The product, a black liquid containing considerable hydrogen fluoride, was steam-distilled, and 276.2 grams of material were obtained. This product was dried with anhydrous calcium chloride and rectified on a 4-foot glass-packed column; the important fractions obtained had the following boiling points: (I) 85.5-91.0° C. (100 mm.), mostly 5-chloro-2-(trifluoromethyl)pyridine; (II) 103.5-106.0° C. (100 mm.), mainly 2-(chlorodifluoromethyl)pyridine; (III) 114.5-118.0° C. (100 mm.), mainly 3,5-dichloro-2-(trifluoromethyl)pyridine; (IV) 71.0-75.0° C. (10 mm.), mainly 5-chloro-2-(chlorodifluoromethyl)pyridine; (V) 89.0-93.0° C. (10 mm.), mainly 3,5-dichloro-2-(chlorodifluoromethyl)pyridine; and (VI) 105.5-108.0° C. (10 mm.), mainly 3,5-dichloro-2-(dichlorodifluoromethyl)pyridine.

Impure 2,4-bis(trichloromethyl)pyridine (418 grams, 1.3 moles) was placed in a 1.5-liter autoclave with 350 grams (17.5 moles) of anhydrous hydrogen fluoride. The mixture was heated for 29.5 hours at a maximum temperature of 204° C. The product was steam-distilled, and 128.0 grams of organic liquid were obtained. This was dried and rectified to yield 2,4-bis(trifluoromethyl)pyridine and a small quantity of chloro-2,4-bis(trifluoromethyl)pyridine.

#### DISCUSSION

During the chlorination of methylpyridines, hydrogen chloride and the methylpyridines react to form hydrochlorides which are not soluble in the liquid pyridines. Instead, the hydrochlorides precipitate and are removed from the sphere of action of the chlorine. This presents a problem, in that the hydrochlorides cannot be chlorinated in the molten state, since they melt only at high temperatures and with decomposition. A solvent such as water, which will dissolve the hydrochlorides as they are formed, is therefore necessary to obtain a homogeneous reaction medium.

A minimum amount of water is added at the beginning of the chlorination, and just sufficient in later stages of reaction to keep the hydrochlorides in solution. After an initial vigorous reaction, the organic layer disappears and the temperature may be raised until water begins to distill from the reaction medium. The rate of chlorine addition and water removal must be carefully regulated during this time to avoid darkening of the chlorination mix-

ture and subsequent tar formation. The presence of water is mandatory during early stages of reaction as the methylpyridines chlorinate only slightly, if at all, in the form of their quaternary salt, but much more readily when the hydrochlorides are in water solution. While some chlorination may take place before conversion to quaternary salts, most is believed to occur as water is being driven off and the partially chlorinated methylpyridines are released from solution. As chlorination progresses, hydrogen atoms in the methyl group attached to ring carbon atoms adjacent to nitrogen are substituted by chlorine atoms; there is a consequent reduction in basicity of the methylpyridines until they no longer form hydrochlorides which are stable in water. When this is true, the partially chlorinated methylpyridines precipitate from the aqueous solution and are readily chlorinated to a further extent. At this point in the process, the presence of water becomes unnecessary. After water has completely distilled, chlorination may be continued to ensure replacement of all hydrogen atoms of the methyl groups with chlorine atoms.

The chlorination of 2,6-dimethylpyridine is exceptionally easy, since substitution of hydrogen by chlorine in the methyl groups rapidly reduces basicity of the compounds. Consequently, partially chlorinated 2,6-dimethylpyridine quickly precipitates from the aqueous solution and is then chlorinated to the 2,6-bis(trichloromethyl)pyridine. 2,4-Dimethylpyridine chlorinates less readily and yields a greater variety of products because one methyl group is farther from the nitrogen atom. 2,4,6-Trimethylpyridine chlorinates easily in the early states, but 2,4,6-tris(trichloromethyl)pyridine is formed only at high temperatures and with prolonged reaction times. The efficiency of this reaction is therefore decreased by chlorinolysis. Chlorination of 2-methylpyridine requires better control and yields a high percentage of ring-chlorinated compounds. 3-Methylpyridine and 4-methylpyridine could not be chlorinated to any identifiable products, probably because the trichloromethyl group in the 3 or 4 position was unable to offset the basicity of the nitrogen atom.

Chlorinations conducted with ring-chlorination catalysts, such as iron and antimony salts, apparently produced no greater quantity of ring-chlorinated compounds than those carried out in the absence of such catalysts. Likewise, strong incandescent lighting seems to have no appreciable effect on composition of the product.

The fluorination of chloro derivatives of the methylpyridines with hydrogen fluoride requires about the same conditions as does that of corresponding benzene derivatives. Temperatures of 200-250° C. are satisfactory under autogenous or superatmospheric

pressures. A longer time is usually required than with chlorinated methylbenzenes, as fluorination catalysts, such as antimony pentachloride, seem to have no effect on fluorination rate. The chlorinated methylpyridines are apparently not fluorinated with antimony trifluoride at atmospheric pressure.

