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SYNTHESIS OF TRICHLOROMETHYL-SUBSTITUTED AZINES FROM DICHLOROMETHYL-SUBSTITUTED AZINES AND CARBON TETRACHLORIDE UNDER INTERPHASE CATALYSIS CONDITIONS

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The reactions of 2- and 3-dichloromethylpyridines and dichloromethylpyrazine with carbon tetrachloride in the presence of aqueous or solid alkali and an interphase catalyst lead to the corresponding trichloromethyl-substituted azines. The CCl_4—solid KOH—18—crown-6 system, in the use of which trichloromethyl-substituted heterocycles were obtained in preparative yields, was the most effective.

Among the diverse reactions with the participation of carbanions generated by the action of alkali hydroxides on CH acids in two-phase systems in the presence of interphase catalysts, halogenation processes with the participation of perhaloalkanes are of particular interest. These compounds, particularly carbon tetrachloride, are strong electrophiles that react with the carbanions with the formation of halogenated products that, depending on the structure, may be final products or may undergo successive transformations [1, 2]. It was recently shown that benzal chlorides that contain electron-donor (Me, Et) or electron-acceptor (NO_2, Cl) substituents in the ring are converted to the corresponding substituted benzotrichlorides in good yields in the system CCl_4—50% aqueous NaOH solution in the presence of (n-dodecyl)trimethylammonium chloride [3, 4].

In a continuation of our research on the synthesis of polychloromethyl-substituted azines [5] in our present research we studied the reactions of dichloromethyl derivatives of pyridine and pyrazine with CCl_4 in the presence of alkali under interphase-catalysis conditions in order to obtain the corresponding trichloromethyl-substituted azines. The starting 2-dichloromethylpyridine (I) and dichloromethylpyrazine (III) were obtained by free-radical chlorination of, respectively, α-picoline and methylpyrazine with N-chlorosuccinimide; 3-dichloromethylpyridine (II) was synthesized by the reaction of 3-formylpyridine with phosphorus pentachloride [5]. The reactions of dichloromethyl-substituted azines I-III with CCl_4 were carried out using a 50% aqueous solution of NaOH in the presence of catalytic amounts of a quaternary ammonium salt (system A: liquid—liquid) or solid KOH in the presence of 18-crown-6

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TABLE 1. Reactions of Dichloromethyl-Substituted Azines with CCl_4 under Interphase-Catalysis Conditions

Starting compound	c of the starting compound, g/ml CCl_4	System	Catalyst	T, °C	Reaction time, h	Conversion, %	Reaction product	Yield of product (by GLC) %
I	0,16	A	$Me_3N^+(n\text{-}C_{12}H_{25})Cl^-$	50	2	100	IV	36
I	0,16	A	$Et_3N^+CH_2PhCl^-$	50	2	75	IV	22
I	0,16	B	18-Crown-6	50	2	100	IV	66*
II	0,12	B	18-Crown-6	50	20	100	V	27*
III	0,1	A	$Me_3N^+(n\text{-}C_{16}H_{33})Br^-$	20...25	5	~100	VI	72
III	0,1	B	18-Crown-6	20...25	3	~100	VI	67
III	0,02	B	18-Crown-6	20...25	4	~100	VI	81; 51*

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*Preparative yield.

as the catalyst (system B: liquid–solid). The course of the reactions was monitored by GLC and chromatographic mass spectrometry.

The reactions of dichloromethyl-substituted azines with CCl_4 under interphase-catalysis conditions were investigated (Table 1). When the chlorination of I was carried out in system A at 50°C, 2-trichloromethylpyridine (IV) was obtained in maximal yield (36%) when Me_3N^+ $(n\text{-}C_{12}H_{25})Cl^-$ was used as the catalyst; the $Et_3N^+CH_2PhCl^-$ catalyst is less effective – the yield of IV is 22% – and IV is not formed at all when a catalyst that is insoluble in the reaction medium – polymerically bonded tributylhexylphosphonium bromide – is used. The process is accompanied by resinification of the reaction mixture. At room temperature in the presence of $Me_3N^+(n\text{-}C_{12}H_{25})Cl^-$ or $Et_3N^+CH_2PhCl^-$ the conversion of dichloride I to trichloride IV proceeds very slowly – after 2 h the conversion of I was ~ 5%. The yield of IV could be increased substantially by carrying out the reaction of dichloride I with CCl_4 in system B. In this case I, just as in system A, undergoes complete conversion after 2 h at 50°C, and the yield of trichloride IV, isolated by vacuum fractionation, is 66%.

$$\underset{\text{I–III}}{\text{Het–CHCl}_2} \xrightarrow[\text{cat.}]{CCl_4/OH^-} \underset{\text{IV–VI}}{\text{Het–CCl}_3}$$

I, IV Het=2-pyridyl II, V Het=3-pyridyl III, VI Het=pyrazinyl

The transformation of II in systems A and B proceeds considerably more slowly than the transformation of dichloride I. When system A is used, a high degree of conversion of dichloride II is not achieved at all. In system B at 50°C the complete conversion of II occurs after 20 h, after which V is isolated in 27% yield by vacuum fractionation.

