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Dedicated to the memory of Professor Raymond N. Castle

This paper presents the chlorination of 3,4,5-trichloropyridazin-6-one and the synthesis of 3,4,5-trichloro-1-(4,5,6-trichloropyridazin-3-yl)pyridazin-6-one.

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In our previous paper [1], the synthesis of 4,5-dichloro-1-(4,5-dichloropyridazin-3-yl)-pyridazin-6-one from 4,5-dichloropyridazin-6-one using phosphorus oxychloride or phosphorus pentachloride has been reported. In connection with our research program for the study on the synthesis of novel multichloropyridazine derivatives, we attempted the chlorination of 3,4,5-trichloropyridazin-6-one and the synthesis of 3,4,5-trichloro-1-(4,5,6-trichloropyridazin-3-yl)pyridazin-6-one.

In this paper, we wish to report the reaction of **1** with phosphorus oxychloride or phosphorus pentachloride and the establishment of the structure for **3**.

3,4,5-Trichloropyridazin-6-one was prepared from 4,5-dichloro-3-nitropyridazin-6-one in good yield by Kweons' method [2]. Chlorination of **1** using phosphorus oxychloride gave only 3,4,5,6-tetrachloropyridazine (**2**) in 81% yield (Method A), whereas treatment of **1** with phosphorus pentachloride furnished **2** (60%) and **3** (23%) (Method B).

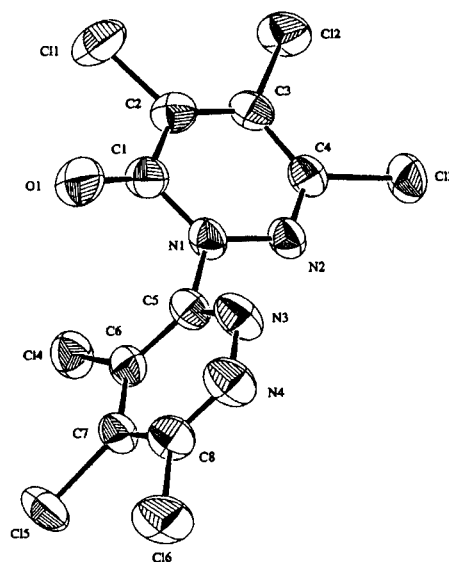
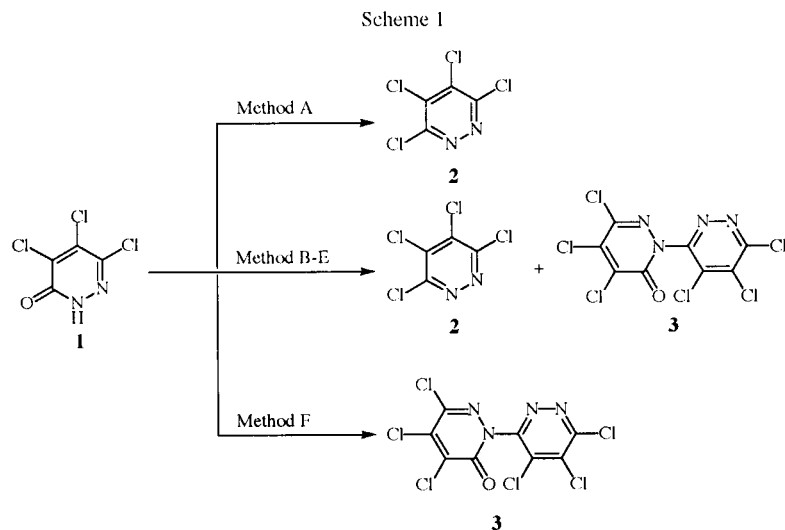


Figure 1. An ORTEP drawing of **3**.



