INVESTIGATION OF THE TRANSFORMATIONS OF 2-TRICHLOROMETHYL-4-METHYLENE-1,3-DIOXOLANES

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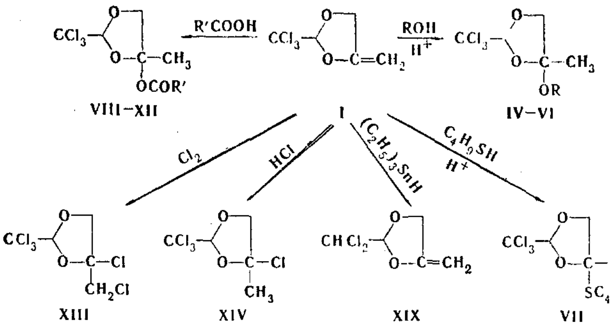
The reactions of 2-trichloromethyl-4-methylene-1,3-dioxolanes with electrophilic and nucleophilic reagents were studied. The conditions that make it possible to carry out the reaction selectively at the double bond with retention of the acetal structure were found. New types of cyclic chloroacetals were synthesized.

With the goal of further investigations of the dependence between the structure and pharmacological action of a number of chlorine-containing cyclic acetals [1], we have obtained several new types of compounds of this sort (Table 1). Their synthesis was based on the reactions of 2-trichloromethyl-4-methylene-1,3-dioxolane (I) and its 5,5-dimethyl (II) and 5-methyl-5-ethyl derivatives (III) [2, 3] with electrophilic and nucleophilic reagents.



Like simple vinyl ethers, the unsaturated trichloroacetals react with alcohols in the presence of acid catalysts. Thiols also form addition products in accordance with the Markovnikoff rule. Anomalous reaction products are not detected in this case. The structure of VII was confirmed by the IR spectrum and analysis by the "mercuric chloride" method [4].

4-Acyl-1,3-dioxolanes VIII-XII were obtained from unsaturated cyclic acetals of chloral. Such compounds are known, for example, as agents for combatting tuberculosis inducers [5]. The reaction is accomplished by mixing the reagents and proceeds exothermically. An acid catalyst is required only in the case of benzoic acid. There is an intense absorption band of a C = O group at 1740 cm^{-1} in their IR spectra.

The addition of chlorine made it possible to realize the transition to cyclic α,β-dichloro ether XIII. The addition of chlorine at −20 to −25°C proceeds exothermically. The reaction is accompanied by a side process − the formation of products of substituent chlorination, the amount of which increases with rising temperature. Partial thermal dehydrochlorination is observed during vacuum distillation of XIII, which is attested to by the appearance in the IR spectrum of a weak absorption band at 1704 cm^{-1}, which apparently corresponds to the endocyclic double bond in the dioxol.*

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*In contrast to the exocyclic double bond in I-III, which is characterized by absorption at 1670 and 1700 cm^{-1} [3].

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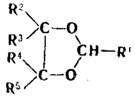
TABLE 1



