PREPARATION OF 2,3,5,6-TETRACHLOROPYRIDINE-2,6-^{14}C

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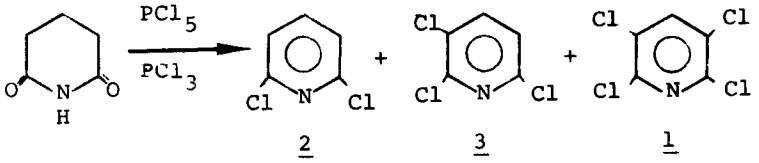
SUMMARY

An 88.6% yield of 2,3,5,6-tetrachloropyridine-2,6-^{14}C (8.99 mCi, 14.5 mCi/mmole) was obtained *via* chlorination of 2,6-dichloropyridine-2,6-^{14}C.

Key Words: 2,3,5,6-Tetrachloropyridine-2,6-^{14}C, Chlorination, Glutarimide-2,6-^{14}C, 2,6-Dichloropyridine-2,6-^{14}C.

INTRODUCTION

A large sample (*ca* 10-15 mCi) of 2,3,5,6-tetrachloropyridine-2,6-^{14}C(1) was required as an intermediate in the preparation of radioactive tracers of chloropyridine based pesticides. A previous method of preparing radiolabeled 1 involved chlorination of glutarimide-2,6-^{14}C with PCl_5(1,2). Unfortunately the reaction favors isomers 2 and 3 depending upon the reaction conditions and 1 can be isolated in only 10-15% yields. Therefore new synthetic routes to radiolabeled 1 were explored.



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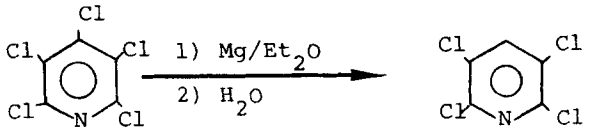
DISCUSSION

I. Mikhailova, et. al, report that pentachloropyridine can be converted to 2,3,5,6-tetrachloropyridine in an 88% yield via magnesium reduction(3). This information in conjunction with the fact that 2,6-dichloropyridine-2,6-^{14}C, prepared in high yield from glutarimide-2,6-^{14}C(4), can a priori afford

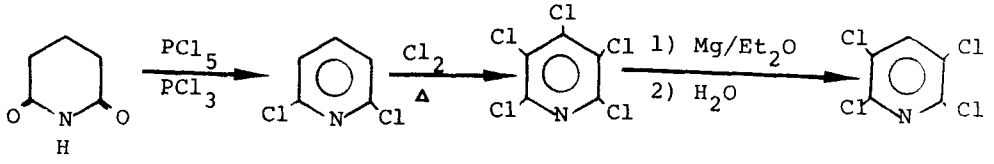


88%

1

pentachloropyridine in >99% yields(5) led the author to consider the reaction sequence depicted in Scheme I below.

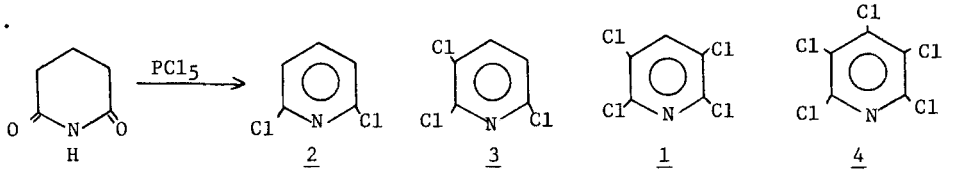
SCHEME I



Unfortunately the results obtained by Mikhailova could not be duplicated under a variety of conditions. Low yields of 1 were isolated in each instance.

Previous chlorination studies of glutarimide with PCl_5 indicated that the chlorinated pyridine of choice would be favored by varying the reaction conditions(4). As the results in Table I (Reaction A) demonstrate, an excess of PCl_5 in PCl_3 at 85°C still favors the formation of 2 and 3.

