

PRODUCTS FORMED IN THE RADIATION SYNTHESIS
OF 5-OXO-TETRAHYDROFURAN-3-CARBOXYLIC ACID DERIVATIVES

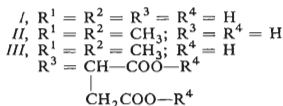
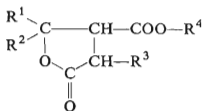
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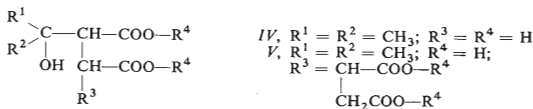
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After the radiation-induced addition of 2-propanol to the diesters of *cis*-2-butenedioic (maleic) acid at 20°C the reaction mixture contains not only the expected lactone-type products, *i.e.*, the derivatives of 2,2-dimethyl-5-oxotetrahydrofuran-3-carboxylic acid (*II*) but also the corresponding hydroxy derivatives, *i.e.*, the derivatives of 3-carboxy-4-methyl-4-hydroxypentanoic acid (*IV*). These hydroxy derivatives are formed as the primary products, however, they are not stable in the solution even in the form of their diesters. Their lactonization accompanied by the splitting off of alcohols proceeds rather slowly. The lactonization rate constant of the di-isopropyl ester of the acid *IV* is $1.61 \cdot 10^{-5} \text{ s}^{-1}$, of the di-*n*-octyl ester of *IV* it is $7.41 \cdot 10^{-6} \text{ s}^{-1}$ at 25°C. At a higher temperature, *e.g.*, during the esterification, the hydroxy derivatives of *IV* are partly lactonized, partly they form the respective unsaturated diesters by splitting off a molecule of water. A series of new esters of the acid *II* and of the triesters of its 4-(1,2-dicarboxyethyl) derivative (telomer 1 : 2) are described and the wavenumbers of the characteristic lactone bands in the region 1777–1786 cm^{-1} in the IR spectra of both types of lactone-esters are given.

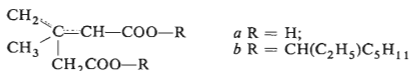
In order to demonstrate the use of high-energy ionizing radiation for the synthesis of organic compounds we have studied¹⁻⁴ the ⁶⁰Co γ -radiation-induced synthesis of the 5-oxotetrahydrofuran-3-carboxylic (paraconic) acid (*I*) derivatives. Some derivatives of this acid can be used as non-toxic acidic components of medicaments (terebic acid), the 2-methyl-2-hexyl derivative as a new original substance for the synthesis of ionons⁵. A number of 2,2-dialkyl derivatives of *I* were prepared by other methods⁵⁻⁹. The most common derivative, the 2,2-dimethyl-5-oxo-tetrahydrofuran-3-carboxylic acid (terebic acid)(*II*) and its ethyl ester are well described compounds. The corresponding hydroxy acid, 3-carboxy-4-methyl-4-hydroxypentanoic (diaterbic) acid (*IV*), is described only in the form of its salts or diethyl ester^{6,7}. Its lactonization rate in the aqueous solution is given in the published literature⁶ by the value of the half-life of 45 min at 50°C, which – assuming that lactonization is a unimolecular reaction – corresponds to the lactonization rate constant $k_{IV} = 2.36 \cdot 10^{-4} \text{ s}^{-1}$.





Esters of the acids *II*, *III*, *IV*, and *V*:

a $\text{R}^4 = \text{C}_2\text{H}_5$; *b* $\text{R}^4 = \text{C}_3\text{H}_7$; *c* $\text{R}^4 = \text{CH}(\text{CH}_3)_2$; *d* $\text{R}^4 = \text{C}_8\text{H}_{17}$; *e* $\text{R}^4 = \text{CH}(\text{C}_2\text{H}_5)\text{C}_5\text{H}_{11}$



