HALOPYRIDINES.

1. SYNTHESIS OF 3,5-DICHLORO-2-PYRIDONE AND 2,3,5-TRICHLOROPYRIDINE

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Trichloroacetonitrile reacts with acrolein to give 2,2,4-trichloro-5-oxopentanonitrile, the cyclization of which to chloropyridines has been examined.

In view of the continuing interest in the chemistry of halopyridines, the development of convenient, simple, ecological methods for their synthesis via polyhalogenated open-chain compounds containing functional groups remains of interest. We have examined the reaction of trichloroacetonitrile (I) with acrolein (II), since the addition product, 2,2,4-trichloro-5-oxopentanonitrile (III) could constitute a convenient synthon for the preparation of halogenated pyridines.

In the presence of benzoyl peroxide or azobisisobutyronitrile, no (III) was formed, since these initiators effectively promote the polymerization of the acrolein. Boiling equimolar amounts of the reactants in acetonitrile or methanol, or in the absence of a solvent [ratios of (I)–(II), 1:2 and 2:1] in the presence of activated Cu_2Cl_2 [1] or bronze [2] for 2-12 h likewise failed to give (III). Yields of around 70% of (III) were, however, obtained on heating the reactants in the presence of copper catalysts in an ampul or a stainless-steel autoclave at 80-90°C. The reaction may be carried out in a solvent (acetonitrile, benzene, or hexane). However, in order to simplify workup of the reaction mixture and isolation of the product (III), it is preferable to carry out the reaction in the absence of a solvent, using a 20-50% excess of the nitrile (I). Identical catalytic activity is shown by Cu, Cu_2Cl_2, $CuCl_2$, and $Cu(CH_3COO)_2$ in amounts of 5-10%. Under these conditions, addition is not accompanied by any significant polymerization of the acrolein.

The IR spectrum of (III) shows absorption characteristic of C=O (1740), C≡N (2250 cm^{-1}), together with bands corresponding to other parts of the molecule. Noteworthy is the very low intensity of the absorption for the nitrile group, apparently as a result of the influence of the adjacent CCl_2 group. The PMR spectrum shows signals for the $C_{(3)}$-$C_{(4)}$ fragment, corresponding to an ABC spin system with coupling constants $^2J_{BC} \approx 16$, $^3J_{AB} \approx 4$, and $^3J_{AC} \approx 8$ Hz.

The product of the addition of chloral to acrylonitrile, 2,4,4-trichloro-5-oxopentanonitrile, is known to cyclize on treatment with acidic reagents (such as $AlCl_3$ and HCl) at high temperatures to 2,3,5-trichloropyridine (IV) [3, 4]. Under similar conditions, (III) behaves differently. On saturation of a solution of this compound in DMF with dry HCl followed by workup of the reaction mixture, the principal product isolated was 3,5-dichloro-2-pyridone (V) in yields of over 90%. By analogy with the reaction sequence described in [3, 4], it might be supposed that the pyridone (V) is formed by hydrolysis of the initially formed trichloropyridine (IV). It was, however, found that no hydrolysis of (IV) to the pyridone (V) occurs under the reaction conditions. However, when dry HCl is passed into a solution of the oxonitrile (III) in dry dibutyl ether, 90% of 2-hydroxy-3,3,5-trichloro-3,4-dihydropyridine (VI) was isolated from the reaction mixture.

Dehydrochlorination of (VI) with triethylamine in dry benzene gave the pyridone (V) in near-quantitative yields.

Hence, the formation of the chloropyridone (V) from the oxonitrile (III) probably occurs as a result of successive cyclization in the presence of HCl, dehydration, hydrolysis to (VI), and finally dehydrochlorination of the dihydropyridone (VI) to the pyridone (V).

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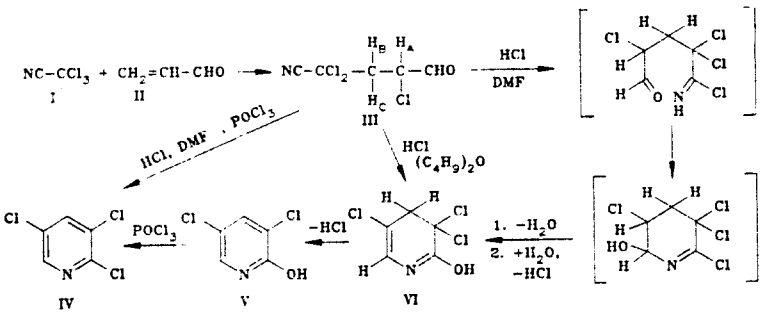

Confirmation of this reaction sequence is the subject of continuing study.

