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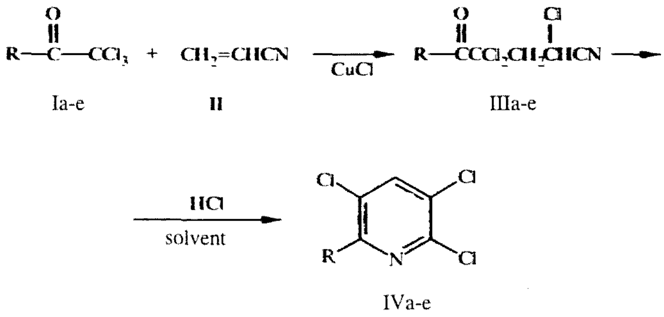
HALOGEN-SUBSTITUTED PYRIDINES
4*. 2,3,5-TRICHLOROPYRIDINES SUBSTITUTED AT POSITION 6

G. A. Shvekhgeimer, K. I. Kobrakov,
and H. A. Toshkhodzhaev

Addition of alkyl(aryl)trichloromethylketones to acrylonitrile in the presence of copper(I) chloride gave chlorine-substituted δ-oxonitriles. Cyclization of the latter was effected by the action of dry hydrogen chloride yielding the corresponding chlorine-containing tetrahydropyridines and pyridines.

During the last decade there has been active development of methods for the preparation of chlorine-substituted pyridines by intramolecular cyclization of the corresponding δ-oxonitriles [1-4]. In particular, the synthesis of 2,3,5-trichloropyridines having an alkyl substituent at position 6 by cyclization of aliphatic δ-oxonitriles has been described [5], the latter being prepared by addition of gem-polyhalonitriles to α,β-unsaturated carbonyl compounds.

We have examined another route to the synthesis of chloropyridines having both alkyl and aryl substituents at position 6: the addition of trichloroacetyl derivatives (I) to acrylonitrile (II) and subsequent cyclization of the δ-oxonitriles (III) so formed to pyridine bases (IV).



I, III, IV: a **R** = **Me**, b **R** = **CCl_3**, c **R** = **Ph**, d **R** = **4-PhC_6H_4**, e **R** = **4-HOC_6H_4**

We found that the desired product III could be obtained by heating, for 26 hours under reflux, a mixture of the trichloromethyl ketone I, acrylonitrile II (in molar ratio I:II = 1:4) and 5% molar CuCl. The yields were, however low – 12 to 18%. Later, we were able to increase the yields to 90% by carrying out the reaction in a sealed glass ampul for 12 to 15 hours at 100 to 110°C.

At lower temperatures and with shorter reaction times, and also when using a $CuCl\cdot Ph_3P$ (1% molar) catalyst system in CH_3CN, the yield of compound III was reduced. The characteristics of the products III are set out in Table 1.

Cyclization of the δ-ketonitriles IIIa-e into 6-substituted 2,3,5-trichloropyridines IVa-e was effected by passing dry hydrogen chloride through a solution of compounds III in DMF for 45 to 60 min. The reaction temperature spontaneously rose over 15-20 min to 90-115°C and then gradually fell to room temperature. The reaction led to the formation of substituted pyridines IVa-e in yields of 85-95% (Table 2).

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*For Communication 3, see [3].

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TABLE 1. Characteristics of Nitriles IIIa-e and VIIb, c

Compound	Empirical formula	bp °C/Pa	PMR Spectrum in $CDCl_3$, δ ppm*				Yield (%)
			CH_2 (2H d.d)		CH(1H, s) or CH_3 (3H, s)	R	
IIIa	$C_6H_6Cl_3NO$	72...73/33	3,23	3,04	4,59	2,44 (3H, s, CH_3)	90
IIIb	$C_6H_3Cl_6NO$	107...108/13	3,47	3,34	4,88	—	93
IIIc	$C_{11}H_8Cl_3NO$	113...115/13	3,37	3,01	4,68	7,06...7,48 (3H, m, м-H_{arom}, n-H_{arom}); 7,95...8,19 (2H, m, *o*-H_{arom})	87
IIId	$C_{12}H_{10}Cl_3NO$	144...145/27	3,66	3,09	4,80	2,30 (3H, s, CH_3); 7,30 (2H, d, м-H_{arom}); 8,12 (2H, d, *o*-H_{arom})	90
IIIe	$C_{11}H_8Cl_3NO_2$	—*2	3,71	3,10	4,85	6,83 (2H, d, м-H_{arom}); 8,10 (2H, d, *o*-H_{arom})	92
VIIb	$C_7H_5Cl_6NO$	—*2	3,10		2,05	—	91
VIIc	$C_{12}H_{10}Cl_3NO$	124...125/23	3,35		2,11	7,51 (3H, m, м-H_{arom} and n-H_{arom}); 8,22 (2H, m, *o*-H_{arom})	88

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*For compounds IIIa-e, coupling constants of CH_2 (H_A & H_B) and CH (H_c) groups were $^2J_{AB} = 9$, $^3J_{AC} = 3$, $^3J_{BC} = 4$ Hz.

