HALOGEN-SUBSTITUTED PYRIDINES.

3.* CYCLIZATION OF ADDUCTS OF α,α-DICHLOROPROPIONITRILE WITH ACRYLIC DERIVATIVES TO CHLOROPYRIDINES

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Reactions of α,α-dichloropropionitrile with acrylic derivatives in the presence of Cu_2Cl_2 gave a series of substituted 2,4-dichloro- and 2-chloro-5-oxoalkanonitriles. Their cyclization to chloropyridines has been studied.

One of the most convenient methods for the synthesis of chloropyridines by which the required compounds can be obtained with substituents variously arranged with respect to one another is the intramolecular cyclization of the corresponding chlorine-containing δ-oxonitriles. It is known that, in this reaction, even insignificant differences in the structure of the δ-oxonitrile have a considerable effect on the cyclization stage leading to differences in the structure of the pyridine bases [1-4]. It seemed expedient to examine the hitherto unreported δ-oxonitriles which are adducts of α,α-dichloropropionitrile I with α,β-unsaturated carbonyl compounds, and their cyclization to the corresponding chloropyridines.

At the present time there is no information in the literature on the reaction of the nitrile I with unsaturated compounds. We have established that the nitrile I reacts with acrolein, vinyl ketones, and derivatives of acrylic acid in the presence of copper-containing catalysts to form adducts which are nitriles of 2,4-dichloro-5-oxoalkanoic acid IIIa-f. In the case of compounds IIa-d, unusual reaction products – the nitriles IVa-d – were also detected.

$$\underset{\text{I}}{NCC(CH_3)Cl_2} + \underset{\text{IIa-f}}{CH_2{=}CHC(O)R} \longrightarrow \underset{\text{IIIa-f}}{NCC(CH_3)ClCH_2CH(Cl)C(O)R} + \underset{\text{IVa-d}}{NCC(CH_3)ClCH_2CH_2C(O)R}$$

II–IV a $R=H$, b $R=CH_3$, c $R=C_2H_5$, d $R=C_3H_7$; II, III e $R=OCH_3$, f $R=Cl$

The formation of nitriles IVa-d can apparently be explained by the stabilization of the intermediate radical $NCC(CH_3)ClCH_2\dot{C}HC(O)R$ by the splitting off of a hydrogen atom from a solvent or alkene molecule [5]. It should be noted that addition of $NCCCL_3$ to compounds IIb-d does not lead to the formation of compounds of the type of IV [1].

On the whole, the reactivity of nitrile I is found to be lower than that of $NCCCl_3$ [1, 2] as is apparent from the considerably longer reaction time necessary to achieve maximum yields of the adducts III, and several secondary reactions (in addition to nitriles IV, β-Cl-propional and the corresponding β-Cl-ethylketones were isolated from the reaction mixture).

The traditional catalyst, Cu_2Cl_2 in CH_3CN was found to be not very effective. A higher yield of the desired products was obtained during the catalyst system $Cu_2Cl_2 \cdot Ph_3P$ (0.5-1.0%) in CH_3CN. Nitriles IIIa-f and IVa-d were separated on a chromatograph column and further purified by distillation in vacuum (Table 1).

Nitriles IIIb-e are formed as a mixture of diastereomers in a 1:1 ratio, as shown by GLC and chromatography-mass spectrometry. In the case of IIIb, the mixture was separated into individual isomers. Nitrile IIIf was, of course, also obtained in the form of a mixture of diasteromers, but this was not detected by the GLC method.

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*For Communication 2, see [1].

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TABLE 1. Physicochemical Characteristics of Compounds IIIa-f and IVa-d