TABLE I.



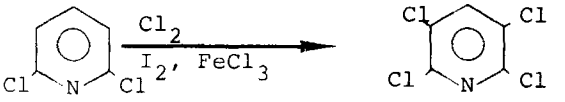
Reaction	Glutarimide mmoles	PCl_5 mmoles	Solvent/ml		Temp. °C	Time hr	Glc Area Percent[1/] 1	2	3	4
A	4.005	23.9	PCl_3	10	85°	0.5	1.6	53.7	42.4	--
B	2.003	10.04	$PhPOCl_2$	5	165°	0.5	54.8	0.0	29.9	0.8
C	2.001	12.00	$PhPOCl_2$	5	165°	0.5	55.8	0.0	20.7	1.4
D	2.009	12.10	$PhPOCl_2$	5	185°	0.5	56.6	0.0	15.3	5.5

[1/] A 0.1 ml aliquot was removed, treated with ice water, extracted with CCl_4 and the CCl_4 extract analyzed.

When the solvent is changed to phenylphosphonic dichloride thereby allowing for the use of higher reaction temperatures, the desired tetrachloro adduct 1 becomes the major component (Reactions B-D). Although, the formation of the pentachloro adduct is enhanced slightly at the expense of 3 by using a higher ratio of PCl_5 (Reaction B verses C) and more predominantly by using higher temperatures (C verses D) the percentage of 1 remains relatively constant. However, the lower temperature is preferred since 1 cannot be readily separated from 4 *via* column chromatography whereas it is easily separated from 3. The product from Reaction B was subsequently isolated and purified *via* column chromatography to afford 56% yield of 1 and a 29% yield of 3 thereby representing an 85% overall yield of chlorinated pyridines.

Finally, direct chlorination of 2,6-dichloropyridine (2) was considered. Smith(6) reported the conversion of 2,6-dichloropyridine to 2,3,5,6-tetrachloropyridine in a 96% yield under atmospheric conditions as depicted in Scheme II.

SCHEME II



48 hr at 180°C 96%

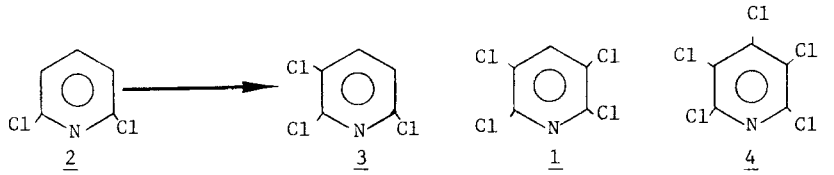
2 1

However, this process involves the continuous addition of chlorine over the reaction period which is undesirable for the required microsynthesis of labeled 1. Therefore, the chlorination of 2 under sealed ampoule conditions was investigated leading to the results depicted in Table II. Reactions A and B were conducted in carbon tetrachloride in the absence of a catalyst. As can be seen a distribution of chlorinated products is obtained. Reaction C involves the chlorination in the absence of a solvent using only $FeCl_3$ as the catalyst. Comparison of the results of Reaction C with those of Reaction D in which iodine was also used clearly indicates that the use of iodine is essential. Reactions E and F were modifications of Reaction D in an attempt to maximize the yield of 1 and minimize the yield of 4 which is difficult to separate from 1 on a microscale. Thus by controlling the ratio of Cl_2:1 (ca 4:1 in Reaction F) the quantity of 1 can be optimized.

The white crystalline isomeric mixture isolated from Reaction F was chromatographed through silica gel and the tetrachloro isomer 1 isolated in two fractions. The first gave 65.6 mg of 1 containing 1.5 glc area percent 4 and the second gave 148.7 mg of 1 containing 0.5% 4. Thus an 84.5% yield of >99% pure 1 was isolated.