It has been found that when the oxonitrile (III) is heated at 170-180°C in an inert atmosphere, or when HCl is passed through the oxonitrile (III) at 25-30°C, no conversion to the pyridine (IV) or the pyridone (V) occurs. When these reactions were carried out at 190-200°C, the mixture resinified after 15-20 min.

The pyridone (V) obtained on treatment with $POCl_3$ was converted in high yield into 2,3,5-trichloropyridine (IV). It was also found that when (III) was cyclized in DMF in the presence of $POCl_3$, the chloropyridine (IV) was formed exclusively. The cyclization may be carried out either as described above, or in an autoclave in solution in benzene at 180-190 °C. Finally, the pyridine (IV) may be obtained by carrying out the addition and cyclization reactions in one vessel, without the intermediate isolation of the oxonitrile (III).

EXPERIMENTAL

GLC was carried out on a Chrom-5 chromatograph with DIP, carrier gas helium (1.8 liters/h), stainless steel column 3700 × 3 mm, with 5% XE-60 on Inerton-Super. PMR spectra were obtained on a Varian T-60 instrument, internal standard TMS. IR spectra were obtained on an IR-75 in thin layers.

2,2,4'-Trichloro-5-oxopenatononitrile (III). A mixture of 21.6 g (150 mmole) of the nitrile (I), 5.6 g (0.1 mole) of acrolein, and 1.98 g (1 mmole) of Cu_2Cl_2 was heated in a sealed glass ampul or an autoclave for 6 h at 90°C. Excess nitrile (I) was removed under reduced pressure, and the mixture diluted with ether, the ether removed, and the residue fractionated to give 14 g (68%) of product, bp 54°C (67 Pa). PMR spectrum ($CDCl_3$): 9.47 (1H, s, CHO), 4.55 (1H, m, A-H), 3.47 (1H, m, B-H), 2.83 ppm (1H, m, C-H). Found, %: C 29.9, H 1.9, Cl 52.7, N 7.1. $C_5H_4Cl_3NO$. Calculated, %: C 29.9, H 2.0, Cl 53.1, N 7.0.

3,5-Dichloro-2-pyridone (V). A solution of 2.0 g (10 mmole) of the oxonitrile (III) in 20 ml of DMF was flushed through with argon for 3 min, then saturated with dry HCl for 15 min. The temperature at this stage rose spontaneously to 110°C, and on cooling the mixture was poured into 70 ml of ice water, basified with 20% aqueous potassium carbonate to pH 7.5, and extracted with ether (6 × 40 ml). The ether layer was dried over $CaCl_2$, and the ether removed to give 1.5 g (91%) of product, mp 179°C (from aqueous ethanol); literature data, mp 179-181°C [5]. PMR spectrum (DMF-D_7): 7.78 (1H, d, $^4J \approx 3.4$ Hz, 6-H), 7.63 ppm (1H, d, $^4J \approx 3.4$ Hz, 4-H). Found, %: C 36.8, H 1.2, Cl 43.2, N 8.6. $C_5H_3Cl_2NO$. Calculated, %: C 36.6, H 1.8, Cl 43.3, N 8.5%.

2-Hydroxy-3,3,5-trichloro-3,4-dihydropyridine (VI). A solution of 2.0 g (10 mmole) of (III) in 20 ml of dry dibutyl ether was flushed through with argon, saturated with dry HCl for 20 min, and heated for 1 h at 90°C. The solvent was then removed under reduced pressure to give 1.8 g (90%) of product, mp 149°C (from benzene–hexane, 2:1). PMR spectrum (DMF-D_7): 6.51 (1H, d, 6-H), 3.55 ppm (2H, s, 4-H). Found, %: C 30.5, H 2.1, Cl 53.2, N 7.0. $C_5H_4Cl_3NO$. Calculated, %: C 29.9, H 2.0, Cl 53.1, N 7.0.