Compound	Empirical formula	Reaction temp., °C	Reaction time, h	Eluent	bp, °C (Pa)	PMR spectra, δ_H, ppm*						Yield, %
						$3\text{-}H_A$	$3\text{-}H_B$	$4\text{-}H_C$	$4\text{-}H_D$	$2\text{-}CH_3$ (c, 3H)	R	
IIIa	$C_6H_7Cl_2NO$	100	26	$CHCl_3$	57,5...58 (16)	2,83	2,28	4,47	—	1,93	9,29 (s, 1H)	35
IIIb†	$C_7H_9Cl_2NO$	105	23	C_6H_6	72...75 (54)	3,083 (2,892)	2,488 (2,463)	4,537 (4,588)	—	2,010 (2,025)	2,432 (s, 1H) [2,422 (s, 1H)]	41
IIIc	$C_8H_{11}Cl_2NO$	105	23	C_6H_6—C_6H_{14}, 10 : 1	79...81 (54)	3,10	2,33	4,46	—	1,96	1,07 (t, 3H), 2,65 (к, 2H)	39
IIId	$C_9H_{13}Cl_2NO$	105	23	C_6H_6—C_6H_{14}, 4 : 1	93...96 (67)	3,10	2,36	4,45	—	1,97	0,92 (t, 3H), 1,62 (к, 2H), 2,65 (q, 2H)	46
IIIe	$C_7H_9Cl_2NO_2$	115	29	$CHCl_3$	67...70 (54)	2,95	2,71	4,40	—	1,95	3,75 (s,3H)	41
IIIf‡	$C_6H_6Cl_3NO$	110	26	—	64...65 (47)	3,14	2,40	4,70	—	1,92	—	36
IVa	C_6H_8ClNO	100	26	C_6H_6—C_5H_{12}, 10 : 1	55 (33)	2,10	2,43	2,60	2,90	1,93	9,65 (s, 1H)	28
IVb	$C_7H_{10}ClNO$	105	23	C_6H_6—$CHCl_3$, 5 : 1	54 (47)	2,13	2,46	2,56	2,90	1,90	2,13 (s, 3H)	18
IVc	$C_8H_{12}ClNO$	105	23	C_6H_6	58,5 (47)	2,03	2,36	2,56	2,90	1,85	1,03 (t, 3H), 2,47 (к, 2H)	15
IVd	$C_9H_{14}ClNO$	105	23	C_6H_6	80...81 (67)	2,11	2,40	2,60	2,91	1,94	0,92 (t, 3H), 1,59 (к, 2H), 2,37 (q, 2H)	21

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*For compounds IIIa-f δ_H was determined from the center of the multiplet. For compounds IVa-d, the boundary values of the multiplets of fragments $3\text{-}CH_AH_B$ and $4\text{-}CH_CH_D$ are quoted. Spectrum of compound IIIb was run in $CDCl_3$, the rest in CCl_4.

†Spectra of the individual diasteromers of IIIb were obtained on a WP-250 instrument and appear as spectra of the ABC spin system of the fragment $-CH_AH_B-CH_CCl_2$ with spin coupling constants $^2J_{AB} = 16$, $^3J_{AC} = 6$, and $^3J_{BC} = 5.55$ Hz for one rotamer, and $^3J_{AB} = 16$, $^3J_{AC} = 4.5$ and $^3J_{BC} = 7.5$ Hz for the other (δ_H values for the second rotamer are given in brackets).

‡Compound (((f was isolated by distillation

TABLE 2. Physicochemical Characteristics of Compounds V-VIIIa-d

Compound	Empirical formula	mp°C*, bp°C (Pa)	PMR spectra, δ, ppm†					Spin-coupling constant, Hz	Yield, % (method)
			NH(s, 1H)	H_4	H_5	3-CH_3 (s, 3H)	R		
Va	$C_6H_7Cl_2NO$	131...132	7,62	4,81 (m, 2H)	—	1,80	5,67 (m, 1H)		81
Vb	$C_7H_9Cl_2NO$	120	8,86	2,93 (d, 2H)	—	1,74	1,95 (s, 3H)	$^2J_{4'4'}=2$	93
Vc	$C_8H_{11}Cl_2NO$	78	8,93	2,86 (d, 2H)	—	1,73	1,10 (t, 3H); 2,33 (q, 2H)	$^2J_{4'4'}=2$	86
Vd	$C_9H_{13}Cl_2NO$	82	9,25	2,83 (d, 2H)	—	1,70	0,97 (t, 3H); 1,60 (q, 2H); 2,31 (m, 2H)	$^2J_{4'4'}=2$	92
VIa	C_6H_6ClNO	162...163; 163 [6]	—	7,23 (m, 1H)	—	2,10	7,30 (m, 1H)		51 (A), 82 (B)
VIb	C_7H_8ClNO	197	11,60	7,16 (s, 1H)	—	1,83	2,10 (s, 3H)		58 (A), 89 (B)
VIc	$C_8H_{10}ClNO$	134	13,10	7,10 (s, 1H)	—	1,96	1,13 (t, 3H); 2,61 (q, 2H)		54 (A)
VId	$C_9H_{12}ClNO$	108	13,60	7,00 (s, 1H)	—	1,93	0,83 (t, 3H); 1,56 (q, 2H); 2,53 (q, 2H)		60 (A), 79 (B)
VIIa	$C_6H_5Cl_2N$	42; 41...42 [4]	—	7,40 (d, 1H)	—	2,26	8,05 (d, 1H)	$^4J_{4'6'}=2$	77 (A), 83 (B)
VIIb	$C_7H_7Cl_2N$	63	—	7,31 (s, 1H)	—	2,26	2,46 (s, 3H)		75 (A), 90 (B)
VIIc	$C_8H_9Cl_2N$	64 (67)	—	7,70 (s, 1H)	—	2,30	1,20 (t, 3H); 2,83 (q, 2H)		79 (B)
VIId	$C_9H_{11}Cl_2N$	68 (40)	—	7,30 (s, 1H)	—	2,20	0,88 (t, 3H); 1,63 (q, 2H); 2,65 (m, 2H)		82 (B)
VIIIa	C_6H_6ClN	71 (2000); 192 [7]	—	6,90 (m, 1H)	7,33 (m, 1H)	2,16	8,03 (m, 1H)		76
VIIIb	C_7H_8ClN	45 (80)	—	6,84 (d, 1H)	7,28 (d, 1H)	2,22	2,36 (s, 3H)	$^3J_{4'5'}=8$	84
VIIIc	$C_8H_{10}ClN$	52 (67)	—	7,13 (d, 1H)	7,58 (d, 1H)	2,35	1,23 (t, 3H); 2,73 (q, 2H)	$^3J_{4'5'}=8$	81
VIIId	$C_9H_{12}ClN$	59,5 (40)	—	6,70 (d, 1H)	7,20 (d, 1H)	2,20	0,80 (t, 3H); 1,56 (q, 2H); 2,49 (t, 2H)	$^3J_{4'5'}=8$	88

