9. N. N. Vorozhtsov, Jr., V. A. Barkhash, and S. A. Anichkina, Dokl. Akad. Nauk SSSR, Ser. Khim., 166, 598 (1966).
10. L. S. Kobrina, Fluor. Chem. Rev., 7, 1 (1974).

FREE RADICAL CHLORINATION OF METHYL DERIVATIVES OF PYRIDINE, PYRAZINE, AND THIAZOLE BY N-CHLOROSUCCINIMIDE

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When methylazines (2-, 3-, and 4-methylpyridines, methylpyrazine) are treated with N-chlorosuccinimide they undergo successive chlorination of the methyl group to give 2-chloromethylpyridine, 2-dichloromethylpyridine, and dichloromethylpyrazine in preparative yields. 3-Dichloromethylpyridine was synthesized from pyridine-3-aldehyde and PCl_5. The primary chlorination products of 4-methylthiazole are 4-methyl-5-chlorothiazole and 5-chloro-4-chloromethylthiazole.

Dichloromethyl aromatic and heterocyclic compounds are precursors of aryl- and hetaryl-chlorocarbenes and -carbenoids which add to the C=C bond of alkenes to form cyclopropanes [1-3]. Various known methods for introducing halogen into the side chain of methylpyridines have been correlated in a review [4]. Different chlorination methods for picolines, Ia-c [4-7], including use of N-chlorosuccinimide (NCS) [7], lead to only small amounts of the dichloromethylpyridines IIIa-c which are found mixed with their mono- (IIa-c) or trichloromethyl analogs (IVa-c). Hence dichloromethyl derivatives are mainly obtained by indirect routes [8-10].

Dichloromethylpyrazine (IIId) could not be obtained by direct chlorination of methylpyrazine (Id); the product was chlorinated in the ring [11] or was the trichloromethylpyrazine (IVd) [12]. The action of one equivalent of NCS led to the chloromethylpyrazine (IId) [7, 11] but the dichloromethylpyrazine (IIId) necessitated a complex multistage synthesis [13, 14]. 4-Dichloromethylthiazole (IIIe) was obtained in a 1:1 mixture with 4-chloromethylthiazole by treating 4-methylthiazole (Ie) with PCl_3 and Cl_2 in oleum [15]. The reaction of Ie with NCS has not been studied.

Our work concerns the reaction of the available methyl heterocycles Ia-e with N-chlorosuccinimide with a view to preparing the dichloromethyl derivatives IIIa-e. The reaction was carried out in CCl_4 with benzoyl peroxide or UV irradiation for initiation. Methylpyrazine (Id) with excess NCS gave only the products of substituting methyl group hydrogens by chlorine (IId, IIId, IVd):

$$\underset{\text{Ia–d}}{\text{Het–CH}_3} \longrightarrow \underset{\text{IIa,b,d}}{\text{Het–CH}_2\text{Cl}} + \underset{\text{IIIa,b,d}}{\text{Het–CHCl}_2} + \underset{\text{IVa–d}}{\text{Het–CCl}_3}$$

I-IV a Het = 2-pyridyl, b Het = 3-pyridyl, c Het = 4-pyridyl, d Het = 2-pyridyl

Chromatography-mass spectrometry (CMS) and the PMR spectra of the reaction mixtures showed that the principal reaction products of Id with NCS are the monochloro and dichloromethylpyrazines (IId, j/z 128, M^+)* and (IIId, m/z 162, M^+), respectively. Small quantities of the trichloromethylpyrazine (IVd, m/z 196, M^+) were formed. Also present in the mixture (1-5%) were 2-methylchloropyrazine (m/z 128, M^+), isomeric with IId (but with an unidentified position for chlorine in the ring) and two chloro derivatives (m/z 162 M^+) isomeric with IIId which,

*Here, and elsewhere, the mass spectrometric peaks are for the ^{35}Cl isotope.