VI

Radiation addition of secondary alcohols to *cis*-2-butenedioic (maleic) acid and to its diesters was used for the preparation⁴ of the 2,2-dialkyl derivatives of the acid *I* and of its esters of the type *II*. By the addition of a second molecule of maleic acid or of its diester, respectively, in the position 4 new compounds, 4-(1,2-dicarboxyethyl)-2,2-dialkyl derivatives of the acid *I* (telomers 1 : 2)³ of the type *III* are formed simultaneously. They have in the position 4 on the assumed γ -lactone ring a rather voluminous fragment (radical) R^3 which can eventually cause a change of the stability of the assumed ring. The presence of the open hydroxy forms *IV* and *V* must be taken into account, particularly in the irradiation of the solutions of diesters of maleic acid. The unsaturated derivative of the form *VI*, formed by splitting off a molecule of water from the carbon skeleton, is another possible product⁵.

The mechanism of the radiation chemical formation of these products was already proposed and discussed in detail¹. As we have shown in connection with the radiation synthesis of the acid *II*, the corresponding hydroxy acid *IV*, the participation of which depends on the initial concentration of maleic acid¹, constitute temporarily a certain part of the reaction mixture during the irradiation. We have therefore assumed that the hydroxy derivatives of the type *IV* and *V* are only intermediates that cannot appear in the final reaction mixture and that only the lactone-type compounds of the type *II* and *III* are the final products. The aim of this study was to find out in what extent these assumptions correspond to the actual situation.

EXPERIMENTAL

Reagents: The purification of maleic acid and of 2-propanol is described in the paper¹. The diesters of maleic acid were prepared by dissolving maleic anhydride in a 5–10 fold weight of the respective alcohol and the formed monoester was esterified by the azeotropic method under the catalysis of 1 weight per cent of concentrated H_2SO_4 .

Radiation Synthesis of the Acids and Esters *II* and *III*

The preparation of the solutions of maleic acid and of its esters in 2-propanol for irradiation and the irradiation of these solutions was similar to that described in paper¹ and in the patents⁴ except that the solutions were irradiated in glass vessels of the volume of 1000–5000 ml. Their initial concentration was within the limits 0.4–1.3 mol l⁻¹. The well-type irradiation unit was equipped with ⁶⁰Co sources of the total activity of 430 TBq. The total absorbed dose ranged from 1.0–3.5 · 10⁵ Gy.

As published elsewhere⁴, the products were isolated by crystallization in the case of free acids and by vacuum distillation in the case of esters. The following compounds were prepared: acid *II*, its esters *IIa–IIe*, and the esters of the telomer *III*, i.e., *IIIa–IIIe*. The telomer *III* itself was prepared by saponification of the ester *IIIa*, the esters *IIId* and *IIIe* were prepared by esterification of the acid *III*. The boiling points of esters, the elemental analysis of the new compounds, the characteristic IR constants, and other data are summarized in Table I.

Reaction Mixture Analysis

The reaction mixtures obtained by irradiation in the 2-propanol solution were analyzed using the liquid chromatograph L-Chrom 50 B (Laboratorní přístroje, Prague). The differential refractometer Knauer (Type 2050, Knauer, Oberursel, Federal Republic of Germany) was used as the detector. The column of the inner diameter of 3 mm and of the length of 250 mm was filled with spherical silica gel of the grain size of 10–12 μm, prepared in this Institute. The mixture hexane–dioxane (9 : 1) was used as the eluent, the flow rate was 30–35 ml h⁻¹, input 40 μl of the irradiated solution with the total concentration of all products 0.4–1.3 mmol ml⁻¹. The reaction mixtures were also analyzed using the thin-layer chromatography (TLC) on silica gel H (Merck) impregnated with 1% NaHSO₄ (cf.³) in the systems hexane–acetone (3 : 1) and benzene–ether (3 : 1). Hydroxy diesters of the type *IV* cannot be prepared as chemical individuals due to their instability. They were quantitatively determined by the above-mentioned chromatographic methods using the respective esters of acid *II* as standards.