Compound	R^1	R^2	R^3	R^4	R^5	Bp, °C (mm)	d_4^{20}	n_D^{20}	MR_D		Empirical formula	Found, %			Calc., %			Yield, %
									found	calc.		C	H	Cl	C	H	Cl	
III	CCl_3	CH_3	C_2H_5	$—CH_2$		54 (2)	1,2781	1,4820	54,60	54,10	$C_8H_{11}Cl_3O_2$	39,3	4,6	43,5	39,2	4,5	43,3	86
IV	CCl_3	H	H	CH_3	OC_2H_5	65—67 (3)	1,3138	1,4580	51,82	52,07	$C_7H_{11}Cl_3O_3$	34,0	4,5	42,9	33,7	4.4	42,6	75
V	CCl_3	H	H	CH_3	OC_4H_9-*n*	98,5 (3)	1,2519	1,4625	61,01	60,98	$C_9H_{15}Cl_3O_3$	39,0	5,4	—	38,9	5,4	—	79
VI	CCl_3	H	H	CH_3	$OCH_2C{\equiv}CH$	97 (2)	1,3782	1,4875	54,20	54,29	$C_8H_9Cl_3O_3$	37,0	3,8	40,9	37,0	3,5	41,0	92
VII	CCl_3	H	H	CH_3	SC_4H_9-*n*	125,5 (1)	1,2890	1,5050	67,62	67,40	$C_9H_5Cl_3O_2S$	36,5	5,0	36,1	36,8	5,1	36,2	76
VIII	CCl_3	H	H	CH_3	$OCOCH_3$	23*	—	—	—	—	$C_7H_9Cl_3O_4$	31,8	3,4	40,4	31,9	3,4	40,4	78
IX	CCl_3	H	H	CH_3	$OCOC_2H_5$	27*	—	—	—	—	$C_8H_{11}Cl_3O_4$	33,9	3,7	—	34,6	4,0	—	64
X	CCl_3	H	H	CH_3	$OCOCCl_3$	70*	—	—	—	—	$C_7H_6Cl_6O_4$	22,9	1,6	—	22,9	1,6	—	92
XI	CCl_3	H	H	CH_3	$OCOC_6H_5$	116,5*	—	—	—	—	$C_{12}H_{11}Cl_3O_4$	44,4	3,4	32,6	44,3	3,4	32,7	58
XII	CCl_3	H	H	CH_3	$OCOC{\equiv}CH$	59*	—	—	—	—	$C_8H_7Cl_3O_4$	35,4	2,6	39,9	35,1	2,6	39,9	86
XIII	CCl_3	H	H	CH_2Cl	Cl	88—89 (5)	1,6364	1,5140	50,47	50,65	$C_5H_5Cl_5O_2$	21,8	1,6	64,4	21,9	1,8	64,6	50
XIV	CCl_3	H	H	CH_3	Cl	74—75 (3)	1,4957	1,4860	46,05	45,71	$C_5H_6Cl_4O_2$	24,9	2,4	58,9	25,0	2,5	59,1	97
XV	CCl_3	CH_3	CH_3	CH_3	OH	95*	—	—	—	—	$C_7H_{11}Cl_3O_3$	—	—	42,6	—	—	42,7	85
XVI	CCl_3	CH_3	C_2H_5	CH_3	OH	90*	—	—	—	—	$C_8H_{13}Cl_3O_3$	—	—	40,5	—	—	40,4	77
XVII	CCl_3	H	H	CH_3	NCS	94,5 (1)	1,4568	1,5360	56,21	55,46	$C_6H_6Cl_3NO_2S$	27,5	2,4	—	27,4	2,3	—	85
XVIII	CCl_3	CH_3	CH_3	CH_3	NCS	110—112 (1)	1,3769	1,5290	65,09	65,85	$C_8H_{10}Cl_3NO_2S$	—	—	37,3	—	—	36,6	60
XIX	$CHCl_2$	H	H	$—CH_2$		50—51 (1)	1,3817	1,4912	35,44	35,68	$C_5H_6Cl_2O_2$	35,7	3,3	42,4	35,5	3,6	42,0	85
XX	$CHCl_2$	CH_3	CH_3	$—CH_2$		65—67 (3)	1,3138	1,4580	51,82	52,07	$C_7H_{11}Cl_2O_2$	42,6	5,1	36,0	42,9	5,1	36,0	80

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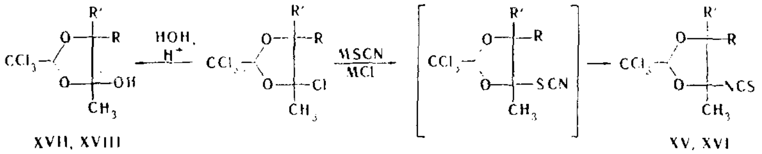
*Melting point.

