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SOME CHEMICAL CONVERSIONS OF 3,3,5-TRICHLORO-2-HYDROXY-TETRAHYDROPYRAN

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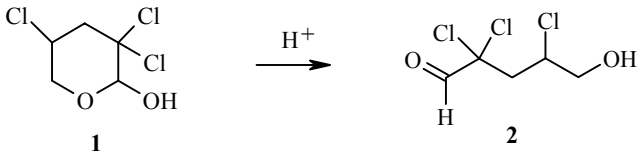
A series of chemical conversions of 3,3,5-trichloro-2-hydroxytetrahydropyran has been carried proceeding both with ring opening and with its retention. Alkylation, acylation, and sulfonylation of the hydroxyl group of the initial ring have been carried out.

Keywords: 3,3,5-trichloro-2-hydroxytetrahydropyran, hydrazones, alkylation, acylation, sulfonylation.

We reported in [1.2] the synthesis of 3,3,5-trichloro-2-hydroxytetrahydropyran by the interaction of chloral with allyl alcohol on heating in acetonitrile in the presence of copper(I) chloride or iron pentacarbonyl. We showed that the reaction is general for various terminal allyl alcohols [3]. In the present work we report several chemical conversions of 3,3,5-trichloro-2-hydroxytetrahydropyran (**1**).

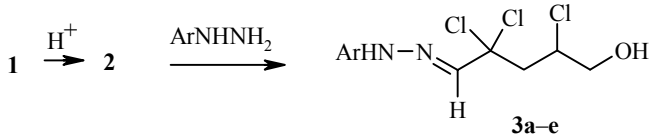
According to data of NMR spectroscopy there is no ring–chain tautomerism in freshly distilled compound **1** [1]. However since 3,3,5-trichloro-2-hydroxytetrahydropyran is a cyclic hemiacetal, opening of the pyran ring might be expected in acidic medium. In reality on recording the ^{1}H NMR spectrum in the presence of strong acids (D_2SO_4, CF_3COOD) the signals at 5.15 and 4.71 ppm, belonging to the proton of the hemiacetal group, are reduced and in the region of 9 ppm a characteristic singlet appears which indicates opening of the hemiacetal ring leading to 2,2,4-trichloro-5-hydroxypentanal (**2**).



1 **2**

However attempts to isolate aldehyde **2** lead to regeneration of the initial ring.

By reacting hydropyran **1** with arylhydrazines we successfully synthesized a series of hydrazones of 2,2,4-trichloro-5-hydroxypentanal **3a-e** (Table 1).



3a–e

3 a Ar = 2,4-$(NO_2)_2C_6H_3$; **b** Ar = 3,5-Cl-Py; **c** Ar = 4-$O_2NC_6H_4$; **d** Ar = Ph; **e** Ar = 4-MeC_6H_4

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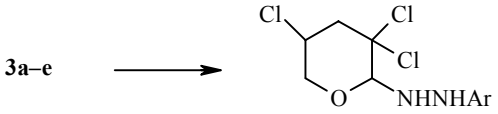
TABLE 1. Physicochemical Characteristics of Compounds **3a-e**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	IR spectrum, $\nu_{C=N}$, cm^{-1}	Yield, %
		C	H	N			
3a	$C_{11}H_{11}Cl_3N_4O_5$	34.20 / 34.26	2.91 / 2.88	14.49 / 14.53	163-163.7	1640	93
3b	$C_9H_9Cl_5N_3O$	33.01 / 32.95	2.52 / 2.49	11.47 / 11.53	163-164	1641	74
3c	$C_{11}H_{12}Cl_3N_3O_3$	38.82 / 38.79	3.51 / 3.55	12.35 / 12.34	159-159.5	1642	85
3d	$C_{11}H_{13}Cl_3N_2O$	44.63 / 44.70	4.46 / 4.43	9.52 / 9.48	147.5-148	1645	73
3e	$C_{12}H_{15}Cl_3N_2O$	46.51 / 46.55	4.53 / 4.48	9.10 / 9.05	157-158	1646	69

Hydrazones obtained were high-melting crystalline solid substances. Absorption bands were observed in the IR spectra of compounds **3a-e** at 1640-1650 cm^{-1} characteristic of the C=N double bond of hydrazones.