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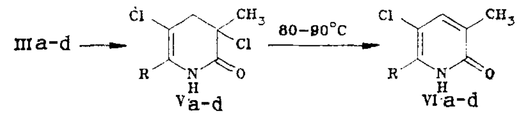
*Compounds Va-d recrystallized from ether; VIa from benzene; VIb-d from water; VIIa, b from 1:1 MeOH-H_2O.

†Spectra of compounds Va-d and VIc run in $CDCl_3$; VIa, VIIc in acetone-D_6; VIb in DMSO-D_6; VId, VIIa, b, d and VIIIa-d in CCl_4.

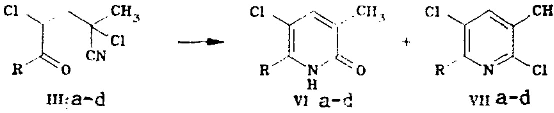
In the IR spectra of compounds IIIa-f and IVa-d, there were bands characteristic for C=O (1737-1740) and C≡N (2243-2250 cm^{-1}) together with bands corresponding to other fragments of the structure.

It was established that cyclization of the nitriles IIIa-d under the influence of dry hydrogen chloride in absolute diethyl ether at 0°C led to the corresponding dihydropyridones Va-d (Table 2).



The dihydropyridones V are thermally unstable and on recrystallization from hexane, heptane, or benzene they lose hydrogen chloride and are converted into pyridones VIa-d. At the same time, dihydropyridones which do not have a methyl group at the 3-position are unaltered on heating to 140°C [1]. The dihydropyridones Va-d are also converted with high yield into the corresponding pyridones by treatment with triethylamine in ether.

It was shown in [1] that cyclization of 2,2,4-trichloro-5-oxonitriles in DMF in the presence of HCl gave, depending on the reaction time, either the corresponding 2,3,5-trichloropyridines (10-15 min, conversion of nitrile 90-95%) or 3,5-dichloropyrid-2-ones (45-60 min, conversion of nitrile 90-95%). Cyclization of the adduct of trichloracetonitrile with acrolein gave only the corresponding pyrid-2-one under all the conditions examined [2]. On treating the nitrile IIIa with hydrogen chloride in DMF, the pyridone VIa is also formed. Different results are obtained with nitriles IIIb-d, probably because of their lower reactivity to cyclization under the conditions described above. Thus, on passing a current of dry HCl for 10-15 min through solutions of nitriles IIIb-d in DMF, the reaction mixture is observed to heat up to 110-120°C and after 30-45 min the temperature begins to fall. Conversion of the oxonitriles IIIb-d over 10-15 min amounts to 20-25% and the product is a mixture of approximately equal quantities of pyridones VIb-d and pyridines VIIb-d with an overall yield of 12-15%.