Opening of the acetal ring, which occurs in the case of alkyl-substituted 1,3-dioxolanes [6], does not occur during the action of hydrogen chloride on 2-trichloromethyl-4-methylene-1,3-dioxolane. The reaction proceeds selectively at the double bond.

In contrast to α-chloroalkyl ethers, the α-chloro atom in the cyclic ethers has less lability in nucleophilic substitution reactions. Thus only ~67% of the active chlorine is titrated in the course of an hour in the titration of an aqueous dioxane solution of XIV with 0.1 N NaOH at room temperature, while α-chloroalkyl ethers are quantitatively hydrolyzed under such conditions [7].

The structures of the compounds were proved by reactions with the participation of the active α-chlorine atom: hydrolysis and reaction with thiocyanate salts.



XVII, XVIII

XV, XVI

M = K, Na, NH_4

The hydrolysis proceeds at room temperature with retention of the acetal structure, which makes it possible to introduce a hydroxyl group directly into the α position relative to the 1,3-dioxolane ring. It is known from the literature data that cyclic α-chloro ethers are completely cleaved under such conditions [8]. The stability of the acetals is explained by the effect of the electron-acceptor trichloromethyl group. Compounds XV, XVI simultaneously contain a chloral acetal fragment and an acetaldehyde hemiacetal fragment. They are stable and are isolated in pure form, in contrast to alkylhemiacetals of acetaldehyde, which are known only in solutions. The IR spectra of XV and XVI each contain two absorption bands at 3580 and 3600 cm^{-1}, which are affiliated with the hydroxyl groups. According to the PMR spectra, a characteristic peculiarity of cyclic hemiacetals XV and XVI is the presence of two signals of methylidyne groups (δ 5.43 and 5.30 ppm for XV, and 5.36 and 5.16 ppm for XVI) and respectively, singlets of OH groups (3.65 ppm for XV, and 3.26 for XVI). On the basis of an analysis of the PMR spectra, it can be assumed that XV and XVI exist as a mixture of cis and trans isomers.

The previously unknown 2-trichloromethyl-4-isothiocyanato-1,3-dioxolanes (XVII and XVIII) were obtained by the reaction of the cyclic α-chloro ethers with thiocyanate salts. This reaction seemed of interest as a method for the preparation of cyclic isothiocyanates, since organic isothiocyanates are used extensively for the synthesis of polymeric materials, medicinals, insectofungicides, photographic materials, and other products [9].

When a mixture of a thiocyanate salt and the appropriate 1,3-dioxolane is heated at 30-50° in acetone for 8-10 h, the reaction proceeds selectively at the chlorine atom in the 4 position without opening of the acetal ring and participation of the CCl_3 group. Complete isomerization of the thiocyanate, which is apapparently formed in the first step, to the isothiocyanate is observed during the reaction. The use of excess thiocyanate salt [10] and heating promote this sort of reaction. Two absorption bands of the $N=C=S$ group at 1970-2045 cm^{-1} are observed in the IR spectra of acetals XVII and XVIII. The PMR spectrum of XVII has two singlets of the CH group (5.30 and 5.53 ppm) and singlets at 1.80 (CH_3) and 4.16 ppm (CH_2). On the basis of this, it can be assumed that it exists as cis and trans isomers.

The 2-trichloromethyl-4-methylene-1,3-dioxolanes were reduced with organotin hydrides in order to pass to cyclic acetals of dichloroacetaldehyde. This reaction, which leads to cyclic acetals of dichloroacetaldehyde (XIX) that contain an exocyclic methylene group, is very convenient, since reduction of the trichloromethyl group by the known method (with zinc in acetic acid [11, 12]) is unsuitable in this case because I-III react with the acid to form an acylal.

