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# HALOGENATED PYRIDINES
# 5.* STRUCTURE OF THE PRODUCTS OF CYCLIZATION OF CHLORINE-CONTAINING δ-OXONITRILES

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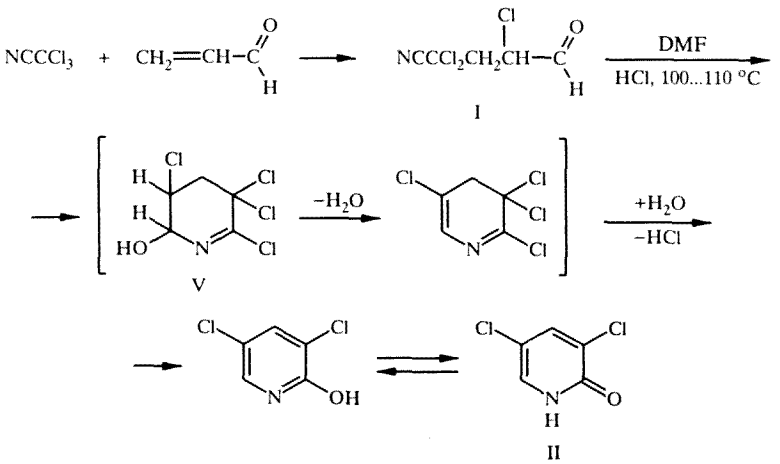
*Cyclization of the nitriles of polychlorinated δ-oxoacids — products of the addition of chloral to acrylonitrile and methacrylonitrile — yielded chlorine-containing tetrahydropyridines. Their structure and some of their chemical properties have been studied.*

Chlorine-substituted pyridines can be efficiently prepared by cyclization of the corresponding δ-oxonitriles containing a determined number of chlorine atoms. The method is highly selective, requires only mild reaction conditions and is environmentally friendly.

The δ-oxonitrile starting materials are prepared by addition of either chlorine-containing oxo compounds to nitriles of α,β-unsaturated carboxylic acids [1-3] of nitriles of polychlorinated carboxylic acids to α,β-unsaturated carbonyl compounds [4-6].

It has been established that the structure of the chlorine-substituted δ-oxonitriles and particularly the relative location of the chlorine atoms in the molecule in many ways determine the structure of the pyridine base formed in the cyclization. Thus, cyclization of the oxonitrile I in DMF at 100-120°C gives the pyridine II [5] and the oxonitrile III under the same conditions yields 2,3,5-trichloropyridine (IV) [1]. The reaction apparently proceeds according to the following scheme:




*For communication 4, see [8].

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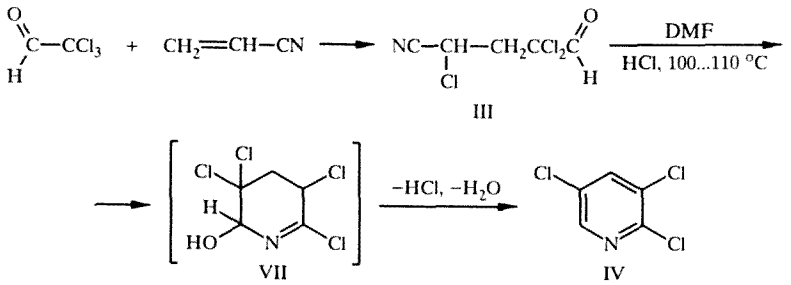
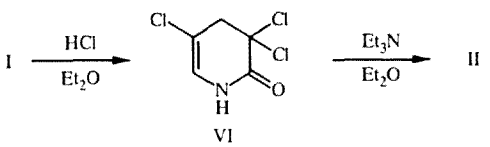


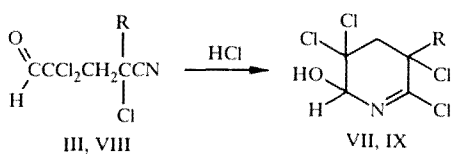
Obviously, separation and study of the intermediate products of the cyclization will lead to a better understanding of the mechanism of the process and hence facilitate optimization of the desired reaction.