On the other hand, reaction of **1** with phosphorus pentachloride in organic solvents at reflux temperature yielded pyridazinylpyridazinone **3** as the main product. Chlorination of **1** with phosphorus pentachloride (1.2 equivalents) in toluene afforded **2** (11%) and **3** (61%) (Method C), and reaction of **1** with 2 equivalents of phosphorus pentachloride in toluene also gave **2** (27%) and **3** (45%) (Method D). Treatment of **1** with phosphorus pentachloride in chlorobenzene yielded **2** and **3** in 43% yield, respectively (Method E). Compound **1**, however, was reacted with phosphorus penta-

bon-oxygen bond. The longest carbon-chlorine bond is C(4)-Cl(3) [1.717 (4) Å], whereas the shortest carbon-chlorine bond is C(6)-Cl(4) [1.686 (4) Å]. The longest carbon-nitrogen bond also is N(1)-C(5) [1.433 (4) Å], whereas the shortest carbon-nitrogen bond is N(2)-C(4) [1.288 (5) Å]. The linkage position of the two rings is N(1)-C(5). The bond lengths of two nitrogen-nitrogen bonds are similar.

Further work including the chemical transformation and biological activity of **3** is under way in our laboratory.

Table 1
Crystal Data and Intensity Measurements for **3**

Crystal Data		Intensity Measurements	
Crystal color, Habit	Colorless, prismatic	Diffractometer	Rigaku AFC7R (rotating anode)
Crystal Dimensions	0.30 X 0.30 X 0.06 mm	Radiation	Cu-Kα (λ=1.54178 Å) Graphite monochromated
Crystal System	Monoclinic	Attenuator	Ni foil (factor = 9.11)
Lattice Type	Primitive	Take-off Angle	6.0°
No. of Reflections Used for Unit Cell	25 (59.0 – 59.9°)	Detector Aperture	3.0 mm horizontal 3.0 mm vertical
Determination (2θ range)		Crystal to Detector Distance	235 mm
Omega Scan Peak	0.22°	Voltage, Current	50 kV, 100 mA
Width at Half-height		Temperature	23.0°
Lattice Parameters	a = 6.930 (2) Å, b = 19.645 (2) Å, c = 10.173 (3) Å, β = 107.70 (2)°, V = 1319.4 (5) Å ³	Scan Type	ω-2θ
Space Group	P2 ₁ /n (#14)	Scan Rate (in ω)	32, 16, 8, 4°/min for each 2θ shell (4<80<100<120<135°) (up to 7 scans)
Z value	4	Scan Width	(1.50 + 0.30 tan q)°
D _{calc}	1.917 g/cm ³	2θ _{max}	135.2°
F ₀₀₀	744.00	No. of Reflections measured	Total: 2573, Unique: 1958 (R _{int} = 0.024)
μ(CuKα)	118.71 cm ⁻¹	Corrections	Lorentz-polarization, Absorption (trans. Factor:0.3234-0.9982) Secondary extinction (coefficient: 1.31081e-05)

chloride in cyclohexane at reflux temperature to give **3** exclusively in 81% yield (Method F).

The structures of **2** and **3** were established by ir, nmr and elemental analyses. The infrared spectrum of **2** did not detect the absorption band of the carbonyl group, whereas that of **3** showed the absorption band of one carbonyl at 1705 cm⁻¹. The carbon-13 nuclear magnetic resonance spectrum of **2** showed only two signals at δ 138.1 and δ 155.3 ppm, whereas that of **3** revealed the signals of eight carbons involving one carbonyl group (at δ 157.0 ppm). X-ray analysis revealed the structure of **3** as shown in Figure 1 (Tables 1–3). Compound **3** contains six carbon-chlorine bonds, five carbon-nitrogen bonds, two nitrogen-nitrogen bonds and one car-

Table 2
Structure Solution and Refinement for **3**

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\sum \omega(F_o - F_c)^2$
Least Squares Weights	$\omega = 1 / s^2(F_o) = [s^2_c(F_o) + (p^2/4)F_o^2]^{-1}$
p-factor	0.0780
No. Observations (I > 2.00 σ(I))	1953
No. Variables	173
Reflection/Parameter Ratio	11.29
Residuals: R; Rw	0.048; 0.079
Goodness of Fit Indicator	1.64
Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. map	0.41 e ⁻ /Å ³
Minimum peak in Final Diff. map	- 0.45 e ⁻ /Å ³