EXPERIMENTAL

The IR spectra of CCl_4 solutions (0.002 M) were obtained with a UR-10 spectrometer. The PMR spectra of CCl_4 solutions were obtained with a JNM-4H-100 spectrometer at room temperature with hexamethyldisiloxane as the internal standard.

The starting 1,3-dioxolanes (I-III) were obtained as in [2, 3]. The physical constants of III and of the products of the transformations are presented in Table 1.

2-Trichloromethyl-4-methyl-4-butoxy-1,3-dioxolane (V). A 0.01 g sample of p-toluenesulfonic acid was added to a mixture of 6.5 g (0.03 mole) of I and 3 g (0.04 mole) of butanol. After the spontaneous heating up of the mixture had ceased, it was held at 80-90° for 1 h and distilled to give 7 g (79%) of V. Compounds IV and VI were similarly obtained.

2-Trichloromethyl-4-methyl-4-butylthio-1,3-dioxolane (VII). A 5.84 g (0.06 mole) sample of freshly distilled n-butyl mercaptan and several drops of hydrochloric acid were added with stirring to 13 g (0.06 mole) of I, and the mixture was heated to 100° for 5 h and neutralized with potassium carbonate. Distillation gave 18.6 g (76%) of VII.

2-Trichloromethyl-4-methyl-4-acetoxy-1,3-dioxolane (VIII). A 20.3 g (0.1 mole) sample of I was mixed with 6.6 g (0.11 mole) of glacial acetic acid, and the mixture was warmed to 50°. The yield of VIII was 20.5 g (78%). Compounds IX, X, and XII were similarly obtained. Sulfuric acid was used as the catalyst for the synthesis of XI, and the mixture was heated at 90° for 30 min.

2-Trichloromethyl-4-chloro-4-chloromethyl-1,3-dioxolane (XIII). Carbon tetrachloride (64 ml) was saturated with chlorine at −20° until the increase in weight was 22.4 g. A 47 g (0.23 mole) sample of I was added to the resulting solution at −20 to −25°, and the mixture was stirred at room temperature for 3 h. The excess chlorine and CCl_4 were removed by passing dry air through the mixture to give 31.7 g (50%) of XIII.

2-Trichloromethyl-4-chloro-4-methyl-1,3-dioxolane (XIV). A stream of dry hydrogen chloride was passed for 1 h into a cooled (0-5°) solution of 13.8 g (0.06 mole) of I in 20 ml of dry CCl_4. The increase in weight was 2.2 g. The excess HCl was removed by passing dry air through the mixture. Distillation gave 15.8 g (97%) of XIV.

2-Trichloromethyl-5,5-dimethyl-4-methyl-4-hydroxy-1,3-dioxolane (XV). A 4.25 g (0.018 mole) sample of II was saturated with dry HCl in the course of 30 min. The increase in weight was 0.67 g. The resulting 2-trichloromethyl-5,5-dimethyl-4-chloro-4-methyl-1,3-dioxolane, without additional purification, was allowed to stand over H_2O in a desiccator for 4 days at room temperature. The resulting crystals were recrystallized from petroleum ether to give 3.9 g (85%) of XV. Compound XVI was similarly obtained.

2-Trichloromethyl-4-methyl-4-isothiocyanato-1,3-dioxolane (XVII). A 15.6 g (0.06 mole) sample of XIV was added dropwise to a solution of 7 g (0.07 mole) of KSCN in 50 ml of absolute acetone, and the mixture was stirred at 50° for 6 h. The precipitate was removed by filtration, and the acetone was distilled off. Vacuum distillation gave 14.5 g (85%) of XVII. Compound XVIII was similarly obtained.

2-Dichloromethyl-4-methylene-1,3-dioxolane (XIX). A 17.47 g (0.08 mole) sample of triethylstannane was added to 17.15 g (0.08 mole) of I, and the temperature rose to 200° as a result of the exothermic reaction. The mixture was cooled and distilled to give 12.2 g (86%) of XIX. Compound XX was similarly obtained.

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