Conversion of the intermediate tetrahydropyridine V formed according to the first scheme takes place via the following steps: splitting off of water, hydrolysis of the chlorine at position 2, and dehydrochlorination from positions 3 and 4. Such a reaction route is confirmed experimentally. When the cyclization reaction was carried out in dry ether at 20-30°C, the dihydropyridone VI was isolated; this is then dehydrochlorinated to the pyridone II [5].



The tetrahydropyridine VII, which is a likely intermediate in the cyclization (according to the second scheme) of oxonitrile III into trichloropyridine IV, has not previously been isolated.

In a study of the influence of reaction conditions for the cyclization of δ-oxonitriles on the structure and yield of pyridine bases, we observed that adducts of chloral and acrylo- and methacrylonitrile (III, VIII) on cyclization in dry ether under the action of HCl at 0-5°C are converted into tetrahydropyridines VII and IX respectively in yields of around 90%.



III, VII R = H; VIII, IX R = Me

The structure and composition of compounds VII and IX were established on the basis of elemental analysis, NMR spectroscopy, and mass spectrometry.

Obviously, in the absence of a hydrogen at the α-position to the hydroxyl group of the tetrahydropyridines VII and IX, dehydration becomes impossible under the conditions studied and hence also subsequent hydrolysis of the chlorine at position 2 and formation of the corresponding dihydropyridones.

As has been noted previously, cyclization of the nitrile III in DMF at elevated temperature results in the formation of pyridine IV, probably because, under these conditions, dehydration (1,4-elimination from positions 3 and 6) and dehydrochlorination from positions 4 and 5 are taking place simultaneously. However, it is not possible to obtain the corresponding chloropyridine from oxonitrile VIII even at high temperature (120-150°C) because the lack of a hydrogen at position 3 of the ring of IX makes a 1,4-elimination impossible.

A study of the chemical behavior of the tetrahydropyridines VII and IX led to some unexpected results. The tetrahydropyridine VII was not converted to the trichloropyridine IV on heating either in benzene at bp or in DMF at 120-150°C with simultaneous passage of a stream of hydrogen chloride. Heating compounds VII and IX with an equimolar quantity of triethylamine or N,N-diethylaniline in diethyl ether gave an unstable compound which rapidly formed tars and whose structure has not been established. Reaction with two moles of triethylamine gave an unidentified tar.

TABLE 1. Bond Lengths for Compound XI

| Bond | $d$, Å | Bond | $d$, Å |
|---|---|---|---|
| $Cl_{(1)}$—$C_{(5)}$ | 1,790(5) | $Cl_{(2)}$—$C_{(5)}$ | 1,783(5) |
| $Cl_{(3)}$—$C_{(3)}$ | 1,802(5) | $O_{(1)}$—$C_{(2)}$ | 1,216(7) |
| $O_{(2)}$—$C_{(6)}$ | 1,402(6) | $O_{(2)}$—$C_{(8)}$ | 1,415(7) |
| $N_{(1)}$—$C_{(2)}$ | 1,340(7) | $N_{(1)}$—$C_{(6)}$ | 1,440(7) |
| $C_{(2)}$—$C_{(3)}$ | 1,531(7) | $C_{(3)}$—$C_{(4)}$ | 1,551(7) |
| $C_{(3)}$—$C_{(7)}$ | 1,558(7) | $C_{(4)}$—$C_{(5)}$ | 1,489(6) |
| $C_{(5)}$—$C_{(6)}$ | 1,529(8) | | |