*2These compounds were purified by passing through a column of L 100/250 silica gel (100 × 100 mm); eluent: hexane for IIIe, CCl_4 for VIIb.

TABLE 2. Characteristics of Substituted Pyridines IVa-e and Tetrahydropyridines VIIIb, c

Compound	Empirical formula	mp °C (solvent)	PMR Spectrum, δ ppm*		Yield % (method)
			4-H (1H, s) or CH_2 (2H, d.d)	R	
IVa	$C_6H_4Cl_3N$	70...71 (hexane)	7,70	2,59 (3H, c, CH_3)	95 (A) 90 (B)
IVb	C_6HCl_6N	58...59 (hexane)	7,50	—	90 (A) 88 (B)
IVc	$C_{11}H_6Cl_3N$	74...75 (hexane)	7,50	7,25 (3H, m, м-H_{arom}); 7,53 (2H, m, *o*-H_{arom})	92 (A) 90 (B)
IVd	$C_{12}H_8Cl_3N$	94...95 (hexane)	7,86	2,40 (3H, s, CH_3); 7,23 (2H, d, *o*-H_{arom}); 7,61 (2H, d, м-H_{arom})	91 (A) 86 (B)
IVe	$C_{11}H_6Cl_3NO$	87...88 (CCl_4)	7,76	6,77 (2H, d, *o*-H_{arom}); 7,57 (2H, d, м-H_{arom})	88 (A) 80 (B)
VIIIb*2	$C_7H_6Cl_7NO$	118...120 (benzene)	3,90	—	87 (A) 86 (B)
VIIIc*2	$C_{12}H_{11}Cl_4NO$	175...177 (benzene)	3,30	7,45 (3H, m, м-H_{arom}), 7,80 (2H, d, *o*-H_{arom})	85 (A)

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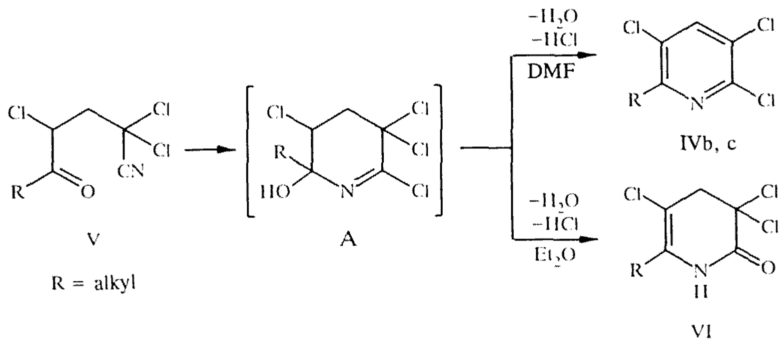
*Spectra of compounds IV run in $CDCl_3$, of VIII in $(CD_3)_2O$.

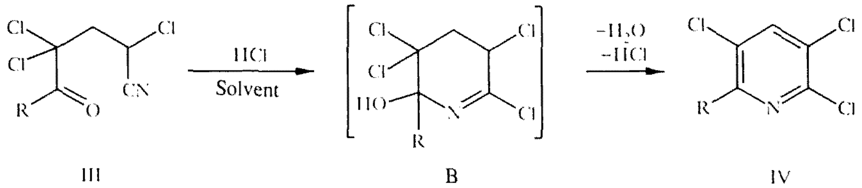
*2Proton signals of CH_3 group of compounds VIIIb and VIIIc were singlets at 2.01 and 1.88 ppm respectively.

Similar products were obtained when cyclization of the nitriles III was carried out in diethyl or dibutyl ether, benzene, or n-hexane.

On the other hand, it was found earlier [5] that in the solvents listed (apart from DMF) the substituted δ-ketonitriles (V) were transformed in a different way by dry HCl at 20-80°C to give 6-alkyl-3,3,5-trichloro-3,4-dihydropyrid-2-ones (VI). The scheme proposed by the authors of [5] for the cyclization of nitriles V in DMF assumed the simultaneous elimination from the intermediate (A) of molecules of HCl and H_2O under the action of solvent and elevated temperature with the formation of pyridine derivatives IV, whereas in the other solvents this intermediate preferentially undergoes dehydration with subsequent hydrolysis of a chlorine to form dihydropyridines VI.