The conversion of dichloromethylpyrazine (III) to trichloromethylpyrazine (VI) in systems A [$Me_3N^+(n\text{-}C_{16}H_{33})Br^-$ as the catalyst] and B (18-crown-6 as the catalyst) takes place at room temperature; the two systems are close in effectiveness. At the same concentration of III in CCl_4 (0.1 g/ml) the yields of VI, according to GLC, are 72% (after 5 h) and 67% (after 3 h) in the use of, respectively, aqueous and solid alkali (the conversion of dichloride III is close to 100% in both cases). Decreasing the concentration of III in CCl_4 to 0.02 g/ml (system B) makes it possible to increase the yield of trichloride VI to 81% (according to GLC data) vis-a-vis a slight increase in the reaction time (4 h). Compound VI was isolated from the reaction mixture in 51% yield by vacuum fractionation and was additionally purified by means of preparative GLC.

Trichloromethyl-susbtituted azines IV and VI were identified from the agreement between the physicochemical characteristics that we obtained and those available in the literature, as well as from data from the PMR and mass spectra (Table 2). Compound V was previously synthesized by others (by liquid-phase chlorination of nicotinic acid with gaseous chlorine in the presence of PCl_3 and $PhPCl_2$ [6] and by gas-phase chlorination of α-picoline with chlorine over an AlF_3–CuCl catalyst [7]); however, the characteristics of trichloride V are not

TABLE 2. PMR and Mass Spectra of IV-VII

Compound	Chemical shift, δ, ppm	m/z (I_{rel}, %)*
IV**	7,33 (m, 1H, 5-H); 7,84 (m, 2H, 3-H, 4-H); 8,64 (m, 1H, 6-H)	195 (11, M^+), 160 (100, $[M^+-Cl]$), 133 (12), 99 (25), 78 (21), 63 (23), 51 (22)
V	7,32 (m, 1H, 5-H); 8,16 (m, 1H, 4-H); 8,61 (m, 1H, 6-H); 9,14 (m, 1H, 2-H)	195 (6, M^+), 161 (100, $[M^+-Cl]$), 63 (18)
VI	8,65 (s, 2H, 5-H, 6-H); 9,29 (s, 1H, 3-H)	196 (13, M^+), 161 (100, $[M^+-Cl]$), 63 (18)
VII	7,12 (s, 1H, $CHCl_2$); 8,40 (d, 1H, J=2,2 Hz)and8,61 (d, 1H, J=2,2 Hz) ring protons	196 (21, M^+), 161 (100 $[M^+-Cl]$), 107, (20), 83 (15), 74 (10), 52 (15)

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*Only the peaks of ions that contain the ^{35}Cl isotope are presented for the chlorine-containing ions.

**According to the data in [9], δ(CCl_4): 7.33, 7.87, and 8.71 ppm.

presented in these studies. The spectral parameters of V (Table 2) confirm its structure unambiguously. Sets of peaks of molecular ions with intensity ratios corresponding to the presence of three chlorine atoms in the molecules of the compounds are observed in the mass spectra of trichloromethyl-substituted azines IV-VI. Characteristic signals of protons of monosubstituted electron-acceptor substituents of the heterocyclic rings of IV-VI are observed in the PMR spectra; the assignment of the signals was made in accordance with the data in [8].

For comparison we also studied the possibility of obtaining IV and VI by free-radical chlorination of I and III. It was shown that prolonged refluxing of I with excess of N-chlorosuccinimide in the presence of benzoyl peroxide leads to the stepwise conversion of dichloride I to IV, but the reaction proceeds very slowly and is accompanied by pronounced resinification, as a consequence of which IV cannot be obtained in an acceptable yield. In the reaction of dichloride III with N-chlorosuccinimide the principal product is not VI but rather the known [10-12] 2-dichloromethyl-3-chloropyrazine (VII), which was isolated by preparative GLC and identified from the PMR and mass spectra (Table 2).