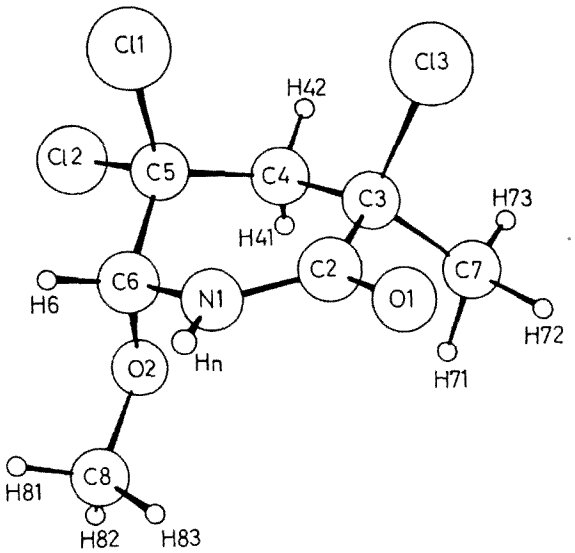
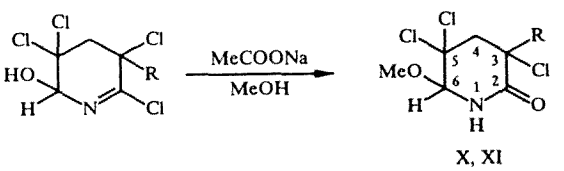



Fig. 1. Structure of 6-methoxy-3-methyl-3,5,5-trichloropiperid-2-one.

On attempting to dehydrochlorinate compounds VII and IX with sodium or potassium acetate in methanol at 50-60°C over 4 hours, the product was not the expected chloropyridines but the derivatives X and XI.




X, XI

X R = H; XI R = Me

The formation of compounds X and XI is explained by the interaction of methanol with the hydroxyl group of the heterocycle and subsequent hydrolysis of the chlorine at position 2. Evidently, this reaction is preferred over other possible reactions, for example dehydrochlorination, or substitution of a chlorine by an acetoxy group. It has been established that methanol does in fact react with heterocycles VII and IX at room temperature with the formation of piperidines X, XI in yields around 70%.

The structure of compounds X and XI has been demonstrated from their PMR spectra, and for the ring XI also by X-ray studies. A general view of the molecule of XI is shown in Fig. 1. Bond lengths and valence angles do not differ from normal values (Tables 1 and 2) and do not require special comment. The heterocycle has a semichair conformation with bending along the $C_{(4)}$-$C_{(6)}$ line equal to 49.6°. The methyl and methoxy substituents are *cis*-oriented relative to each other. The $CH_3$

TABLE 2. Valence Angles for Compound XI

| Angle | $\omega$, deg. | Angle | $\omega$, deg. |
|---|---|---|---|
| $C_{(6)}$—$O_{(2)}$—$2C_{(8)}$ | 114,1(4) | $C_{(2)}$—$N_{(1)}$—$C_{(6)}$ | 126,8(4) |
| $O_{(1)}$—$2C_{(2)}$—$N_{(1)}$ | 121,7(5) | $O_{(1)}$—$C_{(2)}$—$C_{(3)}$ | 119,5(5) |
| $N_{(1)}$—$C_{(2)}$—$C_{(3)}$ | 118,8(5) | $Cl_{(3)}$—$C_{(3)}$—$C_{(2)}$ | 105,3(3) |
| $Cl_{(3)}$—$C_{(3)}$—$C_{(4)}$ | 110,1(3) | $Cl_{(3)}$—$C_{(3)}$—$C_{(7)}$ | 107,7(3) |
| $C_{(2)}$—$C_{(3)}$—$C_{(4)}$ | 114,6(4) | $C_{(2)}$—$C_{(3)}$—$C_{(7)}$ | 108,2(4) |
| $C_{(4)}$—$C_{(3)}$—$C_{(7)}$ | 110,7(4) | $C_{(3)}$—$C_{(4)}$—$C_{(5)}$ | 114,0(4) |
| $Cl_{(1)}$—$C_{(5)}$—$Cl_{(2)}$ | 107,4(3) | $Cl_{(1)}$—$C_{(5)}$—$C_{(4)}$ | 112,9(4) |
| $Cl_{(1)}$—$C_{(5)}$—$C_{(6)}$ | 106,9(4) | $Cl_{(2)}$—$C_{(5)}$—$C_{(4)}$ | 109,9(4) |
| $Cl_{(2)}$—$C_{(5)}$—$C_{(6)}$ | 109,1(4) | $C_{(4)}$—$C_{(5)}$—$C_{(6)}$ | 110,4(4) |
| $O_{(2)}$—$C_{(6)}$—$N_{(1)}$ | 112,3(4) | $O_{(2)}$—$C_{(6)}$—$C_{(5)}$ | 106,5(4) |
| $N_{(1)}$—$C_{(6)}$—$C_{(5)}$ | 108,6(4) | | |