Signals were recorded in the ^1H NMR spectra of compounds **3a-e** for the protons of linear arylhydrazones of 2,2.4-trichloro-5-hydroxyvaleraldehyde at 7.15 (1H, s, CH=N), 2.84 (2H, d, CH_2), 4.11 (1H, m, CH), 3.85 (2H, d, CH_2OH), and at 7.92-8.86 ppm for the aromatic fragment. In addition a series of additional signals were observed in the spectra which were close in chemical shifts to the signals of hydropyran **1**. Thus the signals at 4.94 and 4.65 ppm correspond to the signals of the protons at $C_{(2)}$ of compound **1** (4.78 and 4.14 ppm), the signals at 2.36, 2.67, 2.49, and 2.72 ppm correspond to the signals of protons at $C_{(4)}$ (3.66, 2.59, and 2.64 ppm), the signals at 4.09 and 3.66 ppm may correspond to the signals of protons at $C_{(5)}$ (3.59 and 3.93 ppm), and the signals at 4.43, 4.28, 3.52, and 2.96 ppm may correspond to the signals of protons at $C_{(6)}$ (3.75, 3.43, 2.68, and 1.91 ppm) of compound **1**. Evidently on dissolving the sample in deuterochloroform an intramolecular attack of the hydroxyl group oxygen onto the imine carbon atom occurs, which leads to the formation of 2-(N-aryl)hydrazo-3,3,5-trichlorotetrahydropyrans **4a-e**.

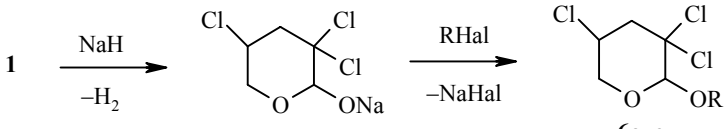


4a–e

We have therefore shown by spectral and chemical methods that in acid solution compound **1** exists in a hemiacetal cyclic modification and as linear 2,2,4-trichloro-5-hydroxypentanal.

We have carried out alkylation, acylation, and sulfonation of the hydroxyl group of the initial compound **1**.

On reaction with sodium hydride in hexane at 0°C hydropyran **1** was converted into alcoholate **5**, subsequent treatment of which with alkyl halides leads to the formation of ethers **6a-c**.



5 **6a–c**

An even more convenient means of alkylating compound **1** proved to be reaction in a two-phase benzene–aqueous NaOH system in the presence of the phase-transfer catalyst triethylbenzylammonium chloride (TEBAC). This reduced the reaction time significantly and increased the yield of the desired compounds.

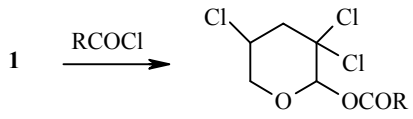
The dependence of yields of 2-alkoxytetrahydropyrans **6a-c** on the reaction conditions and the alkylating agent used are given in Table 2.

TABLE 2. Yields of 2-Alkoxy-3,3,5-trichlorotetrahydropyrans **6a-c**

Compound	Method of synthesis*	Alkylating agent	Empirical formula	Found, % / Calculated, %		bp, °C (mm Hg)	Yield, %
				C	H		
6a	A	Methyl iodide	$C_6H_9Cl_3O_2$	32.76 / 32.83	4.09 / 4.13	112-113 (0.7)	56
	B	Methyl iodide					67
	B	Dimethyl sulfate					74
6b	A	Ethyl bromide	$C_7H_{11}Cl_3O_2$	35.94 / 36.00	4.80 / 4.75	118-119 (0.8)	47
	B	Ethyl bromide					58
	A	Ethyl iodide					56
	B	Ethyl iodide					69
6c	A	Propyl bromide	$C_8H_{13}Cl_3O_2$	38.91 / 38.82	5.33 / 5.29	134-135 (1.0)	43
	B	Propyl bromide					58
	A	Propyl bromide					50
	B	Propyl bromide					66

* Method A is alkylation in hexane in the presence of sodium hydride, B is alkylation in a water–benzene system in the presence of NaOH and a phase-transfer catalyst.

The acylation of compound **1** with acid chlorides and anhydrides was carried out by dissolving the reactants in diethyl ether. Acetyl chloride, acetic anhydride, benzoyl chloride, and 4-nitrobenzoyl chloride were used as acylating agents and compounds **7a-c** (Table 3) were obtained.



7a–c

7 a R = Me, **b** R = Ph, **c** R = 4-$O_2NC_6H_4$

TABLE 3. Physicochemical Characteristics of Compounds **7a-c**

Compound	Acylating agent	Empirical formula	Found, % / Calculated, %			bp, °C (mm Hg)	Yield, %
			C	H	N		
7a	Acetyl chloride	$C_7H_9Cl_3O_3$	33.94 / 33.97	3.61 / 3.67		121-123 (4)	74
	Acetic anhydride						82
7b	Benzoyl chloride	$C_{12}H_{11}Cl_3O_3$	46.58 / 46.56	3.60 / 3.58		152 (1)	68
7c	4-Nitrobenzoyl chloride	$C_{12}H_{10}Cl_3NO_5$	40.61 / 40.65	2.90 / 2.84	4.00 / 3.95	—*	72

* mp 43-46°C.