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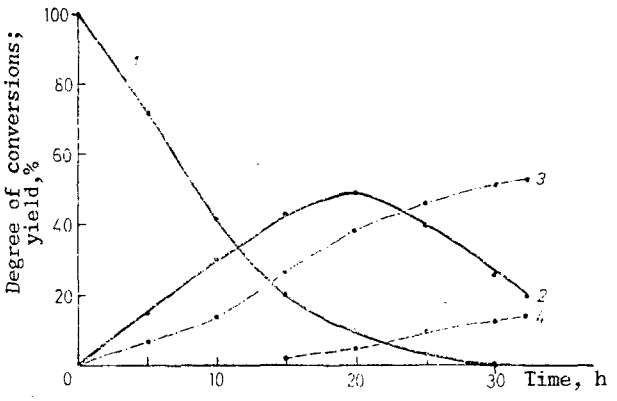


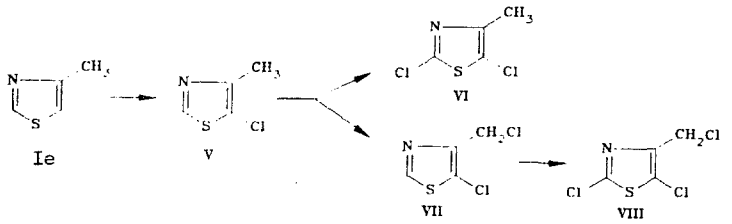
Fig. 1. The dependence of the degree of conversion of methylpyrazine (1) and yield of chloro-(2), dichloro-(3), and trichloromethylpyrazines (4) on the time of the reaction with NCS.

according to PMR spectra, are chloro-2-chloromethylpyrazines with the position of the chlorine in the ring undetermined.

Figure 1 illustrates the conversion of Id and the yields of products with duration of the reaction. The kinetic relationship obtained points to the successive character of the chlorination process: Id → IId → IIId → IVd. According to GLC the maximum yield of the monochloro IId reached 50% (when the yield of the dichloro IIId was approximately 35%). The largest yield of the target IIId was 53% (with 20% of IId and 15% of IVd). Distillation of the reaction mixture in vacuo gave a mixture of chlorination products containing 66% of IIId by GLC and PMR spectral analysis and 15% of IId (the remainder being isomeric with it).

Study of the reaction of α-picoline with NCS in the presence of benzoyl peroxide has shown that the principal reaction products are the corresponding mono- and dichloro derivatives (IIa, IIIa) with small amounts of trichloromethylpyridine (IVa). As for chlorination of Id these products are formed successively. By varying the reagent ratio it is possible to stop the reaction at the stage of principal formation of IIa or IIIa, thereby producing the individual products in preparative yields of 27 and 54%, respectively. Reaction of β-picoline under the same conditions also gave a mixture of three products due to successive chlorination of the CH_3 group but it was not possible to find conditions for selective formation of the desired IIIb. Thus IIIb was alternatively prepared by reaction of pyridine-3-aldehyde with PCl_5 in the presence of pyridine with a yield of 38%. Radical reaction of γ-picoline with NCS over a broad range of reagent ratios led principally to formation of trichloromethyl IVc (m/z 195, M^+) (CMS analysis). These results are in agreement with literature data [4, 10] for the chlorination of γ-picoline.

Chlorination of methylthiazole Ie with NCS and initiation by benzoyl peroxide or UV irradiation led to rapid loss of Ie and principal formation of 4-methyl-5-chlorothiazole (V). The mass spectrum of thiazole V showed a molecular ion (m/z 133) and the PMR spectrum showed methyl group protons (2.33 ppm) and a singlet at 8.59 ppm characteristic of the 2-H proton of 5-chlorothiazole [16]. Continued chlorination causes V in the mixture to decrease and a series of new products to increase. From PMR spectroscopy and CMS the following products were identified: 4-methyl-2,5-dichlorothiazole (VI), 5-chloro-4-chloromethylthiazole (VII), 2,5-dichloro-4-chloromethylthiazole (VIII).



CMS showed traces of other products of further chlorination of the thiazole Ie which contained four chlorine atoms. The mass spectra of V-VIII showed a set of molecular ion peaks whose intensity ratios related to the presence of the corresponding number of chlorine atoms

in the molecules. The PMR spectrum of the mixture of VI-VIII (after vacuum distillation) showed a 0.2:3:1 ratio for VI:VII:VIII. Thus, in contrast to the studied methylazines, the reaction of 4-methylthiazole with NCS occurs with chlorination most readily at the ring 5-position and it was not possible to obtain the desired 4-dichloromethylthiazole.

EXPERIMENTAL

PMR spectra* were recorded on a Bruker WH-90/DS using $CDCl_3$ solvent and TMS internal standard. CMS were recorded on a Kratos MS-25 instrument with ionization energy 70 eV. GLC was recorded on a Chrom-5 chromatograph with flame ionization detector, glass column (2.4 m × 3 mm) packed with 10% E-301 + 2.5% Reoplex-400/Chromosorb W-AW (60-80 mesh) running at 150°C and helium gas flow of 60 ml/min. Experiments with UV irradiation initiation were carried out in a quartz flask using a DPT-400 lamp. Methylpyridines were first purified by distillation. Methylpyrazine and N-chlorosuccinimide were products of Fluka. 4-Methylthiazole was kindly donated by Prof. Yu. P. Kitaev (A. E. Arbuzov Institute, Kazan Affiliate, Academy of Sciences of the USSR).