TABLE 3. Fractional Coordinates of Atoms of the Elementary Cell of Compound XI

| Atom | $x$ | $y$ | $z$ |
|---|---|---|---|
| $Cl_{(1)}$ | 0,3695(1) | 0,0700(2) | 0,1587(1) |
| $Cl_{(2)}$ | 0,3074(1) | -0,3733(2) | 0,1042(1) |
| $Cl_{(3)}$ | 0,6007(1) | 0,0941(3) | 0,1501(1) |
| $O_{(1)}$ | 0,5883(3) | 0,0006(7) | 0,4009(3) |
| $O_{(2)}$ | 0,3817(3) | -0,4839(6) | 0,3250(3) |
| $N_{(1)}$ | 0,4466(3) | -0,1334(8) | 0,3717(3) |
| $C_{(2)}$ | 0,5325(4) | -0,0904(9) | 0,3384(4) |
| $C_{(3)}$ | 0,5604(3) | -0,1573(8) | 0,2182(4) |
| $C_{(4)}$ | 0,4831(3) | -0,2708(8) | 0,1467(4) |
| $C_{(5)}$ | 0,3905(3) | -0,2132(8) | 0,1824(5) |
| $C_{(6)}$ | 0,3769(3) | -0,2566(8) | 0,3097(5) |
| $C_{(7)}$ | 0,6421(3) | -0,3083(8) | 0,2285(5) |
| $C_{(8)}$ | 0,3587(4) | -0,5574(9) | 0,4361(5) |
| $H_{(1)}$ | 0,434(5) | -0,09(1) | 0,436(6) |
| $H_{(41)}$ | 0,487(3) | -0,416(7) | 0,148(4) |
| $H_{(42)}$ | 0,499(3) | -0,228(9) | 0,067(4) |
| $H_{(6)}$ | 0,319(3) | -0,211(7) | 0,335(3) |
| $H_{(71)}$ | 0,628(5) | -0,47(1) | 0,271(7) |
| $H_{(72)}$ | 0,698(5) | -0,25(1) | 0,291(7) |
| $H_{(73)}$ | 0,669(3) | -0,330(8) | 0,149(4) |
| $H_{(81)}$ | 0,412(6) | -0,47(1) | 0,499(8) |
| $H_{(82)}$ | 0,350(5) | -0,72(1) | 0,428(7) |
| $H_{(83)}$ | 0,297(5) | -0,51(1) | 0,449(7) |

group of the methoxy substituent and the $C_{(5)}$ atom are located in the *trans*-position relative to the $C_{(6)}$-$O_{(2)}$ bond, and the torsion angle $C_{(8)}O_{(2)}C_{(6)}C_{(5)}$ is 170°. The conformation is twisted along the $C_{(4)}$-$C_{(5)}$ and $C_{(5)}$-$C_{(6)}$ bonds. The conformation along the $C_{(3)}$-$C_{(4)}$ bond is close to planar — the $C_{(2)}C_{(3)}C_{(4)}C_{(5)}$ torsion angle is 24°.

Attempts to dehydrochlorinate compounds X and XI with a two-fold excess of $(C_2H_5)_3N$ in benzene over 20 h did not meet with success, possibly because the conformation of the molecule is unfavorable for the elimination of HCl as was demonstrated for XI.

To explain the peculiarities of the chemical behavior of the tetrahydropyridines VII and IX it is necessary to study the conformation of these molecules. However, attempts to do this by X-ray diffraction were unsuccessful because crystals of the compound studied, VII, were unstable to radiation — on exposure to radiation they acquired a brown color and the crystal structure was lost.

## EXPERIMENTAL

A Bruker WM-250 instrument was used for $^1H$ and $^{13}C$ NMR spectra with HMDS internal standard. Elemental analyses were carried out on a Carlo Erba-110.