Prior to analysis the prepared compounds were purified by a multiple distillation in high vacuum. The infrared spectra were measured with a double-beam spectrophotometer Perkin–Elmer 225 in cuvettes of the capillary thickness, equipped with windows made of potassium bromide. The elemental analysis was done by the staff of the Analytical Laboratory, Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague, and the ¹H-NMR spectra were measured in the NMR Spectroscopy Laboratory, Prague Institute of Chemical Technology, Prague.

Bis(2-ethylhexyl) Ester of the Acid *VI*

The acid *II* (158 g), m.p. 155–170°C, isolated by crystallization at 0–5°C from the irradiated solution, was esterified by 2-ethylhexanol (10 mol) in the presence of catex Ostion KSP (15 g, in H form) under the simultaneous azeotropic distillation removal of water. After the catex was filtered off, the excess of 2-ethylhexanol was distilled off in vacuum and the remaining mixture of esters was distilled at higher vacuum. The following products were found: 196 g (72.6%) of the ester *IIe*, b.p. 150–151°C/130 Pa and 17.6 g (4.6%) of bis(2-ethylhexyl) ester of the acid *VI*, b.p. 170–172°C/130 Pa. The IR spectrum: 1641 cm⁻¹ (C=C), 1733 cm⁻¹ (COO–R), no absorption at 1780 cm⁻¹ (lactone). ¹H-NMR spectrum: δ = 4.86 ppm (m, CH₂=C). For C₂₃H₄₂.O₄ (382.6) it was calculated: 72.21% C, 11.07% H; found: 72.26% C, 11.09% H. The detection with KMnO₄ solution in the TLC indicated the presence of C=C bonds.

RESULTS AND DISCUSSION

The free 3-carboxy-4-methyl-4-hydroxypentanoic acid (*IV*) was so far never isolated by common chemical methods. Now we have chemically proved indirectly its existence in the mixture with the crystalline 2,2-dimethyl-5-oxo-tetrahydrofuran-3-carboxylic acid (*II*). By the esterification of acid *II*, isolated from the reaction mixture at 0–5°C, with 2-ethylhexanol it has been isolated – along with the main fraction of ester *IIf* – also the diester *VIb* in the amount of 4.6% (most probably it is a mixture of both unsaturated compounds, indicated in the formula), which has been identified by the elemental analysis, IR and NMR spectra. The unsaturated acid *VIa* could be

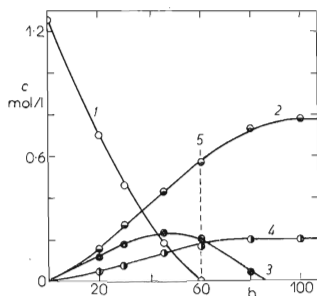


FIG. 1

Product Yields as a Function of Time During and After the Irradiation of 1.3M Solution of Diisopropyl Ester of Maleic Acid in 2-Propanol

Axis x time in h; axis y the conversion of the maleic acid diester and the yields of individual products in mmol ml^{-1} . Dose rate $5.2 \cdot 10^3 \text{ Gy h}^{-1}$, total absorbed dose $3.1 \cdot 10^5 \text{ Gy}$. The mixture was analyzed with TLC on silica gel in the system benzene–ether (3 : 1). 1 Diisopropyl ester of maleic acid (R_F 0.58); 2 ester *IIf* (R_F 0.40); 3 diester *IVc* (R_F 0.28); 4 triester *IIIc* (R_F 0.50); 5 the end of irradiation.

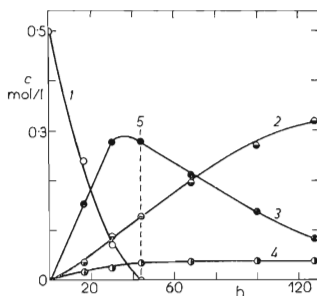


FIG. 2

Product Yields as a Function of Time During and After the Irradiation of 0.6M Solution of Di-n-Octyl Ester of Maleic Acid in 2-Propanol

