CHLORINATION OF DIMETHYLFURAZAN AND SOME PROPERTIES OF THE RESULTING CHLORIDES

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Mono- and polychloromethyl derivatives were synthesized by chlorination of dimethylfurazan with chlorine and sulfuryl chloride. The PMR spectra of the compounds are discussed. The group refraction of the furazan ring, the average value of which is 12.78, was determined.

There is no information in the literature regarding the halogenation of the methyl groups of dimethylfurazan (I). At the same time, halomethyl derivatives of I are of undoubted interest as starting materials for the preparation of functional derivatives of furazan, since one should expect lability of the halogen because of the activating effect of the furazan ring.

For preparative purposes we developed a method for the chlorination of the methyl groups in I with free chlorine and sulfuryl chloride. In contrast to the well-studied chlorination reactions of xylenes and even the closest analog, 3,5-dimethyl-1,2,4-oxadiazole [1], chlorination of furazan I proceeds under more severe conditions. Thus in the case of thermal initiation this reaction proceeds appreciably only at temperatures above 145°C. The use of azobisisobutyronitrile (AIBN) makes it possible to lower the chlorination temperature to 50-80°. Compound I reacts with sulfuryl chloride only in the presence of radical initiators. In all cases chlorination leads to a mixture of mono-, di-, tri-, and tetrachloro derivatives in yields that depend on the overall degree of chlorination. However, practically only 3-chloromethyl-4-methylfurazan (II) is obtained when the degree of conversion of furazan I is no more than 40%. More profound chlorination leads to difficult-to-separate mixture of chloro derivatives. It is therefore better to chlorinate isolated monochloride II to the point of 30% conversion for the preparative synthesis of sym-dichloride III. These conditions are optimal for the preparation of the these most interesting, in a synthetic respect, chloro derivatives of I.

Individual chloro derivatives of I (Table 1) were isolated from the mixtures by distillation with a fine-rectification column with 15 theoretical plates, and their individuality was proved by gas–liquid chromatography (GLC).

In order to separate compounds with a gem-dichloromethyl group from the compounds containing a monochloromethyl group we also used the ability of the latter to undergo quaternization with pyridine.

The structures of isomeric dichlorides III and IV were established from the presence or absence of a signal of the CH_3 group in the PMR spectra.

Thus only the dichloro derivatives of I are produced in the form of two isomers. The absence of isomers with a trichloromethyl group is not unexpected and is in agreement with the results of the radical chlorination of xylenes [2].

The chloro derivatives of I are heavy oily colorless liquids that are insoluble in water but miscible with organic solvents.

The compounds that contain a monochloromethyl group have an appreciable irritating effect on the eyes and skin; the LD_{50} of 3-methyl-4-chloromethylfurazan, determined in white mice by intraperitoneal injection, is 100 mg/kg; this is close to the toxic effect of benzyl chloride [3].

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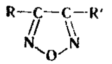
TABLE 1. Chloro-Substituted Dimethylfurazans



Compound	R	R′	bp, °C (mm)	n_D^{20}	d_4^{20}	MR_{found}	Ring R	Empirical formula	Found, %				Calc., %				Chemical shifts of the protons,* ppm		
									C	H	N	Cl	C	H	N	Cl	CH_3	CH_2Cl	$CHCl_2$
II	CH_3	CH_2Cl	63 (8)	1,4625	1,2545	29,06	12,89	$C_4H_5ClN_2O$	36,8	3,8	21,0	26,7	36,2	3,8	21,1	26,8	2,45	4,88	—
III	CH_3	$CHCl_2$	47 (4)	1,4760	1,3898	33,88	12,92	$C_4H_4Cl_2N_2O$	29,3	3,2	16,7	42,3	28,7	2,4	16,8	42,5	2,65	—	7,36
IV	CH_2Cl	CH_2Cl	69 (5)	1,4950	1,4519	33,54	12,56	$C_4H_4Cl_2N_2O$	28,6	2,8	16,6	42,0	28,7	2,4	16,8	42,5	—	5,05	—
V	CH_2Cl	$CHCl_2$	79 (5)	1,5069	1,5531	38,55	12,79	$C_4H_3Cl_3N_2O$	23,7	1,4	13,7	52,8	23,8	1,5	13,9	52,8	—	5,05	7,36
VI	$CHCl_2$	$CHCl_2$	78 (2)	1,5150	1,6415	43,36	12,74	$C_4H_2Cl_4N_2O$	19,8	1,1	12,1	59,9	20,3	0,8	11,9	60,2	—	—	7,36

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*The $\delta^{H}_{CH_3}$ chemical shift in I is 2.28 ppm

The IR spectra of II-VI contain absorption bands at 630-850 (C−Cl) and at 1390-1490 and 1580-1590 cm^{-1} (furazan ring).

A singlet at 2.28 ppm is observed in the PMR spectrum of I; this is very close to the chemical shifts of the methyl groups in the isomeric 2,5-dimethyl-1,3,4-oxadiazole (2.40 ppm) [4]. These values fall within the range of the characteristic signals of methyl groups for many dimethyl derivatives of aromatic carbocycles and heterocycles [5].

A relationship between the chemical shifts of the protons of the methyl or methylene groups and the number of chlorine atoms in the other methyl groups is observed in the PMR spectra of the chlorinated dimethylfurazans. Since this sort of effect is not observed for saturated hydrocarbons with the same number of bonds between the chlorine atoms and the resonating proton, it may be associated with transmission of the negative inductive effect of the CH_2Cl and $CHCl_2$ groups through the furazan ring and (or) with coupling of the closely situated resonating protons in the 3 position with the chlorine atoms in the 4 position directly through space (ortho effect).