A comparison of the results obtained in this research with the known methods for the synthesis of trichloromethyl-substituted azines IV-VI [10, 11, 13, 14] shows that the two-phase catalytic method is distinguished by its simplicity, the mildness of the conditions, and the convenience in carrying it out; it also excludes the possibility of the formation of mixtures of products of chlorination in the side group and in the ring and gives the desired trichloromethyl-substituted azines, the yields of which in most cases exceed the previously obtained yields.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with a Bruker WH-90/DS spectrometer with tetramethylsilane (TMS) as the internal standard. The mass spectra were obtained with a Kratos MS-25 chromatographic mass spectrometer with an ionizing-electron energy of 70 eV. The melting points were determined with a Boetius stage. Gas-liquid chromatography (GLC) was carried out with a Chrom-5 chromatograph with a flame-ionization detector and a glass column (2.4 m by 3 mm) packed with 5% OV-17 on Chromosorb W-HP (80-100 mesh); the carrier gas was helium (50 cm^3/min), and the column temperature was 120°C. Preparative GLC was carried out with a Pye—Unicam 105 chromatograph with a column (2.1 m by 7 mm) packed with 20% SE-30/Chromaton N-AW-DMCS at 180°C.

The starting dichloromethyl-substituted azines were obtained as in [5]. Commercial reagents — 18-crown-6, triethylbenzylammonium chloride, N-chlorosuccinimide (Fluka), cetyltrimethylammonium bromide (Chemapol), and (n-dodecyl)trimethylammonium chloride (Reakhim) — were used in the research.

2-Trichloromethylpyridine (IV). System B. A 14-g (0.25 mole) sample of finely ground KOH was added to a solution of 8 g (50 mmole) of pyridine I and 0.52 g(2 mmole) of 18-crown-6 in 50 ml of CCl_4, and the mixture was stirred for 2 h at 50°C with monitoring of the course of the reaction by GLC of samples periodically selected from the mixture with a microsyringe.

The reaction mixture was diluted with water until the solid phase dissolved, and the aqueous layer was separated and washed with chloroform (three 50-ml portions). The combined organic layer was filtered through a hydrophobic filter (Whatman phase separator, silicon treated), the solvents were removed by distillation in vacuo at room temperature, and the residue was fractionated in vacuo to give 5 g (66%) of IV with bp 50-53°C (0.3 mm) [bp 98°C (15 mm)].

System A. A 150-ml sample of a 50% aqueous solution of NaOH was added to a solution of 16.1 g (0.1 mole) of I and 1 g (3.8 mmole) of (n-dodecyl)trimethylammonium chloride in 100 ml of CCl_4, and the mixture was stirred for 2 h at 50°C. The conversion of I was 100%, and the yield of trichloride IV (according to GLC data) was 36%.

3-Trichloromethylpyridine (V). This compound was synthesized in system B from 3 g (19 mmole) of II, 0.26 g (1 mmole) of 18-crown-6, 25 ml of CCl_4, and 5.3 g (94 mmole) of KOH by a method similar to that used to obtain IV. The reaction was carried out for 20 h at 50°C. Workup gave 1 g (27%) of V with bp 58°C (0.5 mm).

Trichloromethylpyrazine (VI). In system B VI was obtained from 0.81 g (5 mmole) of dichloromethylpyrazine (III), 50 mg (0.2 mmole) of 18-crown-6, 40.5 ml of CCl_4, and 1.4 g (25 mmole) of KOH (20-25°C, 4 h) by a method similar to that described for the synthesis of IV. The yield of trichloride VI, with bp 70°C (1 mm), was 0.5 g (51%); additional purification by preparative GLC gave solid VI with mp 40°C (mp 38-39°C [1-10]).

In system A the reaction of 0.324 g (2 mmole) of III, 3.24 ml of CCl_4, and 6.5 ml of 50% aqueous NaOH solution in the presence of 20 mg (0.05 mmole) of cetyltrimethylammonium bromide at 20-25°C was carried out for 5 h. Analysis by GLC and chromatographic mass spectrometry showed that the principal product was VI (in 72% yield according to GLC).

2-Dichloromethyl-3-chloropyrazine (VII). A 0.12-g (0.5 mmole) sample of benzoyl peroxide and 5.34 g (0.04 mole) of N-chlorosuccinimide were added to a solution of 0.95 g (0.01 mole) of the methylpyrazine in 20 ml of CCl_4, and the mixture was refluxed for 30 h with the periodic addition of N-chlorosuccinimide in portions (four 0.01-mole portions). Analysis by GLC and chromatographic mass spectrometry showed that in the case of complete conversion of the methylpyrazine the principal product was dichloromethyl-substituted pyrazine III. A 2.67-g (0.02 mole) sample of N-chlorosuccinimide was added to the reaction mixture obtained, and the mixture was refluxed for another 6 h, during which III was converted virtually completely to VII. The reaction mass was cooled, the precipitated succinimide was removed by filtration, and the solvent was removed by distillation. The residue consisted primarily of VII (according to GLC the yield was 38% based on the starting methylpyrazine). Purification by preparative GLC gave VII with mp 46°C (mp 45.5-46.5°C [10]).

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