TABLE 4. Physicochemical Characteristics of Compounds **8a-c**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
8a	$C_{12}H_{13}ClO_4S$	40.03 / 40.08	3.70 / 3.64		64-68	73
8b	$C_{11}H_{10}Cl_3NO_6S$	33.83 / 33.82	2.59 / 2.58	3.55 / 3.59	47-50	62
8c	$C_{11}H_{10}Cl_3NO_6S$	33.81 / 33.82	2.56 / 2.58	3.61 / 3.59	68-70	68

The sulfonation of hydropyran **1** was carried out by heating in toluene using *p*-toluenesulfonyl chloride, and 2- and 4-nitrobenzenesulfonamide as sulfonating agents. Compounds **8a-c** were obtained respectively (Table 4).

EXPERIMENTAL

The GLC analysis was carried out on a Chrom 5 chromatograph with a flame ionization detector, helium (30 cm^3/min) as carrier gas, glass columns 3500 × 3 mm with 5% of XE 60 on Inerton-Super (0.20-0.25 mm), and thermostat temperature of 200°C. The ^{1}H NMR spectra were recorded on a Bruker WP 200 (200 MHz) spectrometer in $CDCl_3$, internal standard was TMS.

2,2,4-Trichloro-5-hydroxypentanal 2,4-Dinitrophenylhydrazone (3a). Solution of 2,4-dinitrophenylhydrazine (2 g, 10 mmol) in alcohol was prepared according to the method of [4]. To the freshly prepared solution solution of hydropyran **1** (0.205 g, 1 mmol) in alcohol (2 ml) was added. The mixture was stirred and left overnight. The crystals which precipitated were filtered off and recrystallized from *o*-xylene. Yield 0.37 g. ^{1}H NMR spectrum, δ, ppm: linear form, 7.15 (1H, s, CH=N); 2.84 (2H, d, CH_2); 4.11 (1H, m, CH); 3.85 (2H, d, CH_2OH); 5.92 (2H, br. s, OH, NH); 8.01, 8.22, 8.96 (3H, m, Ar); cyclic form, 4.94, 4.65 (1H, s, CHON); 3.66, 2.59, 2.64 (2H, dd, CH_2); 4.09, 3.66 (1H, m, CHCl); 4.43, 4.28, 3.52, 2.96 (2H, dd, CH_2O); 5.92 (1H, br. s, NH); 8.01, 8.22, 8.96 (3H, m, Ar).

2,2,4-Trichloro-5-hydroxypentanal 3,5-Dichloro-2-pyridylhydrazone (3b). 3,5-Dichloro-2-pyridylhydrazine (1.79 g, 10 mmol) was dissolved in concentrated H_2SO_4 (1.5 ml). Water (2 ml) and ethanol (5 ml) were added to the solution obtained and then solution of compound **1** (0.205 g, 1 mmol) in alcohol (2 ml) was added. The mixture was stirred and left overnight. The solution was diluted with water (30 ml) and neutralized to pH 6 with sodium bicarbonate. The precipitated crystals were filtered off, dried, and recrystallized from *o*-xylene. Yield 0.206 g. ^{1}H NMR spectrum, δ, ppm: linear form, 7.15 (1H, s, CH=N); 2.84 (2H, d, CH_2); 4.11 (1H, m, CH); 3.85 (2H, d, CH_2OH); 5.92 (2H, br. s, OH, NH); 7.75, 8.20 (2H, 2 s, Ar); cyclic form, 4.94, 4.65 (1H, s, CHON); 3.66, 2.59, 2.64 (2H, dd, CH_2); 4.09, 3.66 (1H, m, CHCl); 4.43, 4.28, 3.52, 2.96 (2H, dd, CH_2O); 5.92 (1H, br. s, NH); 7.75, 8.20 (2H, 2 s, Ar).

