SOME CHEMICAL PROPERTIES OF 2-FORMYL-2,5-DIALKOXY(ALKYLTHIO)-2, 3-DIHYDRO-γ-PYRANS

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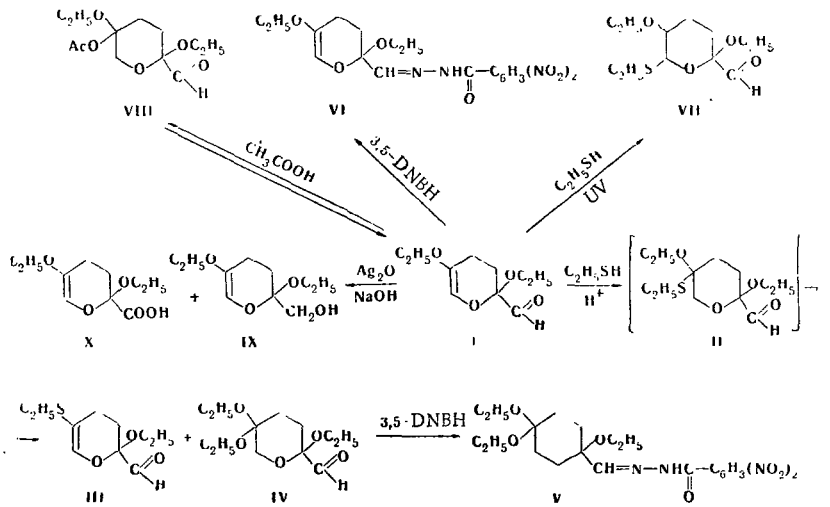
The conditions of heteropolar and radical thiylation of 2-formyl-2,5-diethoxy-2,3-dihydro-γ-pyrans were studied. Oxidation of the carbonyl group occurs along with the Cannizzaro reaction in the reaction of 2-formyl-2,5-diethoxy-2,3-dihydro-γ-pyran with silver oxide in alkaline media. Oxidation of 2-formyl-2,5-dibutylthio-2,3-dihydro-γ-pyran with silver oxide leads to stable 2,5-dibutylthio-2,3-dihydro-γ-pyran-2-carboxylic acid.

In order to study the reactivities of 2,5-dialkoxy(alkylthio)-2,3-dihydro-γ-pyrans (I) and ascertain the biological activity of the derivatives obtained we carried out their reaction with mercaptans under heterolytic and radical conditions. In contrast to ready alcoholysis [1], the thiylation of 2,5-diethoxy-2,3-dihydro-γ-pyran with C_2H_5SH in the presence of HCl and p-toluenesulfonic acid proceeds with difficulty, and the substitution product – 2-formyl-2-ethoxy-5-ethylthio-2,3-dihydro-γ-pyran (III) – is formed rather than the expected 2-formyl-2,5-diethoxy-5-ethylthiotetrahydropyran (II), although II is an intermediate, judging from the PMR spectrum of the reaction mixture (from the decrease in the integral intensity of the HC = signal).

The liberated alcohol, successfully competing with the mercaptan, readily adds to the double bond of starting I to give 2-formyl-2,5-triethoxytetrahydro-γ-pyran (IV), which was characterized by comparison of its PMR spectrum with that of an authentic sample [1] and identified in the form of the derivative formed with 3,5-dinitrobenzoylhydrazide (V). For comparison, we obtained the analogous derivative VI from 2-formyl-2,5-diethoxy-2,3-dihydro-γ-pyran I. Also allowable is an alternative representation of the formation of IV as a consequence of parallel disproportionation of II, but the high-boiling product of this reaction – a dithioketal – was not detected.



In contrast to vinyl ethers [2] and dihydropyran [3, 4], the described thiylation of I under mild conditions (0°, 20-50°, 1 h) occurs slowly, and up to 50% of starting I is recovered. Severe conditions (60-100°, 2 h) pro-

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TABLE 1. PMR Spectra of the Compounds Obtained

Compound	Chemical shifts, δ, ppm						
	H-6	H-5	COH COOH(OH)	H-3,3'; 4,4'	SCH_2	OCH_2	CH_3
IX	5.81	—	2.87	1.62—2,25	—	3.48	1,88
VII	4,93*	3,37	9,27	1,62—1,88	2,62	3.52	1.17
	4,80	3,37	9.43				
	4,60	3.17	9,34				
III	6,56	—	9,43	1,88—2,25	2.40	3,53	1,10
I	5.99	—	9,45	1,62—2,25	—	3,60	1.17
X	5,99	—	8,62	1,62—2,25	—	3,58	0.97
XII	6,53	—	11,2	1,88—2,28	2,63	—	0,94

