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V. F. KUCHEROV, B. G. KOVALEV, G. A. KOGAN, and L. A. YANOVSKAYA

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Abstract

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SYNTHESIS AND GEOMETRIC CONFIGURATION OF DIETHYL ESTERS OF DODECAPENTAENE-2,4,6,8,10-DIOIC-1,12 AND HEXADECAHEPTAENE-2,4,6,8,10,12,14-DIOIC-1,16 ACIDS

(Presented by Academician B. A. Kazanskii, February 4, 1961)

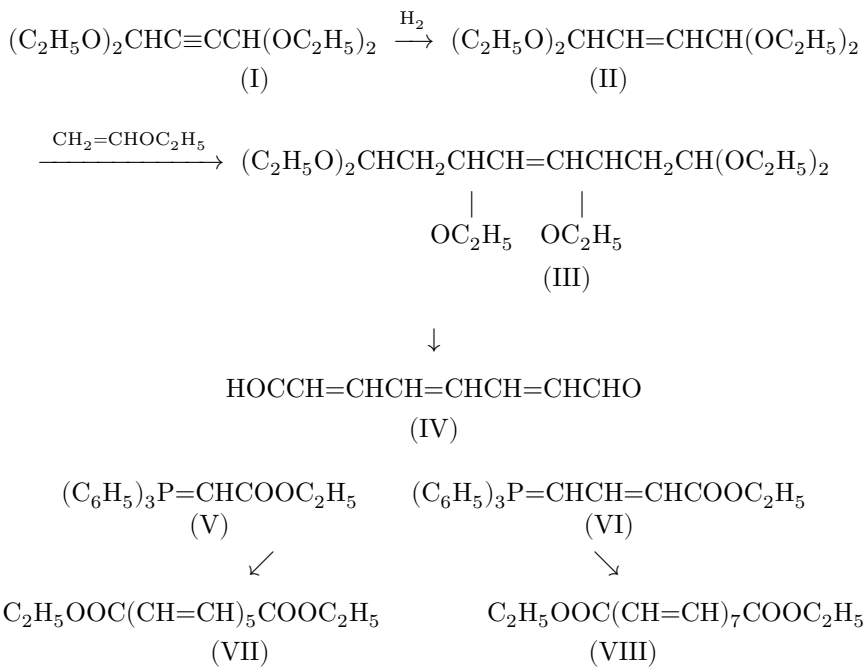
In 1936, R. Kuhn and Grundmann ([1]) developed a general method for the synthesis of polyene dicarboxylic acids based on polyene monocarboxylic acids and by this multistage and complicated route synthesized hexadecaheptaene-2,4,6,8,10,12,14-dioic-1,16 acid (decrocetin) ([2]).

Investigations of recent years have shown that polyene dicarboxylic acids of the type $HOOC(CH{=}CH)_nCOOH$, being metabolites of a number of fungi and microorganisms ([3,4]), are rather widely distributed in nature. In particular, in 1953 Brockmann and Grote ([5]) isolated from the culture liquid of *Streptomyces limosus* the yellow pigment limocrocin, which proved to be a derivative of decrocetin ([6]). All this makes topical the development of convenient methods for the synthesis of polyene dicarboxylic acids, which undoubtedly may possess interesting antibiotic properties.

We applied to the synthesis of diethyl esters of the type $C_2H_5OOC(CH{=}CH)_nCOOC_2H_5$ ($n = 5, 7$) a combination of the reaction of chain extension with acetylene vinyl ethers and the Wittig reaction, which had previously been used by us for the synthesis of esters of alkoxydicarboxylic acids of the type $C_2H_5OOCCH{=}CH(CH_2CH(OC_2H_5))_nCH_2CH{=}CHCOOC_2H_5$ ([7]). The same route was used by Isler for the synthesis of crocetin ([8–10]).