2-Chloromethylpyridine (IIa). N-Chlorosuccinimide (8 g, 0.061 mole) was added to α-picoline (2.3 g, 0.025 mole) and benzoyl peroxide (0.33 g, 0.0014 mole) in CCl_4 (70 ml) and refluxed for 2 h. A further aliquot of N-chlorosuccinimide (4 g, 0.03 mole) and benzoyl peroxide (0.33 g) was added and refluxing continued for a further 2.5 h. The solution was decanted, CCl_4 removed at room temperature, and the residue distilled in vacuo to give IIa (0.85 g, 27%) with bp 40°C/1mm Hg (lit. data [7] = 39-42°C/1mm Hg). PMR and mass spectral data were in agreement with those given for IIa in [7].

2-Dichloromethylpyridine (IIIa). N-Chlorosuccinimide (75 g, 0.56 mole) was added to a solution of α-picoline (6.9 g, 0.074 mole) and benzoyl peroxide (5 g, 0.021 mole) in CCl_4 (200 ml) and refluxed for 9 h. The succinimide was filtered off, the filtrate evaporated at room temperature, and the residue fractionated in vacuo to give IIIa (6.5 g, 54%) with bp 76° (1.5 mm Hg): lit. data [7] bp = 55-57°C (1 mm Hg); PMR and mass spectra agreed with [5, 7].

3-Dichloromethylpyridine (IIIb). PCl_5 (26.8 g, 0.13 mole) was added to a solution of 3-formylpyridine (10.7 g, 0.1 mole) and pyridine (7.9 g, 0.1 mole) in benzene (150 ml) and refluxed for 30 min. The mixture was cooled, washed with NaOH solution (5%, 2 × 100 ml), and water (100 ml). The organic layer was separated and dried with magnesium sulfate, benzene was evaporated and the residue fractionated in vacuo to give IIIb (6.2 g, 38%) with bp 62-65°C (1.2 mm Hg). PMR spectrum: 6.77 (1H, s, $CHCl_2$); 7.3-8.9 ppm (4H, m, Ar). Mass spectrum, m/z (%): 161 (M^+, 16), 126 (M^+ −Cl, 100), 99 (11), 63 (15).

Chlorination of Methylpyrazine (Id). N-Chlorosuccinimide (5.34 g, 0.04 mole) was added to a solution of methylpyrazine (0.94 g, 0.01 mole) and benzoyl peroxide (0.12 g, 0.5 mmole) in CCl_4 (20 ml) and refluxed for 30 h with periodic addition of N-chlorosuccinimide (4 × 0.01 mole). The reaction mixture was cooled, filtered, CCl_4 distilled off, and the residue distilled in vacuo collecting the fraction with bp 50°C (0.5 mm Hg); according to [14] bp of IIId = 105-108°C (18 mm Hg). The mixture (1.1 g) contained 66% of reaction product IIId, 15% of IId, and 19% of two isomers of chloro-2-chloromethylpyrazine (PMR data). PMR spectrum of IIId: 6.75 (2H, s, $CHCl_2$); 8.59 (2H, m, 5-H, 6-H); 9.04 ppm (1H, s, 3-H). Mass spectrum, m/z 162 (M^+, 36), 127 (M^+ −Cl, 100), 100 (10), 73 (29). Mass spectum of IId 128 (M^+, 100), 93 (M^+ −Cl, 72), 66 (13), 39 (16).

Chlorination of 4-methylthiazole (Ie). N-Chlorosuccinimide (45 g, 0.25 mole) was added to a solution of Ie (2.5 g, 0.025 mole) and benzoyl peroxide (0.33 g, 0.0014 mole) in CCl_4 (70 ml) and refluxed for 1 h. The mixture was cooled, samples taken and their PMR spectra and CMS taken to show that Ie had disappeared and that the main reaction product was V (greater than 95%). PMR spectrum: 2.33 (3H, s, CH_3); 8.59 ppm (1H, s, 5-H). Mass spectrum, m/z: 133 (M^+, 100), 106 (40), 105 (11), 98 (35), 89 (14), 71 (56), 45 (11). The reaction mixture was then refluxed for a further 30 h, cooled, filtered, the CCl_4 evaporated and the residue distilled in vacuo collecting the fraction with bp 72-79°C (0.5 mm Hg). The yield was 3.5 g of mixture which NMR spectroscopy showed to contain 71% of VII, 24% of reaction product VIII, and 5% of VI. Compound VII, PMR spectrum: 4.70 (2H, s, CH_2Cl); 8.67 ppm (1H,