A greater reaction time (45-60 min) increases the conversion to 50-60% and alters the ratio of products VI:VII to 2:1 with an overall yield of pyridine bases of 40%. Quantitative conversion of nitriles IIIa-d can be achieved by passing a current of HCl and heating the reaction mixture to 90-100°C for 3 h. The yield of compounds VI and VII here amounts to 70% but the main product is still the pyridone VI (ratio VI:VII = 5:1). Cyclization of nitriles IIIa-d in DMF in the presence of 100-120% $POCl_3$ leads exclusively to pyridines VIIIa-d in 70-80% yield. However, in this case the maximum conversion (85-90%) is reached after a reaction time of 50-60 min. Since it has been established by special experiments that under the experimental conditions used pyridones VI are not converted into pyridines VII in the presence of $POCl_3$, the role of the $POCl_3$ apparently consists in the bonding of the water which separates in the course of the reaction, thereby preventing the hydrolysis of the pyridines VII. In fact, if, 15 min after the beginning of the reaction, one adds $POCl_3$ to the reaction mixture then after 30-45 min the quantity of pyridone which had formed after 15 min remains practically unchanged and the amount of pyridine increases to 40-50%.

Pyridines VII can be prepared from the nitrile I and alkenes IIa-d in one stage (heating in an autoclave at 180-190°C, 3 h, 1% $Cu_2Cl_2 \cdot Ph_3P$, 120% $POCl_3$) but the yield does not then exceed 30-35%.

Cyclization of nitriles IVa-d was also studied in the presence of $POCl_3$ in DMF. The corresponding pyridines VIIIa-d (Table 2) were isolated as the main products of the reaction.

Attempts to obtain pyridine bases from nitriles IIIe, f under the conditions described did not meet with success.

EXPERIMENTAL

Monitoring of the progress of the reactions and the purity of the products was effected by GLC on a Chrom-5 chromatogram with a flame ionization detector, helium carrier gas (1.8 liter/h), and a glass column 3700 × 3 mm packed with 5% XE-60 on Inerton-Super (0.20-0.25 mm) and by TLC on Silufol plates. Melting points were determined on a Boetius microblock.

PMR spectra were run on a Varian T-60 with TMS internal standard and IR spectra on a Specord IR-75 in KBr disks or as thin films.

Characteristics of the compounds prepared are set out in Tables 1 and 2. Elemental analyses for C, H, N in the prepared compounds were in agreement with the calculated values.

Nitriles of 2-Methyl-2,4-dichloro-5-R-5-oxopentanoic Acids (IIIa-f) and Nitriles of 2-Methyl-2-chloro-5-R-5-oxopentanoic Acids (IVa-d). A mixture of 200 mmole nitrile I, 150 mmole alkene II, 0.5 mmole Cu_2Cl_2, and 0.5 mmole Ph_3P in 35 ml dry CH_3CN was heated in a sealed glass ampul. On completion of heating, the low boiling material was distilled off at 133 Pa and 100 ml ether was added to the residue, the solution filtered, and the ether removed in a rotary vacuum evaporator. The mixture of oxonitriles was separated on a 900 × 40 mm column of silica gel L 100/250, eluting initially the dichloroderivative III and then, with a different solvent, the monochloroderivative IV.

3-Methyl-3,5-dichloro-6-R-3,4-dihydropyrid-2-ones (Va-d). A solution of 10 mmole oxonitrile IIIa-d in 10 ml absolute diethyl ether as cooled to 0°C, swept out with argon and saturated with dry HCl over a period of 1.5 h and then left overnight at 10-15°C. The reaction mixture was then concentrated at 15°C to 4-5 ml and kept at −5°C. The precipitated crystals of dihydropyridone V were filtered off and the mother liquor concentrated to half volume, depositing a further quantity of compound V which was combined with the first and the crystals dried in vacuum.

3-Methyl-5-chloro-6-R-pyrid-2-ones (VIa-d). A. A solution of 20 mmole oxonitrile IIIa-d in 20 ml dry DMF was swept out with argon and saturated with dry HCl at such a rate that the temperature of the reaction mixture did not exceed 120°C and after 40 min, when the temperature began to fall, the flask, and its contents were placed in an oil bath at 90°C and saturation with HCl continued. After 3 h the cooled mixture was poured into 100 ml ice water, extracted with 5 × 50 ml ether, and the ether layer washed with 50 ml water and dried over $CaCl_2$. After removing the ether, the mixture was separated on a column 150 × 10 mm with silica gel L 100/250, eluting the pyridine VII with hexane and the pyridone VI with chloroform.

B. To a solution of 50 mmole dihydropyridone Va-d in 20 ml absolute ether was added, with stirring, 50 mmole Et_3N in 10 ml ether. The mixture was stirred for 1 h at room temperature, the precipitate of $Et_3N{\cdot}HCl$ filtered off and the ether evaporated to yield the pyridone VI.