2,2,4-Trichloro-5-hydroxypentanal 4-Nitrophenylhydrazone (3c) was obtained analogously from 4-nitrophenylhydrazine (2 g, 13 mmol) and compound **1** (0.205 g, 1 mmol). Yield 0.186 g. ^{1}H NMR spectrum, δ, ppm: linear form, 7.15 (1H, s, CH=N); 2.84 (2H, d, CH_2); 4.11 (1H, m, CH); 3.85 (2H, d, CH_2OH); 5.92 (2H, br. s, OH, NH); 7.52, 8.12 (4H, 2 d, Ar); cyclic form, 4.94, 4.65 (1H, s, CHON); 3.66, 2.59, 2.64 (2H, dd, CH_2); 4.09, 3.66 (1H, m, CHCl); 4.43, 4.28, 3.52, 2.96 (2H, dd, CH_2O); 5.92 (1H, br. s, NH); 7.52, 8.12 (4H, 2 d, Ar).

2,2,4-Trichloro-5-hydroxypentanal Phenylhydrazone (3d). Mixture of phenylhydrazine hydrochloride (0.4 g, 7 mmol) and compound **1** (0.205 g, 1 mmol) in ethanol (10 ml) was boiled for 8 h. The solution was cooled and the precipitated solid filtered off. The solid was washed with sodium bicarbonate

solution, dried, and recrystallized from benzene. Yield 0.127 g. ^{1}H NMR spectrum, δ, ppm: linear form, 7.15 (1H, s, CH=N); 2.84 (2H, d, CH_2); 4.11 (1H, m, CH); 3.85 (2H, d, CH_2OH); 5.92 (2H, br. s, OH, NH); 7.04-7.12 (5H, m, Ar); cyclic form, 4.94, 4.65 (1H, s, CHON); 3.66, 2.59, 2.64 (2H, dd, CH_2); 4.09, 3.66 (1H, m, CHCl); 4.43, 4.28, 3.52, 2.96 (2H, dd, CH_2O); 5.92 (1H, br. s, NH); 7.04-7.12 (5H, m, Ar).

2,2,4-Trichloro-5-hydroxypentanal 4-Methylphenylhydrazone (3e). Mixture of 4-methylphenylhydrazine (0.4 g, 3 mmol), concentrated HCl (0.2 ml), and compound **1** (0.205 g, 1 mmol) in ethanol (10 ml) was boiled for 8 h. The solution was cooled, diluted with water (20 ml), the precipitated solid was filtered off, washed with sodium bicarbonate solution, dried, and recrystallized from benzene. Yield 0.129 g. ^{1}H NMR spectrum, δ, ppm: linear form, 7.15 (1H, s, CH=N); 2.84 (2H, d, CH_2); 4.11 (1H, m, CH); 3.85 (2H, d, CH_2OH); 5.92 (2H, br. s, OH, NH); 7.02, 7.62 (4H, 2 d, Ar); cyclic form, 4.94, 4.65 (1H, s, CHON); 3.66, 2.59, 2.64 (2H, dd, CH_2); 4.09, 3.66 (1H, m, CHCl); 4.43, 4.28, 3.52, 2.96 (2H, dd, CH_2O); 5.92 (1H, br. s, NH); 7.02, 7.62 (4H, 2 d, Ar).

2-Alkoxy-3,3,5-trichlorotetrahydropyrans (General Procedure). A. Solution of compound **1** (0.41 g, 2 mmol) in absolute benzene (5 ml) was added with ice-cooling to sodium hydride (0.05 g, 2 mmol) washed with hexane. The mixture was stirred for 1 h 30 min until hydrogen evolution had finished. The alkylating agent (2 mmol) was added dropwise with stirring to the obtained suspension of alcoholate. Stirring was stopped after 2 h, the solution was filtered, and benzene evaporated. The residue was distilled in vacuum.

B. Mixture of 40% NaOH solution (5 ml), with a solution of compound **1** (2 mmol), and alkylating agent (2 mmol) in benzene (5 ml) was stirred for 1 h at 0°C in the presence of TEBAC (0.01 mmol). The benzene layer was separated, and dried over magnesium sulfate. The solvent was evaporated, and the residue distilled in vacuum.

3,3,5-Trichloro-2-methoxytetrahydropyran (6a). ^{1}H NMR spectrum, δ, ppm: 4.67, 4.59 (1H, s, OCHO); 4.27, 4.30, 4.39, 4.41 (2H, dd, CH_2O ring); 4.11, 4.07 (1H, m, CHCl); 2.01, 2.05, 2.32, 2.39 (2H, dd, CH_2); 3.52 (3H, s, CH_3).

3,3,5-Trichloro-2-ethoxytetrahydropyran (6b). ^{1}H NMR spectrum, δ, ppm: 4.86, 4.78 (1H, s, OCHO); 4.29, 4.32, 4.40, 4.42 (2H, dd, CH_2O ring); 4.11, 4.07 (1H, m, CHCl); 2.01, 2.05, 2.32, 2.39 (2H, dd, CH_2 ring); 3.72 (2H, q, CH_2O); 1.15 (3H, t, CH_3).