The readily available tetraethyl acetal of maleic dialdehyde (II), obtained by hydrogenation of tetraethyl acetal of butynedial (I) in the presence of Lindlar catalyst, served as the starting product. Chain extension of (II) with vinyl ethyl ether was carried out in the presence of boron trifluoride etherate. Saponification of the resulting 1,1,3,6,8,8-hexaethoxyoctene-4 (III) with phosphoric acid gave octatriene-2,4,6-dial-1,8 (IV) in good yield. By the Wittig reaction between (IV) and carbethoxymethylenephosphorane (V) or carbethoxyvinylmethylenephosphorane (VI), the diethyl esters of dodecapentaene-2,4,6,8,10-dioic-1,12 acid (VII) and hexadecaheptaene-2,4,6,8,10,12,14-dioic-1,16

acid (VIII) were obtained. Thus, a general, simple, and accessible route has been developed for the synthesis of polyene dicarboxylic acids with an odd number of conjugated double bonds, which can be used to obtain any higher compounds of this type:



To determine the geometrical configuration of all the compounds obtained above, their IR spectra were studied in the region of the out-of-plane deformation vibrations of C–H bonds (700–850 and 900–1000 cm^{-1}), and, for compounds with one double bond (II) and (III), additionally the stretching vibrations of the double bond in the Raman spectra (in the regions 1652–1662 and 1668–1678 cm^{-1}). It was found that the starting compound (II) is not an individual compound and contains an admixture of the trans isomer (the presence of bands at 1652 and 1674 cm^{-1}), and consequently hydrogenation of (I) proceeds nonstereospecifically. All the other compounds, (III), (IV), (VII), and (VIII), have the completely trans configuration, and their IR spectra contain bands of the out-of-plane deformation vibrations of C–H bonds only in the region 900–1000 cm^{-1}. In the Raman spectrum of (III) there is a band only at 1668 cm^{-1} (trans configuration at the double bond); consequently, already the chain-extension reaction of diacetal (II) is accompanied by complete change of the geometrical configuration.

The diethyl ester of descrocetin (VIII) obtained by us proved identical with that described by Kuhn, for which the trans configuration had previously been accepted only on the basis of the method of synthesis.

Experimental Part

Tetraethyldiacetal of maleic dialdehyde (II). 103.2 g (0.448 mole) of tetraethyldiacetal of butynedial (I) (obtained by the procedure described in the literature ([11])) was hydrogenated in 150 ml of hexane in the presence of 10 g of Lindlar catalyst at 18° and 758 mm. After absorption of 11 l of H_2 (theoretically 11.1 l required), the hydrogenation stopped. The catalyst was filtered off, thoroughly washed with hexane, the solvent was distilled off, and the residue was distilled. There was obtained 86.3 g (83% of theory) of tetraethyldiacetal of maleic dialdehyde (II), b.p. 93-95° at 3.5 mm, $n_D^{15.5}$ 1.4254 ([12]). Raman spectrum: 1652, 1674 cm^{-1}.

1,1,3,6,8,8-Hexaethoxyoctene-4 (III). To a mixture of 90.7 g (0.39 mole) of tetraethyldiacetal of maleic dialdehyde (II) and one drop of boron trifluoride etherate, heated to 30°, 56.16 g (0.76 mole) of vinyl ethyl ether was added gradually at such a rate that the temperature did not exceed 30-35°. The mixture was heated for an hour at 40-45°, then diluted with ether, washed with 5% sodium hydroxide solution and with water, and dried over fused potassium carbonate. After removal of the solvent, the residue was distilled, and 84.7 g (64.5% of theory) of ether acetal (III) was obtained, b.p. 134-138° at 0.5 mm, n_D^{15} 1.4373. Raman spectrum: 1668 cm^{-1}.