The group refraction, found by substraction of the group refractions of the side chains according to Vogel from the established molecular refraction, was determined for the furazan ring.

The average value of the group refraction is 12.78.* This value is considerably lower than the group refraction of the furazan ring calculated via an additive scheme and is close to the group refraction of the isomeric 1,3,4-oxadiazole ring [4]. The depression of the molecular refraction places furazans in the general series of heteroaromatic five-membered systems such as the furan, pyrrole, and thiophene systems, which also display considerable negative deviations from additivity [8].

EXPERIMENTAL

Chromatographically pure dimethylfurazan was used in this study. The chlorine was purified with sulfuric acid prior to the reactions. The sulfuryl chloride was freshly distilled. The azobisisobutyronitrile was recrystallized twice from alcohol and had mp 105°C.

The PMR spectra of the compounds were recorded with a YaMR-5535 spectrometer at 40 MHz. The chemical shifts of the protons were measured relative to tetramethylsilane.

3-Methyl-4-chloromethylfurazan (II). A) An 84-g (0.85 mole) sample of I was treated with a strong stream of chlorine at 145-150° for 12 h. Vacuum distillation of the mixture yielded 41 g (69%) of II and 40 g of unchanged furazan I.

B) A 173.5-ml (2.14 mole) sample of sulfuryl chloride was added in five portions at 65-70° to 210 g (2.14 mole) of I in which 6.25 g (0.04 mole) of azobisisobutyronitrile was dissolved. Each portion of sulfuryl chloride was added after completion of the vigorous reaction. The mixture was then heated gradually to 90-95° for 3 h, after which it was distilled to give 97 g (79.7%) of II and 120 g of furazan I.

Polychloromethylfurazans. A 200-g (2.04 mole) sample of I was treated with a strong stream of chlorine at 150-155° for 21 h, after which the mixture was subjected to distillation with a fine-rectification column to give 51 g of 3-methyl-4-chloromethylfurazan (II), with bp 63-64.5° (8 mm), 17 g of 3-methyl-4-dichloromethylfurazan (III), with bp 47-48° (4 mm), 35 g of 3,4-bis(chloromethyl)furazan (IV), with bp 69-71° (5 mm), and 33 g of 3-chloromethyl-4-dichloromethylfurazan (V), with bp 79-80° (5 mm).

3,4-Bis(dichloromethyl)furazan (VI). A mixture (30 g) consisting, according to results of gas−liquid chromatography, of 3,4-bis(dichloromethyl)furazan (53%) and 3-chloromethyl-4-dichloromethylfurazan (47%) was obtained by chlorination of 15 g (0.15 mole) of I for 50 h under the conditions of the preceding experiment. A mixture of 21.3 g of this mixture, 8g of pyridine, and 25 ml of absolute alcohol was refluxed for 3 h, after which the alcohol and excess pyridine were removed in vacuo, and the residue was treated with 100 ml of CCl_4. The extract was washed with water acidified with HCl and dried over anhydrous $MgSO_4$. Vacuum distillation yielded 9.5 g of VI.

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*The value found for I by the method in [6] is 12.68, as compared with 12.71 found for unsubstituted furazan by the method in [7].

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STUDY OF THE MECHANISM OF THE POLAROGRAPHIC REDUCTION OF N-ACYLSYDNONEIMINES

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The polarographic reduction of the N-phenylcarbamoyl derivative of 3-(β-phenylisopropyl)-sydnoneimine ("sidnokarb") in aqueous alcohol media was investigated. It is shown that, depending on the protonation rate of both the starting depolarizer and the intermediates in the reduction of sidnokarb, six or four electrons may be consumed to give, in the first case, a derivative of the amino acid amide and ammonium ions and, in the second case, the corresponding hydrazine derivative.

The polarographic behavior of N-exo-acyl derivatives of sydnoneimines have received little study – the effect of the pH on the limiting current and $E_{1/2}$ has been investigated, and, in analogy with sydnones and sydnoneimine salts, preliminary considerations relative to the possible mechanism of the reduction of N-acylsydnoneimines have been expressed [1]. Insofar as the polarography of N-carbamoyl derivatives is concerned, there are not data except the $E_{1/2}$ values of several compounds [2] in the literature. Considering that N-acylsydnoneimines have recently attracted the attention of researchers in connection with the high pharmacological activity of representatives of this class of compounds [3-5], it was of interest to make a more detailed study of their polarographic reduction. The N-phenylcarbamoyl derivative of 3-(β-phenylisopropyl)sydnoneimine (I, "sidnokarb"), which is a medicinal preparation that is a highly effective central nervous system (CNS) stimulator [5], was selected as the subject of the investigation. We have recently made a detailed study [6] of the polarography of the salt of the corresponding 3-(β-phenylisopropyl)sydnoneimine, and a comparison of the behavior of the latter compound on a dropping mercury electrode with that of sydnoneimine I makes it possible to evaluate the effect of an N-exocyclic grouping.

The study of the polarographic behavior of sidnokarb I was carried out in buffered and unbuffered media containing 50% ethanol. One distinctly expressed polarographic wave, the limiting current of which decreases somewhat as the pH increases, is observed in the reduction of sidnokarb in acidic media. At pH 3-6, in addition to the principal wave, an additional wave with a voltage drop, the height of which depends markedly on the pH of the medium,* appears prior to the discharge current. The $E_{1/2}$ value of the principal reduction wave of sidnokarb itself depends on the pH of the medium and is shifted to negative potentials as the pH increases. At

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*This wave has the properties of a surface catalytic wave of hydrogen evolution and is determined by protonation of the intermediates, absorbed on the mercury electrode, in the reduction of sidnokarb; a similar phenomenon has been observed in the reduction of the 3-(β-phenylisopropyl)sydnoneimonium cation [6].

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