3,3,5-Trichloro-2-propoxytetrahydropyran (6c). ^{1}H NMR spectrum, δ, ppm: 5.06, 4.96 (1H, s, OCHO); 4.29, 4.32, 4.40, 4.42 (2H, dd, CH_2O ring); 4.11, 4.07 (1H, m, CHCl); 2.01, 2.05, 2.32, 2.39 (2H, dd, CH_2); 3.40 (2H, t, CH_2O); 1.52 (2H, m, CH_2); 0.91 (3H, t, CH_3).

2-Acyloxy-3,3,5-trichlorotetrahydropyrans (General Procedure). The acylating agent (10 mmol) was added to solution of compound **1** (2.05 g, 10 mmol) in ether (10 ml). The mixture was stirred for 1 h at room temperature, the solvent evaporated, and the residue distilled in vacuum.

2-Acetoxy-3,3,5-trichlorotetrahydropyran (7a). ^{1}H NMR spectrum, δ, ppm: 5.26, 5.31 (1H, s, OCHO); 4.42, 4.45, 4.49, 4.54 (2H, dd, CH_2O); 4.11, 4.07 (1H, m, CHCl); 2.06, 2.11, 2.45, 2.49 (2H, dd, CH_2); 2.01 (3H, s, CH_3).

2-Benzoyloxy-3,3,5-trichlorotetrahydropyran (7b). ^{1}H NMR spectrum, δ, ppm: 7.46-7.84 (5H, m, C_6H_5); 5.53, 5.42 (1H, s, OCHO); 4.41, 4.44, 4.49, 4.52 (2H, dd, CH_2O); 4.13, 4.09 (1H, m, CHCl); 2.12, 2.16, 2.47, 2.50 (2H, dd, CH_2).

3,3,5-Trichloro-2-(4-nitrobenzoyloxy)tetrahydropyran (7c). 4-Nitrobenzoyl chloride (1.85 g) was added to solution of compound **1** (2.05 g, 10 mmol) in ether (10 ml). The mixture was stirred for 1 h at room temperature, the solvent evaporated, and the residue recrystallized from hexane. Bright yellow, readily-melting crystals (2.55 g) were obtained. ^{1}H NMR spectrum, δ, ppm: 8.03-8.24, (4H, 2 d, C_6H_4); 5.55, 5.38 (1H, s, OCHO); 4.42, 4.45, 4.50, 4.52 (2H, dd, CH_2O); 4.12, 4.07 (1H, m, CHCl); 2.13, 2.18, 2.49, 2.52 (2H, dd, CH_2).

3,3,5-Trichlorotetrahydro-2-pyranyl Sulfonates (General Procedure). Solution of sulfonyl chloride (1 mmol) in toluene (1 mmol) was added to solution of compound **1** (0.205 g, 1 mmol) in toluene (1.5 ml). The mixture obtained was heated for 1 h at 85°C, and the solvent evaporated. The residue was recrystallized from hexane.

3,3,5-Trichlorotetrahydro-2-pyranyl *p*-Toluenesulfonate (8a). ^{1}H NMR spectrum, δ, ppm: 7.37-7.86 (4H, dd, C_6H_4); 5.22, 4.95 (1H, s, OCHO); 4.28, 4.31, 4.36, 4.42 (2H, 2 d, CH_2O); 4.10, 4.08 (1H, m, CHCl); 2.06, 2.13, 2.40, 2.43 (2H, dd, CH_2); 2.42 (3H, s, CH_3).

3,3,5-Trichlorotetrahydro-2-pyranyl 2-Nitrobenzenesulfonate (8b). ^{1}H NMR spectrum, δ, ppm: 7.91-8.32 (4H, m, C_6H_4); 5.20, 4.96 (1H, s, OCHO); 4.32, 4.33, 4.39, 4.43 (2H, dd, CH_2O); 4.11, 4.05 (1H, m, CHCl); 2.09, 2.13, 2.36, 2.40 (2H, dd, CH_2).

3,3,5-Trichlorotetrahydro-2-pyranyl 4-Nitrobenzenesulfonate (8c). ^{1}H NMR spectrum, δ, ppm: 8.32-8.87 (4H, dd, C_6H_4); 5.21, 4.98 (1H, s, OCHO), 4.30, 4.32, 4.37, 4.43 (2H, dd, CH_2O); 4.12, 4.07 (1H, m, CHCl); 2.07, 2.12, 2.39, 2.43 (2H, dd, CH_2).

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