The latter process was subsequently applied to 2,6-dichloropyridine-2,6-^{14}C affording 146.7 mg of white crystalline product containing the isomer distribution listed for Reaction G in Table II. Using this data a ca 88.5% yield of radiolabeled 1 was determined. Concurrent research demonstrated that the removal of the pentachloro isomer 4 was unnecessary for the application intended since the by-products derived

TABLE II. CHLORINATION OF 2,6-DICHLOROPYRIDINE.



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Reaction	2 mmoles	Cl_2 mmoles	Solvent	Catalysts	Temp. °C	Time hr	Glc Area Percent 1	2[1]	3	4
A	1.27	15	CCl_4	None	275	20	54	0.3	1.9	43
B	1.19	16.5	CCl_4	None	250	20	57	0.3	29	14
C	1.29	3.05	None	$FeCl_3$	200	4	--	98.5	1.5	--
D	1.17	∿36(0.8 ml)[2]	None	$FeCl_3/I_2$	200	4	92.0	0.3	--	4.9
E	1.17	(0.3 ml)	None	$FeCl_3/I_2$	190	4	60.5	2.0	32.9	0.8
F	1.16	(0.2 ml)	None	$FeCl_3/I_2$	200	8	96.1	0.2	0.8	1.9
G	0.70	(0.25 ml)	None	$FeCl_3/I_2$	200	8	91.7	0.7	--	7.1

1. The low percentages observed (0.2-0.7%) are probably due to an impurity.

2. A given volume of Cl_2 was added at this stage which could be measured much more accurately than the procedure used for the previous results (density ∿1.6 mg/µl).

therefrom could be much more easily removed at a later stage in that process. Therefore, the radiolabeled sample was not subjected to further purification.

CONCLUSION

2,3,5,6-Tetrachloropyridine-2,6-^{14}C can now be prepared in moderate to high yield either *via* reaction of glutarimide-2,6-^{14}C and PCl_5 or by chlorination of 2,6-dichloropyridine-2,6-^{14}C. Although 4 cannot be easily separated from 1 *via* column chromatography, the purification could *a priori* be accomplished *via* preparative GLC as suggested by thé glc analyses listed below.

High temperature chlorination of 2,6-dichloropyridine with PCl_5 is also reported to afford 1 in a 71% yield(7). However, this reaction was not investigated in the present study.

GLC ANALYSES

GLC analyses were conducted using a Hewlett Packard Model 5830A instrument containing a 2'x4' mm glass column packed with 10% SE 30 on Chromasorb WHP, 80-100 mesh (Conditions: 100-250°C at 20°/min, time at 100°C=2.0 minutes, time at 250°C = 5.0 minutes). The chlorinated pyridines possessed the following retention times:

Pyridine	Retention Time (min.)
2 (2,6-Cl_2)	2.8
3 (2,3,6-Cl_3)	4.2
1 (2,3,5,6-Cl_4)	5.1
4 (2,3,4,5,6-Cl_5)	6.2

The observed retention time differences favor purification by preparative GLC.

EXPERIMENTAL

Grignard Reaction of Pentachloropyridine. I. A 100 ml 3-necked flask equipped with a condenser, dropping funnel, and stirring bar was heated with a heat gun and allowed to cool under a N_2 atmosphere. To the flask was added 253.1 mg (1.007 mmole) of pentachloropyridine(4), 37.2 mg (1.54 mmole) of Mg turnings and 10 ml of anhydrous Et_2O. The mixture was heated to reflux under a N_2 atmosphere. A 300 µl sample was removed after 2.0 hr (via syringe cap over one neck), treated with saturated aqueous NH_4Cl solution and analyzed by GLC. No reaction was detected. An additional 54.8 mg of Mg turnings (2.26 mmole) was added followed by the dropwise addition of 154 µl of ethyl bromide (2.021 mmole) in 10 ml of Et_2O over a 20 minute period. After 2.5 hr at reflux, a sample was isolated and analyzed in the above manner to afford 65.3 area % 4 and 24.0 area % 1. After 15.0 hr the Et_2O solution was treated with aqueous NH_4Cl, dried ($MgSO_4$), filtered, and the filtrate analyzed by GLC to contain 4.3 area % 4, 24.9 area % 1 and a multitude of other products possessing high GLC retention times.