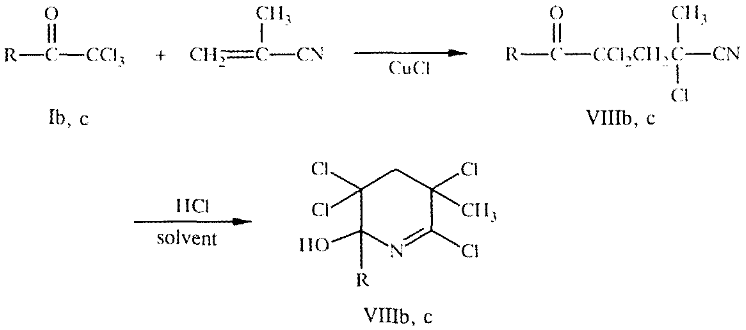
In the case of nitriles III, the first stage of the cyclization is probably the formation of the intermediate (B) in which, in the absence of a hydrogen atom vicinal to the hydroxyl group, 5,6-dehydration is not possible and, independently of solvent type, the aromatic ring is formed by simultaneous 3,6-dehydration and 4,5-elimination of HCl.



In support of the proposed scheme we prepared, from ketones Ib, c and methacrylonitrile, the δ-ketonitriles VII. The reactions were carried out in sealed glass ampuls at 130°C with 15 h reaction time and a 1:4 molar ratio of ketone to nitrile in the presence of 5% molar CuCl.

The characteristics of the δ-ketonitriles so prepared are given in Table 1.

The products VII on cyclization must be transformed into tetrahydropyridine derivatives in which there is no hydrogen at position 3 and hence 3,6-dehydration is not possible. In fact, cyclization of nitriles VII yielded, independently of the solvent used and the reaction temperature (20-125°C), 6-substituted 2,3,4,4-tetrachloro-3-methyl-6-hydroxy-3,4,6-tetrahydropyridines (VIII).



EXPERIMENTAL

A Bruker WM-250 spectrometer was used to obtain PMR spectra with TMS as internal standard. Infrared spectra were run on a Perkin Elmer 983G instrument as thin films on KBr disks. Gas–liquid chromatography was carried out on a Chrom-5 FID with helium carrier gas and a glass column 3700 × 3 mm packed with 5% XE-60 on Inerton Super. Thin layer chromatography was effected on Silufol UV-254 plates. Elemental analysis was carried out on a Carlo Erba 110 instrument; the results were in accordance with calculations.

Nitriles of 5-R-5-Oxo-2,4,4-trichlorovaleric acid (IIIa-e). A mixture of 100 mmole trichloromethylketone I, 150 mmole acrylonitrile, and 5 mmole CuCl was heated in a sealed ampul in an autoclave for 12 h at 110°C. After cooling, the ampul was opened, the excess nitrile evaporated in vacuum and the remaining mixture dissolved in 100 ml ether, filtered, the ether evaporated on a rotary evaporator and the residue distilled in vacuum. Nitrile IIIe after distillation was further purified by column chromatography.

Nitriles of 5-R-2-methyl-5-oxo-2,4,4-trichlorovaleric acid (VIIb, c) were prepared in a similar manner from trichloromethyl ketones and methacrylonitrile at 115°C, 15 h reaction time. Nitrile VIIb was further purified on a silica gel column.

6-R-2,3,5-Trichloropyridines (IVa-e). A. A solution of 10 mmoles oxonitrile III in 20 ml redistilled DMF was purged with argon and then saturated with dry HCl over 45 min at such a rate as to keep the temperature at 90-115°C. The reaction mixture was poured into ice water, extracted with 5 × 50 ml ether and the combined extracts dried over $CaCl_2$. Evaporation of the ether yielded pyridine IV which was recrystallized from the appropriate solvent.

B. A solution of 10 mmole oxonitrile in 20 ml dry diethyl ether was purged with argon and saturated with dry HCl over 1 h at 10-15°C. The reaction mixture was left to stand overnight and the crystals of IV which deposited were filtered off and dried in vacuum.

6-R-6-Hydroxy-3-methyl-2,3,5,6-tetrachlorotetrahydropyridines (VIIIb, c). A solution of 10 mmole oxonitrile VII in 20 ml redistilled DMF was purged with argon and saturated with dry HCl over 45-60 min at 100-130°C. The reaction mixture was poured into ice water and extracted with 5 × 50 ml ether. The combined extracts were dried over $CaCl_2$ and the ether evaporated to yield VIII.

The tetrahydropyridine VIII was also prepared in dry ether by the method B described above for the preparation of pyridines IV.

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