Axis x time in h; axis y the conversion of the maleic acid diester and the yields of individual products in mmol ml^{-1} . Dose rate $5.4 \cdot 10^3 \text{ Gy h}^{-1}$, total absorbed dose $1.9 \cdot 10^5 \text{ Gy}$. The mixture was analyzed with liquid chromatography. The chromatographic conditions — cf. the Experimental, Di-n-octyl ester of maleic acid ($V_e = 1.23 \text{ ml}$); 2 ester *IId* ($V_e = 4.44 \text{ ml}$); 3 diester *IVd* ($V_e = 3.45 \text{ ml}$); 4 triester *IIId* ($V_e = 1.52 \text{ ml}$, 1.88 ml, 2.33 ml); 5 the end of irradiation.

formed only by splitting off water from the hydroxy acid *IV*. Diester *VIb* was evidently formed only during the distillation by splitting off water from the diester of the hydroxy acid *IV* formed originally by esterification.

The study of the radiation addition of 2-propanol on the diesters of maleic acid with liquid chromatography revealed that the ester-lactone products are formed from diesters as the secondary products, too.

From Figs 1 and 2 it is evident that the diesters of hydroxy products of the type *IV* ($R^3 = H$) can be found in the reaction mixture even several tens of hours after irradiation and after the completion of the reaction of the maleic acid diester. In the case of *n*-octyl diester they can be found even in excess. The lactonization rate at 25°C has been calculated from the decreasing parts of the respective plots in Figs 1 and 2, the obtained values being $k_{IVb} = 1.61 \cdot 10^{-5} \text{ s}^{-1}$ in the case of diisopropyl ester *IVb*, and $k_{IVd} = 7.41 \cdot 10^{-6} \text{ s}^{-1}$ in the case of di-*n*-octyl ester *IVd*. The diester *IVb* was found in the irradiated mixture already with the thin-layer chromatography on silica gel ($R_F = 0.28$ in the system benzene-ether 3 : 1). No direct proof of the presence of the tetraester of the hydroxy acid of the type *V* (telomer 1 : 2) could be found. From the shape of the curves for the formation of triester-lactones *IIIc* and *IIId* (Figs 1 and 2) it follows that the amount of these compounds does not increase after the irradiation is ended so that the lactonization of their precursors *Vc* and *Vd* is probably rather fast and they cannot appear in the final reaction mixture in a sufficient concentration.

The isolation of produced esters by distillation yielded always only the lactone-monoesters *II* and lactone-triesters *III* (telomers 1 : 2). The lactone structure of both these types of products was confirmed by the IR spectra (by the characteristic absorption band of lactones at 1780 cm^{-1}). The very intense band $\nu(\text{C=O})$ in the region $1777-1793 \text{ cm}^{-1}$ was chosen to prove the presence of the saturated γ -lactone ring (cf.¹⁰). A band $\nu(\text{C=O})$ of the ester in the region $1730-1736 \text{ cm}^{-1}$ and the band $\nu(\text{C=O})$ of the lactone in the region $1780-1784 \text{ cm}^{-1}$ were observed in the IR spectra of all prepared esters of the acid *II*. The lactone rings in the spectra of analogous triesters of the acid *III* revealed themselves by the bands at 1777 to 1786 cm^{-1} , the bands of esters were observed at $1731-1737 \text{ cm}^{-1}$. Summarizing, the following lactone-esters have been synthesized by the radiation-induced reaction: ethyl, *n*-propyl, isopropyl, *n*-octyl, and 2-ethylhexyl esters of 2,2-dimethyl-5-oxo-tetra-hydrofuran-3-carboxylic acid (*II*), and triethyl, triisopropyl, tri-*n*-octyl, and tris(2-ethylhexyl) esters of 2,2-dimethyl-4-(1,2-dicarboxyethyl)-5-oxo-tetrahydrofuran-4-carboxylic acid (*III*) (telomer 1 : 2). Their elemental analysis and some physical properties are summarized in Table I.

According to the results of the liquid chromatography the type *III* products are always a mixture of about three components. These mixture could be separated neither by vacuum distillation nor by TLC and they behaved as a single compound. However, their elemental composition as well as the IR spectra always correspond

to the respective lactone-triesters. They are evidently a mixture of isomers because the parent acid *III* has 3 centers of chirality.