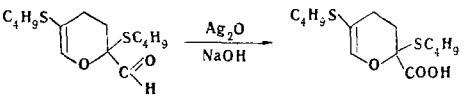
* Doublets: $J_{5,6} = 2.4$, $J_{5,6} = 1.6$, and $J_{6,5} = 8.9$ Hz.

mote polymerization, which did not occur in the reaction of mercaptans with dihydropyran [5]. Thiylation in the presence of SO_2 at 20° by the method in [6] does not occur, whereas at 60° in an ampul it leads to the liberation of ethanol, the yield of which corresponds to splitting out of both ethoxy groups in starting I. This confirms the reactivity of the ketal group in 2 position, as in [5]. However, we were unable to isolate the individual cleavage product because of resinification. Thiylation of I by means of UV irradiation leads to anti-Markownikoff addition product VII in 84% yield.

5-Unsubstituted dihydropyrans [7] add carboxylic acids to the double bond under mild conditions to give unstable addition products. The reaction with carboxylic acids is significant in the investigation of the biological activity of the 2,5-dialkoxy-2,3-dihydro-γ-pyrans. Attempts to add acetic acid to I were unsuccessful even when HCl and p-toluenesulfonic acid were used as catalysts. Under mild conditions (40°), despite the observed exothermic effect, disappearance of the double bond in the reaction mixture (by PMR spectroscopy), and a perceptible increase in the viscosity of the medium, starting I (up to 80%) was recovered when the mixture was fractionated. Addition product VIII is difficult to isolate by fractionation even at 0.1 mm, possibly because of easy splitting out of CH_3COOH (reversible reaction) and the polymerization of I, which is peculiar to acrolein dimers of the type in [8].

Oxidation of I with silver oxide in alkaline media leads to 2-methylol-2,5-diethoxy-2,3-dihydro-γ-pyran (IX) and 2,5-diethoxy-2,3-dihydro-γ-pyran-2-carboxylic acid (X). Like unsubstituted 2,3-dihydropyran-2-carboxylic acid [9, 10], crystalline acid X is very rapidly converted to a viscous liquid, which is 80% potentiometrically titrated (based on monomer X). In our case the conversion has irreversible character, since fractionation leads to decomposition of the compound. The formation of the lactone form in analogy with [11, 12] was not observed.

In contrast to I, only 2,5-dibutylthio-2,3-dihydro-γ-pyran-2-carboxylic acid (80%), which is stable in the monomeric form but cannot be vacuum fractionated, is formed in the oxidation of 2-formyl-2,5-dibutylthio-2,3-dihydro-γ-pyran.



XI XII

EXPERIMENTAL

The PMR spectra (see Table 1) were recorded with a Tesla BS 487B spectrometer (80 MHz) with hexamethyldisiloxane as the standard.

Reaction of I with Ethyl Mercaptan. A 9.6-g (0.15 mole) sample of ethyl mercaptan was added to a cooled (to 0°) mixture of 30.1 g (0.15 mole) of 2-formyl-2,5-diethoxy-2,3-dihydro-γ-pyran and 0.03 g (0.17 mmole) of p-toluenesulfonic acid, and the mixture was stirred at room temperature for 1.5 h and at 40° for 15 min. It was then neutralized with a methanol solution of sodium methoxide (calculated amount) and subjected to vacuum fractionation to give 15.4 g of dimer I, containing 15-20% IV, and 9.6 g (60% based on the converted I) 2-formyl-2-ethoxy-5-ethylthio-2,3-dihydro-γ-pyran (III) with bp 111-111.5° (2 mm), n_D^{20} 1.4930, and d_4^{20} 1.1062. Found: C 55.9; H 7.7; S 14.3%; MR_D 56.78. $C_{10}H_{16}O_3S$. Calculated: C 55.5; H 7.4; S 14.8%; MR_D 57.01. IR spectrum, ν, cm^{-1}: 1630 (C=C) and 1747 (C=O).

In contrast to the intensity of the starting material, the intensity of the double bond in the spectrum of this compound is considerably stronger and is approximately equal to the intensity in the spectrum of the thioacrolein dimer.