#### PROPERTIES OF COMPOUNDS

Although these compounds are derivatives of pyridine, they have no basic properties. No hydrochloride precipitates when hydrogen chloride is bubbled through a benzene solution of the chlorinated or fluorinated methylpyridine. These compounds are not hydrochlorides or hydrofluorides, as shown by their insolubility in water and solubility in organic liquids such as ether, benzene, and petroleum ether. 2,6-Bis(trifluoromethyl)pyridine is a solid fluoro compound with interesting solubility properties, being soluble in alcohols as well as ethers and hydrocarbons. Chloro-2,6-bis(trifluoromethyl)pyridine is completely miscible

with 95% ethyl alcohol. Table I gives the chemical analysis and properties of the compounds.

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## (FLUORINATED HETEROCYCLIC COMPOUNDS)

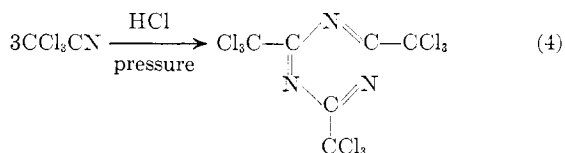
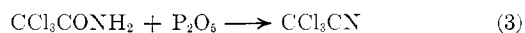
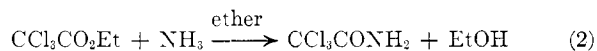
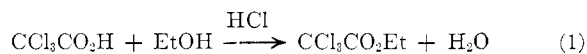
### (*Perhaloalkyl*) triazines

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2,4,6-TRIS(trichloromethyl)-1,3,5-triazine was prepared by polymerizing trichloroacetonitrile with anhydrous hydrogen chloride at a pressure of 800 pounds per square inch. Trichloroacetonitrile was produced from trichloroacetamide made by ammonolysis of ethyl trichloroacetate. 2,4,6-Tris(trichloromethyl)-1,3,5-triazine was fluorinated with hydrogen fluoride and antimony pentachloride both at atmospheric and superatmospheric pressure. Eight new 2,4,6-tris(chlorofluoromethyl)-1,3,5-triazines were obtained. Physical constants and experimental data are reported.

TRIAZINES have been reported to exhibit exceptional stability to heat and hydrolysis (2), and it was believed that introduction of fluorine should increase stability and result in non-flammable compounds with a wide liquid range which might be suitable as heat transfer agents. The allylic nature of the chlorine atoms to be substituted made the known 2,4,6-tris(trichloromethyl)-1,3,5-triazine relatively easy to fluorinate. The series of reactions used in the preparation of this intermediate follows:



The 2,4,6-tris(trichloromethyl)-1,3,5-triazine was fluorinated with anhydrous hydrogen fluoride and antimony pentachloride

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at both atmospheric and superatmospheric pressures. Table I gives the compounds prepared, their physical properties, and their halogen analyses.

#### 2,4,6-TRIS(TRICHLOROMETHYL)-1,3,5-TRIAZINE

The series of reactions outlined previously is described, and optimum yields are reported. Twenty-two hundred fifty grams (13.8 moles) of trichloroacetic acid and 3200 grams (70 moles) of absolute ethanol were placed in a 12-liter flask equipped with a reflux condenser. Ten milliliters of concentrated hydrochloric acid were added, and the flask was heated for 6 hours at reflux temperature. The reaction mixture was then distilled at atmospheric pressure through a short Vigreux column. The fraction boiling at 162-165° C. (750 mm. mercury) was collected as ethyl trichloroacetate, boiling at 164.0° C. Twenty-one hundred seventy-five grams (11.4 moles) of the ester were obtained; the yield and conversion were 83%.

Twenty-one hundred seventy-five grams (11.4 moles) of ethyl trichloroacetate were dissolved in 2 liters of anhydrous diethyl ether, and the solution was placed in a three-neck 5-liter flask equipped with a gas inlet tube. The solution was cooled to ice temperature, and anhydrous ammonia was bubbled slowly into the reaction mixture over a period of 20 hours. Trichloroacetamide separated immediately from solution. The flow of ammonia was then stopped and the remaining liquid removed by distillation. Sixteen hundred thirty grams (10.4 moles) of trichloroacetamide were obtained; the yield and conversion were 91%.

Nine hundred seventy-two grams (6.0 moles) of trichloroacetamide and 284 grams (2.0 moles) of phosphorus pentoxide were intimately mixed, and the mixture was placed in a 3-liter distilling flask. The flask and contents were heated electrically with a Glascol heating mantle placed around the flask. The reaction proceeded smoothly, trichloroacetonitrile distilling from the reaction mixture as rapidly as formed. Additional amounts of phosphorus pentoxide were introduced during the reaction until a total of 994 grams (7.0 moles) had been added. Seven hundred