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s, 5-H). Mass spectrum, m/z: 167 (M^+, 21), 132 (M^+ –Cl, 100), 105 (46), 79 (11), 69 (14). Compound VIII, PMR spectrum: 4.58 ppm (s, CH_2Cl). Mass spectrum, m/z: 201 (M^+, 20), 170 (15), 166 (M^+ –Cl 100), 105 (50), 79 (16), 69 (14). Compound VI, PMR spectrum: 2.22 ppm (s, CH_3); mass spectrum, m/z: 167 (M^+, 100), 132 (M^+ –Cl, 58), 123 (21), 106 (74), 105 (24), 79 (23), 71 (84), 70 (12), 69 (12). Chlorination of Ie with UV initiation gave similar results.

LITERATURE CITED

1. K. Steinbeck and J. Klein, Angew. Chem. Int. Ed., 20, 773 (1981).
2. K. I. Rubina, Yu. Sh. Gol'dberg, and M. V. Shimanskaya, Khim. Geterotsikl. Soedin., No. 8, 1138 (1985).
3. I. E. Dolgii, K. N. Shavrin, I. V. Krylova, and O. M. Nefedev, Izv. Akad. Nauk SSSR, Ser. Khim., No. 10, 2380 (1986).
4. W. Mathes and H. Schüly, Angew. Chem., 75, 235 (1963).
5. F. Raschig, FRG Patent No. 1204231, Chem. Abstr., 64, 2063f (1966).
6. G. Whittaker, Eur. Patent 65358, Chem. Abstr., 98, 143282c (1983).
7. G. R. Newkome, G. E. Kiefer, Y. -J. Xia, and V. K. Gupta, Synthesis, No. 8, 676 (1984).
8. G. Jones, D. R. Sliskovic, B. Foster, J. Rogers, An. K. Smith, and M. Y. Wong, J. Chem. Soc., Perkin I, No. 1, 78 (1981).
9. N. Katagiri, R. Niwa, Y. Fuvuya, and T. Kato, Chem. Pharm. Bull., 31, 1833 (1983).
10. B. R. Brown, D. L. Hammick, and B. H. Thenlis, J. Chem. Soc., No. 5, 1145 (1951).
11. A. Hirschberg and P. Spoerri, J. Org. Chem., 26, 2356 (1961).
12. E. J. J. Grabowski, E. W. Tristram, R. Tull, and P. I. Pollak, Tetrahedron Lett., No. 56, 5931 (1968).
13. J. D. Behun and R. Levine, J. Org. Chem., 23, 406 (1958).
14. B. Klein, N. E. Natman, and M. E. O'Donnel, J. Org. Chem., 28, 1682 (1963).
15. J. Kollonitsch, US Patent 3299083, Chem. Abstr., 68, 49542n (1968).
16. J. V. Metzger (editor), Thiazole and Its Derivatives, Part 1, Wiley, New York (1979), p. 69.

MASS SPECTROMETRIC STUDY OF THIOCARBAMOYL-SUBSTITUTED 2-AMINOTHIAZOLES AND 2-IMINOTHIAZOLINES.

1. ALIPHATIC DERIVATIVES

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Electron impact mass spectra of 10 thioureido derivatives of thiazole amino- and iminostructure are studied. The main difference between them appears in the ratio of peak heights of the 2-aminothiazolyl (2-iminothiazoline) and thiazolyl(thiazolinylidene)-2-isothiocyanate ions. A series of decay processes is revealed which occur through rearrangement in the thioureide chain and upon rupture of bonds in the heterocycle.

Fragmentation mass spectrometry in a number of cases represents the most suitable method for identification of isomeric compounds. Among these are 2-amino- and 2-imino- derivatives of benzothiazoles [1, 2], thiazoles [3], and systems analogous to them with other heteroatoms [4]. Knowledge of the similiarities and differences of decay of isomeric compounds is so useful that in some reactions the isomeric composition of the products was impossible to predict earlier [5].

Also, a change in the nature of substituents can complicate interpretation of mass spectra and disrupt the quantitative relation between contributions of characteristic ions. Relative to these questions, we studied mass spectra of a number of thiazole-containing thioureas of general formula

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