2-Formyl-2,5,5-triethoxytetrahydropyran (IV). A 7.5-g (0.12 mole) sample of ethyl mercaptan was added to a mixture of 24.1 g (0.12 mole) of I and 0.1 g (0.5 mmole) of p-toluenesulfonic acid, and the mixture was heated to 40° and maintained at this temperature for 1 h. It was then treated with sodium carbonate solution and extracted with ether. The ether extract was dried with $MgSO_4$, the ether was removed, and the residue was fractionated to give 2.7 g (10%) of 2-formyl-2,5,5-triethoxytetrahydropyran (IV) with bp 97-98° (2 mm), n_D^{20} 1.4510, and d_4^{20} 1.0884 [1]. Found: C 58.1; H 8.4%; MR_D 60.89. $C_{12}H_{22}O_5$. Calculated: C 58.6; H 8.9%; MR_D 62.04.

A 0.4-g (90%) sample of hydrazone V, with mp 199°, was obtained when 0.5 g (2 mmole) of IV was heated with 0.25 g (1 mmole) of 3,5-dinitrobenzoylhydrazide in alcohol at 60° for 30 min. Found: C 50.1; H 5.8; N 12.4%. $C_{19}H_{26}O_9N_4$. Calculated: C 50.3; H 5.7; N 12.3%.

A 0.5-g (72%) sample of hydrazone VI, with mp 174°, was obtained when 0.7 g (3.5 mmole) of I was heated with 0.38 g (1.5 mmole) of 3,5-dinitrobenzoylhydrazide in alcohol at 60° for 45 min. Found: C 50.2; H 4.6; N 13.7%. $C_{17}H_{20}O_8N_4$. Calculated: C 50.0; H 4.9; N 13.7%.

2-Formyl-2,5-diethoxy-6-ethylthiotetrahydro-γ-pyran (VII). A mixture of 12.4 g (62 mmole) of 2-formyl-2,5-diethoxy-2,3-dihydro-γ-pyran and 21.7 ml (0.31 mole) of ethyl mercaptan was maintained under the UV light of a PRK-2 lamp (1000 Wt) in a quartz test tube with a reflux condenser for 7 h. It was then subjected to vacuum fractionation to give 12.6 g (84%) of VII with bp 135° (3 mm), n_D^{20} 1.4787, and d_4^{20} 1.099. Found: C 54.9; H 8.4; S 12.0%; MR_D 67.6. $C_{12}H_{22}O_4S$. Calculated: C 55.0; H 8.4; S 12.2%; MR_D 68.3. IR spectrum, ν, cm^{-1}: 1742 (C=O).

Oxidation of 2-Formyl-2,5-diethoxy-2,3-dihydro-γ-pyran. Solutions of 36 g (0.21 mole) of $AgNO_3$ in 20 ml of H_2O and 12.7 g (0.32 mole) of NaOH in 20 ml of water were added dropwise simultaneously to a water-cooled solution of 21.1 g (0.105 mole) of I in 40 ml of dioxane, after which the temperature of the mixture was slowly raised to room temperature, and it was allowed to stand at this temperature for 3 h with vigorous stirring. The precipitated Ag_2O was removed by filtration and washed five to seven times with water. The filtrate and wash waters were extracted with ether. The solvent was removed, and the residue was fractionated to give 5.3 g (21%) of 2-methylol-2,5-diethoxy-2,3-dihydro-γ-pyran with bp 88° (2 mm), n_D^{20} 1.4705, and d_4^{20} 1.0921. Found: C 59.5; H 8.9%; MR_D 51.3. $C_{10}H_{18}O_4$. Calculated: C 59.4; H 9.0%; MR_D 52.1. IR spectrum, ν, cm^{-1}: 1722 (C=O), 3450 (OH), and 1680 (C=C).

Chloroform was added to the aqueous portion remaining after extraction with ether, and the mixture was acidified with the calculated amount of HCl at 5-10° and extracted with chloroform. The extract was dried with $MgSO_4$ and concentrated slightly at room temperature. It was then cooled, and the precipitate was removed by filtration to give 5.0 g (22%) of 2-carboxy-2,5-diethoxy-2,3-dihydro-γ-pyran with mp 93°. Found: C 55.9; H 7.9%. $C_{10}H_{16}O_5$. Calculated: C 55.6; H 7.4%. A viscous liquid (9.3 g), with n_D^{20} 1.4680, remained in the mother liquor after evaporation of the solvent. Potentiometric titration with $(C_4H_9)_4NOH$ in methanol confirmed the presence of 80% carboxyl groups based on X.