II. Reaction I was repeated using Et_2O previously dried over sodium. After 9.5 hr at reflux 10.5 area % 4 and 31.5 area % 1 were observed.

Reaction of Glutarimide and PCl_5-A. To a 50 ml round bottomed flask equipped with a stirring bar, condenser and $CaCl_2$ drying tower was added 453.1 mg (4.005 mmole) of glutarimide, 10 ml of PCl_3, and 4.98 g (23.9 mmole, 6 eq) of PCl_5. The mixture was placed in an 85°C oil bath for 0.5 hr. The resultant clear yellow solution was cooled to ca -5°C, treated slowly with 35 ml of ice-H_2O and the

resultant mixture stirred 0.5 hr. The mixture was extracted continuously with 10 ml of n-pentane over an 8 hr period and the n-pentane layer analyzed by GLC to contain 53.7 area % 2, 42.4 area % 3 and 1.6 area % 1.

B. To a 50 ml round bottomed flask equipped with a stirring bar, condenser, and drying tower was added 226.5 mg (2.003 mmole) of glutarimide, 5 ml of phenylphosphonic dichloride and 2.09 g (10.04 mmole) of PCl_5. The mixture was placed in a 165°C oil bath. After 0.5 hr, a 0.1 ml sample was removed, treated and analyzed as described in Table I. The remaining solution was cooled and treated with ice-water. The resultant mixture was made basic with 20 ml of 20% NaOH and extracted with 1-20 ml- and 2-10 ml- portions of n-pentane. The n-pentane extracts were dried ($MgSO_4$) filtered, and the solvent removed from the filtrate in vacuo affording 370.1 mg of residual yellow oil. The oil was chromatographed through 100 g of Brinkman Silica gel G60 with 1:1 (v/v) n-hexane:$CHCl_3$ to afford upon isolation and solvent removal 250.2 mg of 1 (97.3 glc area % pure;, 1.122 mmole, 56.0% yield) and 111.5 mg of 3 (96.2 glc area % pure, 0.588 mmole, 29.3% yield).

C-D. Procedure identical to that for Reaction B except that the product was not isolated. See Table I for conditions.

Chlorination of 2,6-Dichloropyridine-Reaction A. In CCl_4. To a glass ampoule was added 187.7 mg (1.27 mmole) of 2,6-dichloropyrine(2). Chlorine, ca 6 ml, was collected in a calibrated gas trap at -78°C (dry ice-acetone) and transferred to the ampoule by cooling the ampoule to -78°C and allowing the gas trap to warm. The ampoule was sealed, wrapped in asbestos tape and placed in a S.S. bomb half filled with H_2O. The bomb was sealed, back pressured to 1200 psi,

placed in a rocker-heater and heated to 275°C. Heating and rocking were continued for 20.0 hr. The bomb was cooled to 5°C, the N_2 pressure released and the bomb opened. The ampoule was cooled to -78°C and opened. It possessed a moderate pressure (HCl). The ampoule was warmed to room temperature and the contents analyzed by GLC affording the results in Table I.

Reaction B. Repetition of Reaction A under the conditions given in Table I.

Reaction C. 2,6-Dichloropyridine (191.1 mg, 1.291 mmole) and $FeCl_3$ (4.8 mg) were dissolved in Et_2O and the solution transferred to a glass ampoule. The Et_2O was removed under N_2. The Cl_2 was collected in a tared trap at -78°C, weighed (216 mg, 3.05 mmole), and transferred to the ampoule in the previously described manner. The ampoule was sealed, placed in a S.S. bomb and heated at 200°C for 4.0 hr. The ampoule was cooled, opened, and the contents extracted with Et_2O. The Et_2O layer was analyzed by GLC to afford the results in Table I.