$C_{20}H_{40}O_6$.	Found	% :	C	63.26;	63.52;	H	10.50;	10.60
	Calculated	% :	C	63.75;		H	10.71	

Octatriene-2,4,6-dial-1,8 (IV). A mixture of 94.7 g of ether acetal (III), 15 ml of water, 8 g of 85% phosphoric acid, and 230 ml of dioxane was boiled in the presence of traces of hydroquinone in a stream of nitrogen for 7 hours, slowly distilling off the water—alcohol—dioxane azeotrope (1 drop in 5 sec.) and simultaneously adding to the reaction mixture, at the same rate, a mixture of dioxane with water, 4 : 1. The reaction mixture was poured into 1.5 l of cold water, and the reaction product was thoroughly extracted with chloroform. After drying with magnesium sulfate and distilling off the solvent, 19.6 g of dialdehyde (IV) was isolated, m.p. 144-145° (from a mixture of chloroform with ether), and 21.2 g of unhydrolyzed ether acetal (III) was regenerated. The yield of dialdehyde (IV) was 74.1%, calculated on the ether acetal that entered into the reaction. λ_{max} (alcohol) 317 mμ (ε = 3000); IR spectrum (in chloroform): 1623 (double bonds), 1667 (conjugation of double bond with C=O), 992.1 cm^{-1} (hydrogen vibrations at trans-C=C bond).

$C_8H_8O_2$.	Found	% :	C	70.16;	70.15;	H	6.08;	5.94
	Calculated	% :	C	70.57;		H	5.92	

Diethyl ester of dodecapentaene-2,4,6,8,10-dioic-1,12 acid (VII). A solution of 1.36 g (0.01 mole) of dialdehyde (IV) and 6.98 g (0.02 mole) of carbethoxymethylenephosphorane (V) [13] in 150 ml of benzene was boiled for 6 hr in

a stream of nitrogen. After removal of the solvent, the residue was treated with 15 ml of methanol, and 0.5 g of ester (VII) was obtained. From the mother liquor, by evaporation and treatment of the residue with 8 ml of methanol, 0.7 g of ester (VII) was isolated; on repeating this operation, a further 0.4 g of ester (VII) was obtained. In all, 1.6 g of ester (VII) was obtained (57% of theory) in the form of light-yellow plates with m.p. 157.5–159.5° (from a mixture of chloroform with methanol). λ_{max} (chloroform): 270, 368, 388 mμ (ε = 4,400, 99,500, 95,500). IR spectrum (in oil): 1597 (very weak band), 1623, 1696 (CO group conjugated with a double bond), 1012 cm^{-1} (hydrogen vibrations at a trans-C=C bond).

$C_{16}H_{20}O_4$.	Found	% :	C	69.56;	69.52;	H 7.58; 7.40
	Calculated	% :	C	69.54;		H 7.30

Diethyl ester of hexadecaheptaene-2,4,6,8,10,12,14-dioic-1,16 acid (diethyl ester of descrocetin) (VIII). To a solution of 9.37 g (0.025 mole) of carbethoxyvinylmethylenephosphorane (VI) [14] in 300 ml of benzene, with water cooling, a solution of 1.36 g (0.01 mole) of dialdehyde (IV) in 150 ml of benzene was added dropwise over the course of an hour. The mixture was boiled in a stream of nitrogen (bath 106–110°) for 5 hr. On the following day, the crystals (VIII) that had separated were removed. The residue was evaporated in vacuo, treated with methanol, and the crystals were filtered off; this operation was repeated twice. In all, 0.3 g of diethyl ester of descrocetin (VIII) was obtained with m.p. 210.5–211.5°, λ_{max} (chloroform) 255 mμ (ε = 27,000), λ_{max} (pyridine) 417.5, 443 mμ, which corresponds to the literature data [2]. IR spectrum: 1595 (very weak band), 1623, 1696, 1014 cm^{-1} (hydrogen vibrations at a trans-C=C bond); in the region 700–850 cm^{-1} no bands were detected.

The ultraviolet spectra were recorded on an SF-4 instrument, the infrared spectra on an IKS-12 instrument, and the combinational scattering spectra on an ISP-51 instrument.

Institute of Organic Chemistry
named after N. D. Zelinsky, Academy of Sciences of the USSR

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Note: Figure translations are in progress. See original paper for figures.