Table 3
Atomic coordinates and B_{iso}/B_{eq} for **3**

Atom	X	Y	z	B_{eq}
Cl(1)	-0.3077(2)	0.27575(7)	0.3490(2)	5.78(3)
Cl(2)	-0.1126(2)	0.42088(5)	0.4279(1)	5.02(3)
Cl(3)	0.3629(2)	0.43047(5)	0.5461(1)	4.96(3)
Cl(4)	0.2924(2)	0.15749(6)	0.2509(1)	4.53(2)
Cl(5)	0.6211(2)	0.03999(7)	0.3296(1)	5.69(3)
Cl(6)	0.8803(2)	0.02782(7)	0.6423(2)	6.16(3)
O(1)	0.0046(5)	0.1668(2)	0.4387(4)	5.75(9)
N(1)	0.2749(5)	0.2388(1)	0.4991(3)	3.46(6)
N(2)	0.3641(5)	0.3007(2)	0.5297(3)	3.49(6)
N(3)	0.5308(6)	0.1778(2)	0.6520(3)	4.56(7)
N(4)	0.6751(7)	0.1297(2)	0.6865(4)	5.03(8)
C(1)	0.0674(6)	0.2253(2)	0.4529(4)	3.88(8)
C(2)	-0.0548(6)	0.2868(2)	0.4257(4)	3.88(8)
C(3)	0.0296(6)	0.3485(2)	0.4556(4)	3.49(7)
C(4)	0.2454(6)	0.3527(2)	0.5102(4)	3.51(7)
C(5)	0.4169(6)	0.1836(2)	0.5240(4)	3.43(7)
C(6)	0.4352(5)	0.1433(2)	0.4152(4)	3.49(7)
C(7)	0.5817(6)	0.0933(2)	0.4511(4)	3.55(7)
C(8)	0.6971(6)	0.0891(2)	0.5888(4)	4.15(8)

$$B_{eq} = (8/3)\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha)$$

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Magnetic resonance spectra were obtained on a Varian Unity Plus 300 or a Bruker FTNMR-DRX 500 spectrometer with chemical shift values reported in δ units (part per million) relative to an internal standard (tetramethylsilane). Infrared spectral data were obtained on a Hitachi 270-50 spectrophotometer. Elemental analyses were performed with a Perkin Elmer 240C. X-Ray diffraction data were obtained with a Rigaku AFC7R diffractometer with filtered Cu-K α radiation and a rotating anode generator. Open-bed chromatography was carried out silica gel 60 (70-230 mesh, Merck) using gravity flow. The column was packed as slurries with the elution solvent.

Chlorination of 3,4,5-Trichloropyridazin-6-one (**1**).

Method A.

A mixture of **1** (1.0 g, 5.014 mmoles) and phosphorus oxychloride (10 ml) was refluxed for 24 hours. After cooling to room temperature, the reaction mixture was poured into ice water (100 ml) with stirring. The saturated sodium bicarbonate solution (50 ml) was added to the mixture with stirring. The product was filtered and washed with water (50 ml) and dried in air to give only compound **2** in 81% (0.881 g) yield, mp 84-85° (lit. [2] 85-86°); ir (potassium bromide): 1505, 1480, 1360, 1290, 1200, 1120, 1090, 890, 800, 630 cm^{-1} ; ^{13}C nmr (deuteriochloroform): δ 138.1, 155.3 ppm.

Anal. Calcd for $\text{C}_4\text{N}_2\text{Cl}_4$: C, 22.05; N, 12.86. Found: C, 22.15; N, 12.90.

Method B.