Dehydrochlorination of (VI). To a solution of 0.4 g (2 mmole) of the dihydropyridine (VI) in 50 ml of dry benzene was added with stirring 0.2 g (2 mmole) of Et_3N in 10 ml of dry benzene. The mixture was boiled for 4 h, the triethylamine hydrochloride filtered off, and the benzene evaporated to give 0.31 g (95%) of the pyridone (V), mp 175-176°C (from benzene–hexane, 2:1).

2,3,5-Trichloropyridine (IV). A. A mixture of 0.98 g (6 mmole) of the pyridone (V) and 4.6 g (30 mmole) of $POCl_3$ was heated in a sealed glass ampul for 3 h at 190°C. When the reaction was complete, the mixture was poured onto ice, and the solid filtered off. Yield 0.97 g (87%), mp 50°C; literature mp 49-50°C [3].

B. A solution of 2.0 g (10 mmole) of (III) and 1.53 g (10 mmole) of $POCl_3$ in 20 ml of DMF was flushed through with argon, saturated with dry HCl for 20 min, the temperature rising to 115°C. When the reaction was complete, the mixture was poured into 100 ml of ice water, and the crystals which separated were filtered off and dried to give 1.45 g (79%) of product, mp 50°C.

C. A solution of 2.0 g (10 mmole) of (III) and 1.53 g (10 mmole) of $POCl_3$ in 20 ml of dry benzene was heated in a stainless-steel autoclave for 1 h at 190°C. The benzene was removed, and the residue treated with 20 ml of water, extracted with ether (2 × 10 ml), the ether layer dried over $CaCl_2$, and the ether evaporated to give 1 g (76%) of product, mp 50°C.

D. A mixture of 6.48 g (45 mmole) of the nitrile (I), 1.68 g (30 mmole) of acrolein, and 0.3 g (1.5 mmole) of Cu_2Cl_2 in 25 ml of dry benzene was heated in a stainless-steel autoclave for 5 h at 90°C, then 4.6 g (30 mmole) of $POCl_3$ was added and heating continued for 30 min at 180°C. The benzene was removed, and the residue treated with water, extracted with ether (4 × 40 ml), the ether layer dried over $CaCl_2$, and the ether evaporated to give 3.8 g (70%) of product, mp 50°C.

Hydrolysis of (IV) under the Experimental Conditions. A stream of dry HCl was passed through a solution of 1.46 g (8 mmole) of the pyridine (IV) and 0.144 g (8 mmole) of water in 15 ml of DMF for 1 h, maintaining the temperature at 110-115°C. When the reaction was complete, the mixture was poured into ice water, and the solid filtered off to give 1.4 g (96%) of the pyridine (IV), mp 50°C.

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CRYSTAL AND MOLECULAR STRUCTURE OF 7,7-DIMETHYL-2,3-DI(4-METHOXYPHENYL)-5-OXO-5,6,7,8-TETRAHYDROQUINOLINE

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An x-ray crystallographic investigation of 7,7-dimethyl-2,3-di(4-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydroquinoline, obtained by the hydrolysis of its oxime, was undertaken. The oxime, together with the isomeric oxime of 7,7-dimethyl-2,4-di(4-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydroquinoline, is formed in the reaction of 5,5-dimethyl-2-[1,3-di(4-methoxyphenyl)-3-oxopropyl]cyclohexane-1,3-dione with hydroxylamine hydrochloride.

2,4-Diphenyl-5-oxo-5,6,7,8-tetrahydroquinoline oxime is formed in the reaction of 2-(1,3-diphenyl-3-oxopropyl)cyclohexane-1,3-dione with hydroxylamine hydrochloride [1]. We found that, in addition to the expected 2,4-diaryl-5-oxohydroquinoline oxime (II), 5,5-dimethyl-2-[1,3-(4-methoxyphenyl)-3-oxopropyl]cyclohexane-1,3-dione (I) under analogous conditions forms a compound to which the structure of the isomeric 2,3-diaryl-5-oxohydroquinoline oxime (III) was assigned on the basis of the data from IR and PMR spectroscopy [2].

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