Reaction D. A sealed glass ampoule containing 172.8 mg of 2,6-dichloropyridine (1.168 mmole), 7.1 mg of $FeCl_3$, 0.8 ml of Cl_2 and 4 crystals of I_2 was placed in the 0.5 L S.S. bomb and pressured to 1100 psi as described in Reaction A. The bomb was heated at 190-220°C for 4.0 hr, cooled, and the ampoule opened as described in Reaction A. The contents were extracted with 5 ml of Et_2O and 5 ml of H_2O, respectively, the phases mixed well, and the Et_2O layer analyzed by GLC to afford the results listed in Table I.

Reaction E. The ampoule contained 173.1 mg (1.170 mmole) of 2, 7.1 mg of $FeCl_3$, 0.3 ml of Cl_2 and 9.2 mg of I_2.

Reaction F. The ampoule contained 171.6 mg (1.159 mmole) of 2, 8.0 mg of $FeCl_3$, 0.2 ml of Cl_2 and 9.5 mg of I_2. The product was isolated by extracting alternately with five-1 ml-H_2O and five-1 ml-CH_2Cl_2, respectively. The extracts were placed in a 25 ml pear shaped flask, stirred well, and the CH_2Cl_2 layer analyzed to afford the results in Table I.

The CH_2Cl_2 was washed three times with H_2O and filtered through $MgSO_4$ into a 25 ml pear shaped flask. The solvent was removed *in vacuo* to afford 227.7 mg of off-white crystalline solid. The residue was dissolved in 1 ml of 1:1 (v/v) n-hexane;benzene and chromatographed through 300 g of Brinkman Silica Gel G60. The 2,3,5,6-tetrachloropyridine (1) was isolated in two fractions containing 60 ml and 150 ml of solution, respectively. The fractions were filtered and the solvent removed *in vacuo* affording 65.6 mg and 148.7 mg, respectively, of 1. The former fraction contained 98.5 area % 1 and 1.5 area % 4 and the latter contained 99.5% 1 and 0.5% 4, respectively, by GLC analysis.

Reaction G. 2,3,5,6-Tetrachloropyridine-2,6-^{14}C. To a 25 ml pear shaped flask containing 103.4 mg of white crystalline solid consisting of 98.5 GLC area % radiolabeled 2 (0.688 mmole, 9.98 mCi, 14.5 mCi/mmole) and 1.35 GLC area % radiolabeled 3 (0.008 mmole, 0.12 mCi) was added 8.4 mg of $FeCl_3$. The contents were dissolved in *ca* 1 ml of Et_2O and the solution transferred to a *ca*. 12 ml glass ampoule. The flask was rinsed with 4-0.5 ml-Et_2O and the rinses added to the ampoule. The Et_2O was removed under a slow N_2 purge,

care being taken not to lose any radioactivity. Iodine, 9.1 mg, was added and the ampoule cooled to -78° under a N_2 atmosphere. The ampoule was connected to the Cl_2 gas trap containing 0.25 ml of Cl_2 and the Cl_2 transferred in the usual manner. The ampoule was sealed, wrapped in asbestos tape, and placed in the S.S. reactor half filled with H_2O. The reactor was back-pressured to 900 psi, placed in the rocker-heater and heated at 200-210°C for 8.0 hr (reactor pressure=1550-1800 psi). The ampoule was removed and opened in the usual manner, and the residual yellow solid extracted with 4 ml of H_2O and subsequently with 5-2 ml-CH_2Cl_2. The phases were mixed well and the CH_2Cl_2 phase separated and analyzed by GLC. The CH_2Cl_2 solution was washed with two-100 ml-H_2O and filtered through $MgSO_4$ into a 50 ml pear shaped flask. The solvent was removed *in vacuo* affording 146.7 mg of white crystalline solid containing 91.7 GLC area % 1 (0.620 mmole, 88.5% yield) and 7.07 GLC area % 2 (0.04 mmole, 5.7% yield).

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