A mixture of **1** (3 g, 15.04 mmoles) and phosphorus pentachloride (6 g, 28.8 mmoles) was refluxed for 3 hours. After

cooling to room temperature, the reaction mixture was poured into ice water (500 ml) with stirring. The resulting precipitate was filtered and dissolved in chloroform (80 ml). The chloroform solution was dried over anhydrous magnesium sulfate. The solution was coevaporated with silica gel (3 g) under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (5 x 2.5 cm). The column was eluted with *n*-hexane. Fractions containing **2** ($R_f = 0.54$, chloroform) were combined and evaporated under reduced pressure to afford **2** in 60% (1.95 g) yield. This product was identical with **2** that was prepared by the Method A. Fractions containing **3** ($R_f = 0.26$, chloroform) were also combined and evaporated under reduced pressure to give **3** in 23% (0.655 g) yield, mp 150-152°; ir (potassium bromide): 1705, 1580, 15200, 1380, 1330, 1300, 1260, 1210, 1170, 970, 905, 840, 800, 740, 605 cm^{-1} ; ^{13}C nmr (deuteriochloroform): δ 136.5, 137.3, 138.4, 138.6, 138.8, 153.4, 154.0, 157.0 ppm.

Anal. Calcd. for $\text{C}_8\text{N}_4\text{Cl}_6\text{O}$: C, 25.23; N, 14.71. Found: C, 25.35; N, 14.82.

Method C.

A solution of **1** (1 g, 5.014 mmoles), phosphorus pentachloride (1.25 g, 6.017 mmoles) and toluene (25 ml) was refluxed for 16 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure. After dissolving the residue in chloroform (30 ml), the solution was washed with excess water. The solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2 x 4 cm). The column was eluted with *n*-hexane. Fractions involving **2** ($R_f = 0.54$, chloroform) were combined and evaporated under reduced pressure to give **2** in 11% (0.12 g). Fractions containing **3** ($R_f = 0.26$, chloroform) were combined and evaporated under reduced pressure to give **3** in 61% (0.58 g) yield.

Method D.

A solution of **1** (1 g, 5.014 mmoles), phosphorus pentachloride (2.09 g, 10.28 mmoles) and toluene (25 ml) was refluxed for 10 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure. After dissolving the residue in chloroform (40 ml) and water (40 ml), the organic layer was separated and washed with excess water. The solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2.5 x 6 cm). The column was eluted with chloroform/*n*-hexane (1:1, v/v). Fractions involving **2** ($R_f = 0.54$, chloroform) were combined and evaporated under reduced pressure to give **2** in 27% (0.295 g) yield. Fractions containing **3** ($R_f = 0.26$, chloroform) were combined and evaporated under reduced pressure. The residue was recrystallized from ethyl acetate/*n*-hexane (1:3, v/v) to give **3** in 45% (0.396 g) yield.

Method E.

A mixture of **1** (0.5 g, 2.507 mmoles), phosphorus pentachloride (0.6 g, 3.01 mmoles) and chlorobenzene (10 ml) was refluxed for 3 hours. After cooling to room temperature, water (40 ml) was added to the mixture. The organic layer was separated and washed with excess water. The organic solution was applied to the top of an open-bed silica gel column (2.5 x 6 cm). The column was eluted with *n*-hexane (100 ml) and then chloroform/*n*-hexane (1:1, v/v). Fractions involving **2** ($R_f =$

0.54, chloroform) were combined and evaporated under reduced pressure to give **2** in 43% (0.236 g) yield. Fractions containing **3** ($R_f = 0.26$, chloroform) were also combined and evaporated under reduced pressure to afford **3** in 43% (0.205 g) yield.

Synthesis of 3,4,5-Trichloro-1-(4,5,6-trichloropyridazin-3-yl)-pyridazin-6-one (**3**).

Method F.

A solution of **1** (0.5 g, 2.507 mmoles), phosphorus pentachloride (0.6 g, 3.01 mmoles) and cyclohexane (15 ml) was refluxed for 39 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure. The residue was dissolved in chloroform (10 ml) and water (10 ml). The organic layer was separated, and dried over anhydrous magnesium sulfate. The resulting solution was applied to the top of an open-bed silica gel column (2.5 x 7 cm). The column was eluted with chloroform/*n*-hexane (1:1, v/v). Fractions containing the product were combined and evaporated under reduced pressure. The crude product was recrystallized from chloroform/*n*-hexane (1:3, v/v) to yield only **3** in 81% (0.387 g) yield.