3-Methyl-2,5-dichloro-6-R-pyridines (VIIa-d). A. A mixture of 150 mmole pyridone VIa-d and 750 mmole $POCl_3$ was heated in a sealed glass ampul for 4 h at 190°C, cooled, poured into 100 ml ice water and when the decomposition of the $POCl_3$ was complete the mixture was extracted with 4 × 40 ml ether, the extract dried over $CaCl_2$ and the ether removed to yield the pyridine VII.

B. A mixture of 200 mmole oxonitrile IIIa-d and 250 mmole $POCl_3$ in 30 ml dry DMF was swept out with argon and then saturated with dry HCl for 45 min at 125°C. The cooled reaction mixture was poured into 200 ml ice water, extracted with 5 × 75 ml ether, the ether layer washed with 50 ml water and dried over $CaCl_2$. After evaporation, 50 ml hexane was added to the oil which remained and the solution filtered through a 40 mm deep layer of silica gel. The hexane was distilled off in vacuum to yield the pyridine VII.

3-Methyl-2-chloro-6-R-pyridines (VIIIa-d) were prepared from the corresponding oxonitriles IVa-d by a method similar to B for pyridines VIIa-d.

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ALKYLATION OF 4-PICOLINIUM SALTS UNDER PHASE TRANSFER CONDITIONS

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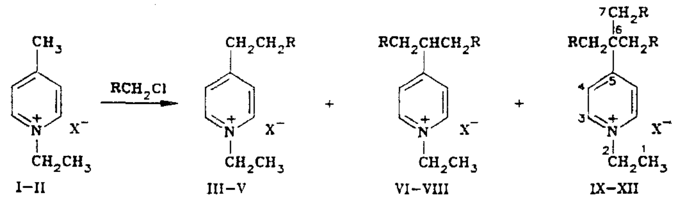
Alkylation of 1-ethyl-4-methylpyridinium bromide by allyl, benzyl and propargyl chlorides has been effected under conditions of phase transfer catalysis in a solid phase—liquid system (K_2CO_3—$CHCl_3$). Using the example of alkylation by allyl chloride, the effect of the concentration and the nature of the catalyst, the concentration of the base, and the temperature on the yield of mono-, di-, and trisubstituted products has been studied. The reactivity of the alkyl chlorides increases in the order allyl < benzyl < propargyl. When the reaction is carried out in a liquid—liquid system (25% aqueous NaOH—$CHCl_3$) the Br^- anion of the starting material is replaced by Cl^-, in contrast to the K_2CO_3—$CHCl_3$ system.

Alkylation of picolines is most frequently carried out with organolithium compounds [1] but these are time-consuming and expensive. Phase transfer catalysis has recently become widely used for the alkylation of CH-acids but this reaction has been little studied for picolines and only the quaternary salts of 2- and 4-methyl-, 2,6-dimethyl, and 2,4,6-trimethylpyridines have been alkylated by methyl iodide in an aqueous NaOH—CH_2Cl_2 system with tetrabutylammonium hydroxide as catalyst [2].

Extending the work into a series of unsaturated pyridine compounds [3], we carried out the alkylation of 1-ethyl-4-methylpyridinium bromide [1] by allyl, benzyl, and propargyl chlorides. To optimize the reaction conditions, we studied the effect of concentration and catalyst type, the concentration of the base, and the temperature on the yield in the alkylation of compound I by allyl chloride in a solid phase—liquid system. Chloroform was chosen as the solvent and anhydrous K_2CO_3 as the base.



I, III–XI X=Br; II, XII X=Cl; III, VI, IX R=CH=CH$_2$; IV, VII, X R=C≡CH; V, VIII, XI, XII R=C$_6$H$_5$

As can be seen from Fig. 1, alkylation will also occur without a phase transfer catalyst but the presence of a catalyst (dicyclohexano-18-crown-6, DCH-18-C-6) leads to an increasing yield of the product of complete alkylation IX as the catalyst concentration increases. It was established earlier [4] that crown ethers and quaternary ammonium salts do not transfer CO_3^{2-} into the organic phase. We suggest that in the process which we have studied, deprotonation of the salt I takes place on the surface of the solid carbonate and the anion so formed is transferred to the organic phase in the form of an ion pair with the crown ether complex and a potassium cation. After more than 20% DCH-18-C-6 has been added, there is no further significant increase in the yield of IX which is evidence of the cyclic nature of the formation and breakdown of the ion pair with the crown ether complex [4].

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