From the obtained results it may be reasoned that under mild radiation synthetic conditions (temperature $\sim 25^{\circ}\text{C}$, absence of any catalysts, $\text{pH} \sim 7.0$ in the case of esters, $\text{pH} 3.5-7.0$ in the case of acids) the primary products are the unstable hydroxy derivatives, from which the compounds of the type *IV* were proved to exist in the reaction mixture. In the course of the isolation of these primary products

TABLE I

Elemental Analysis and the Physical Constants of the Ester-Lactones — Derivatives of the Acid *I*

Compound R^4	Formula (mol.mass)	Calc./Found		B.p., $^{\circ}\text{C}/\text{kPa}$	$\nu(\text{C}=\text{O})$ cm^{-1}
		% C	% H		
<i>II</i> , $\text{R}^1 = \text{R}^2 = \text{CH}_3$; $\text{R}^3 = \text{H}$					
<i>IIa</i> ^a	$\text{C}_9\text{H}_{14}\text{O}_4$	—	—	144—147/	1 732
C_2H_5	(186.2)	—	—	2.0	1 780
<i>IIb</i>	$\text{C}_{10}\text{H}_{16}\text{O}_4$	59.98	8.05	147—150/	1 732
<i>n</i> - C_3H_7	(200.2)	59.71	8.10	2.0	1 780
<i>IIc</i> ^b	$\text{C}_{10}\text{H}_{16}\text{O}_4$	59.98	8.05	145—149/	1 730
<i>i</i> - C_3H_7	(200.2)	60.43	8.01	2.1	1 781
<i>II d</i>	$\text{C}_{15}\text{H}_{26}\text{O}_4$	66.64	9.69	151—155/	1 736
<i>n</i> - C_8H_{17}	(270.4)	66.70	9.74	0.13	1 784
<i>II e</i>	$\text{C}_{15}\text{H}_{26}\text{O}_4$	66.64	9.69	150—151/	1 734
<i>i</i> - C_8H_{17}	(270.4)	66.74	9.79	0.13	1 782
<i>III</i> , $\text{R}^1 = \text{R}^2 = \text{CH}_3$; $\text{R}^3 = \begin{array}{c} -\text{CH}-\text{COO}-\text{R}^4 \\ \\ \text{CH}_2\text{COO}-\text{R}^4 \end{array}$					
<i>III a</i>	$\text{C}_{17}\text{H}_{26}\text{O}_8$	56.97	7.31	135—145/	1 735
C_2H_5	(358.4)	57.30	7.42	$1.3 \cdot 10^{-2}$	1 777
<i>III c</i>	$\text{C}_{20}\text{H}_{32}\text{O}_8$	59.98	8.05	150—165/	1 731
<i>i</i> - C_3H_7	(400.5)	59.93	7.97	$1.3 \cdot 10^{-2}$	1 778
<i>III d</i>	$\text{C}_{35}\text{H}_{62}\text{O}_8$	68.82	10.23	178—189/	1 737
<i>n</i> - C_8H_{17}	(610.9)	68.80	10.34	$1.3 \cdot 10^{-3}$	1 786
<i>III e</i>	$\text{C}_{35}\text{H}_{62}\text{O}_8$	68.82	10.23	157—165/	1 737
<i>i</i> - C_8H_{17}	(610.9)	68.97	10.16	$1.3 \cdot 10^{-3}$	1 779

^a Ref. ⁹, b.p. 138—140 $^{\circ}\text{C}/1.1$ kPa. ^b M.p. 43—45 $^{\circ}\text{C}$.

lactonization takes place during the distillation removal of the excess alcohol (at the temperatures up to 60°C) so that stable lactone acids or esters *II* and *III* are isolated. If the reaction mixture is treated at higher temperatures (*e.g.*, during the esterification) the hydroxy groups are partially split off and the unsaturated compounds *VI* are formed.

The presumed hydroxy derivatives of the type *V* were not found in the reaction mixture. The concentration of these products is probably very low and it cannot be increased, *e.g.*, by the distillation removal of 2-propanol from the reaction mixture, due to their thermal instability.

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