2,5-Dibutylthio-2,3-dihydro-γ-pyran-2-carboxylic Acid (XII). Solutions of 17.5 g (0.102 mole) of $AgNO_3$ in 15 ml of H_2O and 6.2 g (0.155 mole) of NaOH in 15 ml of H_2O were added dropwise simultaneously to a cooled (water stream) solution of 14.8 g (51 mmole) of XI in 100 ml of dioxane, after which the temperature of the mixture was slowly raised to room temperature and maintained at room temperature with vigorous stirring for 3 h. The precipitated Ag_2O was removed by filtration and washed five to seven times with water. The filtrate and the wash waters were extracted with ether. The calculated amount of concentrated HCl was added to dropwise at 10° to the aqueous portion remaining after extraction with ether, and the organic layer was separated. The aqueous layer was extracted with ether, and the extract and organic layer were dried with $MgSO_4$. The ether was removed to give 12 g (80%) of XII. For purification, a solution of the salt was again obtained and extracted with ether to remove the impurities. Ether extracts were obtained after acidification with the calculated amount of HCl and were dried with $MgSO_4$. Thorough removal of the ether in vacuo (oil pump) gave XII with n_D^{20} 1.5300 and d_4^{20} 1.1358. Found: C 55.1; H 8.0; S 21.0%; MR_D 82.44; $C_{14}H_{24}O_3S_2$. Calculated: C 55.3; H 7.9; S 21.2%; MR_D 83.36. IR spectrum, ν, cm^{-1}: 1630 (C=C), 1720 (C=O), and 3300 (OH).

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SYNTHESIS OF PYRYLIUM SALTS AND HETEROCYCLIC NITROGEN BASES FROM CYCLOALKENYLACETIC ACID ESTERS

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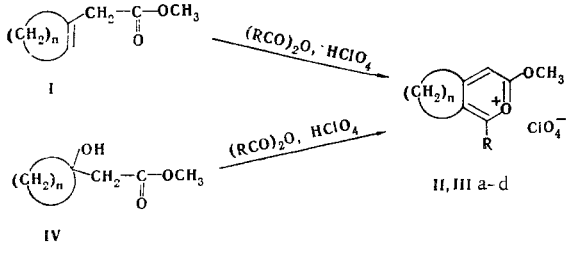
2-Alkyl-6-methoxy-3,4-tetramethylene- and 3,4-pentamethylenepyrylium perchlorates were obtained by acylation of cycloalkenylacetic acid esters with aliphatic acid anhydrides. 2-Methyl-6-methoxy[2,3-c]cholestanopyrylium perchlorate was similarly synthesized. 2-Alkyl-3,4-tetramethylene-6-pyridones were isolated by treatment of 2-alkyl-6-methoxy-3,4-tetramethylenepyrylium perchlorates with excess concentrated ammonium hydroxide. 2-Methyl-3,4-pentamethylene-6-aminopyridine was obtained by the action of excess concentrated ammonium hydroxide on 2-methyl-6-methoxy-3,4-pentamethylenepyrylium perchlorate.

In a continuation of our study of the acylation of β,γ-unsaturated compounds [1, 2] and homoveratric acid esters [3] and in order to synthesize previously unknown 2-alkyl-6-methoxy-3,4-tetramethylene- and 3,4-pentamethylenepyrylium salts and their nitrogen derivatives we studied the acylation of methyl cycloalkenylacetates (I) with aliphatic acid anhydrides (acetic, propionic, butyric, and valeric) in the presence of 70% perchloric acid.

As a result of the reaction we obtained 2-alkyl-6-methoxy-3,4-tetramethylenepyrylium perchlorates (IIa-d) and 3,4-pentamethylenepyrylium perchlorates (IIIa-d) in 25-50% yields.



I-IV n = 4, 5; II, III a R = CH_3; b R = C_2H_5; c R = n-C_3H_7; d R = n-C_4H_9

We were unable to isolate pyrylium salts in the acylation of cyclopentenylacetic esters in view of their extreme hygroscopic character. Cyclic hydroxy esters IV, obtained directly via the Reformatskii reaction, are readily dehydrated under the conditions of the acylation to olefins and subsequently undergo diacylation. The pyrylium salts formed in this case were isolated in the form of oils, which were converted to the corresponding nitrogen bases without further purification by the action of excess concentrated ammonium hydroxide. The yields of the nitrogen compounds ranged from 74 to 83%.

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