The results of elemental analyses were in agreement with calculations.

**Tetrahydropyridines VII and IX**. Dry hydrogen chloride was passed for 1 h through a solution of 0.1 mole oxonitrile III or VIII in 75 ml dry ether at −5°C. The temperature was maintained below 0°C. The solution was then left in a refrigerator overnight. The crystals which deposited were filtered off, washed with 25 ml cold ether and 25 ml pentane and recrystallized from benzene.

**6-Hydroxy-2,3,5,5-tetrachloro-3,4,5,6-tetrahydropyridine (VII, $C_5H_5ONCl_4$)**, mp 134-135°C. PMR spectrum (acetone-$D_6$) (δ ppm): 8.65 (1H, br.s, OH), 6.25 (1H, m, 6-H), 4.87 (1H, m, 3-H), 3.43 (1H, m, 4b-H), 3.32 (1H, m, 4a-H). Yield 18.5 g (79%).

**6-Hydroxy-3-methyl-2,3,5,5-tetrachloro-3,4,5,6-tetrahydropyridine (IX, $C_6H_7ONCl_4$)**, mp 130-131°C. PMR spectrum (acetone-$D_6$) (δ ppm): 8.62 (1H, br.s, OH), 6.24 (1H, m, 6-H), 3.11 (1H, m, 4b-H), 2.93 (1H, m, 4a-H), 1.38, (3H, c, $CH_3$). Yield 19.5 g (78%).

**Piperidones X and XI**. A. To a solution of 0.008 mole tetrahydropyridine VII or IX in 4 ml methyl ethyl ketone was added 0.012 mole sodium acetate and the mixture heated at 70°C for 4 h with continuous stirring. After cooling, 100 ml water was added to the reaction mixture and the mixture left in a refrigerator overnight. The crystals which formed were filtered off and recrystallized from benzene.

B. A solution of 0.008 mole tetrahydropyridine VII in 2 ml methanol was kept for 2 h at room temperature. The methanol was evaporated and the residue recrystallized from 1:1 ether−hexane.

**6-Methoxy-3,5,5-trichloropiperid-2-one (X, $C_6H_8O_2NCl_3$)**, mp 130-131°C. PMR spectrum (acetone-$D_6$) (δ ppm): 7.40 (1H, br.s, NH), 4.68 (1H, m, 6-H), 4.62 (1H, m, 3-H), 3.52 (3H, s, $OCH_3$), 3.20 (1H, m, 4b-H), 3.10 (1H, m, 4a-H). Yield 15.8 g (68%).

**6-Methoxy-3-methyl-3,5,5-trichloropiperid-2-one (XI, $C_7H_{10}O_2NCl_3$)**, mp 109-110°C. PMR spectrum (acetone-$D_6$) (δ ppm): 7.38 (1H, br.s, NH), 4.65 (1H, m, 6-H), 4.51 (1H, m, 3-H), 3.51 (3H, s, $OCH_3$), 3.01 (1H, m, 4b-H), 2.93 (1H, m, 4a-H), 1.34 (3H, s, $CH_3$). Yield (Method A) 17.6 g (71%), (Method B) 0.12 g (61%).

**X-ray Structural Study of Piperidone XI.** The well-defined crystals of $C_7H_{10}NO_2Cl_3$ belong to the monoclinic system: $a$ = 14.765(4), $b$ = 6.092(2), $c$ = 11.738(3) Å; $\gamma$ = 92.87(4)°, $V$ = 1064.5(9) Å, M = 246.51, $d$ = 1.553 g/cm$^3$, $z$ = 4, space group $P2_{1/n}$.

A total of 1267 independent nonzero reflections were obtained on a DAR-UM automatic diffractometer with Cu Kα radiation and a graphite monochromator.

The structure was determined by a direct statistical method. The hydrogen atoms were localized objectively from a differential synthesis of the elementary density. Refinement of the structure in full-matrix anisotropy (for H atoms by isotope) of approximation were completed for R = 0.053 ($R_w$ = 0.039). All the calculations were carried out on a PC-AT using the CSD program of [7]. The coordinates of the atoms are set out in Table 3.

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