X-Ray Structural Analysis of Compound **3**.

Data collection: A colorless prismatic crystal of $C_8N_4OCl_6$ having approximate dimensions of 0.30 x 0.30 x 0.06 mm was mounted on a glass fiber.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range $58.97 < 2\theta < 59.87^\circ$ corresponded to a primitive monoclinic cell with dimensions: $a = 6.930$ (2), $b = 19.645$ (2), $c = 10.173$ (3) Å, $\beta = 107.70$ (2)°, $V = 1319.4$ (5) Å³. For $Z = 4$ and molecular weight = 380.83, the calculated density is 1.92 g/cm³. The systematic absence of: $h0l: h+l \neq 2n$, $0k0: k \neq 2n$, uniquely determine the space group to be: $P2_1/n$ (#14). The data were collected at a temperature of 23 ± 1 °C using the ω - 2θ scan technique to a maximum 2θ value of 135.2° . Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.22° with a take-off angle of 0.6° . Scans of $(1.50 + 0.30 \tan \theta)^\circ$ were made at speeds of 32.0, 16.0, 8.0 and $4.0^\circ/\text{min}$ (in omega) for each 2θ shell ($4.0 < 80.0 < 100.0 < 120.0 < 135.0^\circ$). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of 7 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.8 mm and the crystal to detector distance was 235 mm. The computer-controlled slits were set to 3.0 mm (horizontal) and 3.0 mm (vertical).

Data Reduction: Of the 2573 reflections which were collected, 1598 were unique ($R_{int} = 0.024$). The intensities of three representative reflections were measured after every 150 reflections. No decay correction was applied.

The linear absorption coefficient, μ , for Cu-K α radiation is 118.7 cm^{-1} . An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.32 to 1.00. The data were corrected for Lorentz polarization effects. A correction for secondary extinction was applied (coefficient = $1.31081e-05$).

Structure Solution and Refinement: The structure was solved by direct methods [3] and expanded using Fourier technique [4]. The non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement [5] was based on 1953 observed reflections ($I > 2.00 \sigma(I)$) and 173 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of: $R = \sum ||F_o| - |F_c|| / \sum |F_o| = 0.048$; $R_w = \sqrt{\sum \omega(|F_o| - |F_c|)^2} / \sum \omega F_o^2 = 0.079$.

The standard deviation of an observation of unit weight [6] was 1.64. The weighting scheme was based on counting statistics and included a factor ($p = 0.078$) to downweight the intense reflections. Plots of $\sum w(|F_o| - |F_c|)^2$ versus $|F_o|$, reflection order in data collection, $\sin \theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.41 and $-0.45 \text{ e}^{-1}/\text{Å}^3$, respectively. Neutral atom scattering factors were taken from Cromer and Wabers [7]. The values for the mass attenuation coefficients are those of Creagh and Hubbel [8]. All calculations were performed using the teXsan [9].

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- [6] Standard deviation of an observation of unit weight: $\sqrt{\sum \omega(|F_o| - |F_c|)^2 / (N_o - N_v)}$. Where: $N_o = \text{number of observations}$, $N_v = \text{number of variables}$.
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- [8] D. C. Creagh and J. H. Hubbell, "International Tables for Crystallography", vol. C, (A. J. C. Willson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).
- [9] teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992) crystallographic software package of Molecular Structure Corporation.
- [10] The ADC (atomic designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ± 4 lattice translations from the origin

(TA = 5, TB = 5, TC = 5) can be represented. The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure is given below. For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN = 1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the

ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis. An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit. Symmetry Operators: (1) X, Y, Z; (2) 1/2-X, 1/2+Y, 1/2-Z; (3) -X, -Y, -Z; (4) 1/2+X, 1/2-Y, 1/2+Z.