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Original Scientific Paper

Structure Determination of Isomeric Pyronopyrones Synthetized from 2,4-Dioxo-4-(4-hydroxy-6-methyl-2-pyrone-3-yl) Butyric Acid Ethyl Ester*

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Two isomeric pyronopyrones were obtained by cyclization of 2,4-dioxo-4-(4-hydroxy-6-methyl-2-pyrone-3-yl) butyric acid ethyl ester in glacial acetic acid or acetic anhydride.

The structures of the compounds are discussed on the basis of their infrared, ultraviolet, ^1H NMR, ^{13}C NMR and mass spectra as well as chemical properties observed.

INTRODUCTION

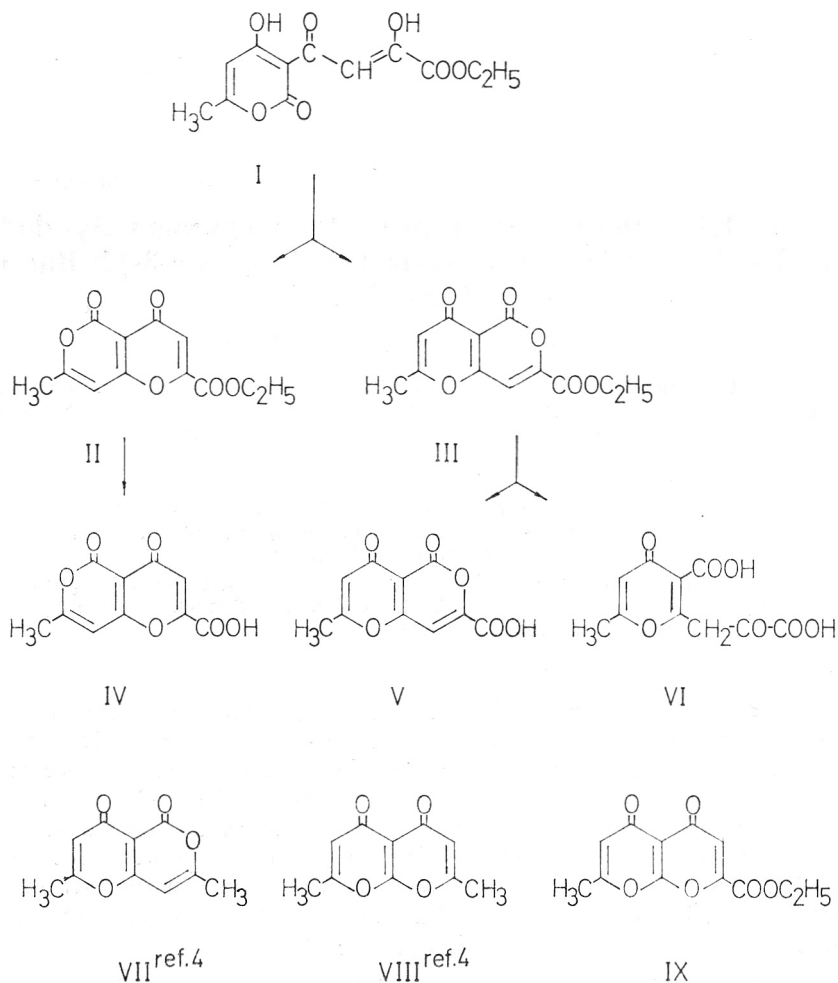
Following the main objective to synthesize polycarbonyl compounds and to convert these to polycyclic products^{1,2}, the ketonic system of dehydroacetic acid was extended by condensation with diethyloxalate in the presence of sodium ethoxide as catalyst³. The obtained 2,4-dioxo-4-(4-hydroxy-6-methyl-2-pyrone-3-yl) butyric acid ethyl ester (I) yielded, after refluxing in glacial acetic acid or acetic anhydride, two isomeric derivatives with a pyronopyrone nucleus (II and III). Analogous nucleus was found to be present in the isomerisation product (VII) of the perchlorate of (VIII) initially formed during acetylation of dehydroacetic acid catalysed by perchloric acid⁴.

On the basis of the observed chemical reactions and recorded spectral data, structure II was assigned to the isomer with a m. p. 228—231 °C slightly soluble in acetic acid, and structure III to the isomer very soluble in cold acetic acid, having a m. p. 160—163 °C.

DISCUSSION

Compound II was obtained in higher yield if the condensation was performed in acetic anhydride. TLC analysis indicated that pyronopyrone II was formed immediately after mixing I with acetic anhydride. Further, a higher yield of isomer II, obtained by dissolving I in conc. H_2SO_4 (at 0 °), confirmed the presumption that this pyronopyrone was a product of dehydration of compound I, in agreement with the proposed structure II.

*Taken in part from the Master of Science Thesis (A. Brbot, University of Zagreb, 1974) awarded in 1975 by »Krka« — Pharmaceutical and Chemical Works, Novo Mesto.



The highest yield of isomer **III** was obtained in glacial acetic acid (10–12 hrs). Compounds **II** and **III** were hydrolyzed and characterized as acids **IV**, **V** and **VI** as shown in Scheme. While the compound **III** was easily hydrolyzed at room temperature giving acids **V** and **VI**, isomer **II** was more stable so that only acid **IV** was obtained.

Ir Spectra

The presence of ethoxycarbonyl group complicated the interpretation of ir spectra. The absorption bands which could be assigned to the carbonyl groups of 2-pyrone, 4-pyrone, and ester⁵⁻⁸ were observed in the ir spectra of both isomers.

Uv Spectra

The similarity of the uv spectra of **II** and **III**, and the comparison with the data reported for pyronopyrone **VII** prepared by Praill and Whitar⁴

clearly show (Table I) that II, III and VII have identical cromophores^{4,9,10}, excluding cromophore IX, which theoretically could be also expected. However, no evidence was obtained for the presence of this third isomer in the reaction mixture.

This is consistent with recently reported data that the additions of carboxyl or ethoxycarbonyl group to a 2- or 4-pyrone nucleus do not appreciably alter the characteristics of the chromophore¹¹.

TABLE I
Uv Data

	λ_1 (nm)	$\log \epsilon_1$	λ_2 (nm)	$\log \epsilon_2$
II	248	4.18	301	3.96
III	245	4.06	305	3.97
VII ^{ref. 4}	239	4.27	298	4.00

¹H NMR Spectra

The ¹H NMR spectra of compounds II and III are very similar and it was difficult to obtain conclusive evidence for the differentiation between the two isomeric structures.

The fact that with sweep width of 100 Hz the signals at 2.33 and 2.38 were resolved as doublets, and signals at 6.28 and 6.27 as quartets ($J \sim 0,7$ Hz) supports the chemical shifts values given for protons on C-3 and C-8 consistent with published data^{13,14}.

However, only in the light of other results which confirmed the structures of isomers, the ¹H NMR data could be definitely assigned as shown in Table II¹⁰⁻¹².

TABLE II
¹H NMR Data, δ ppm

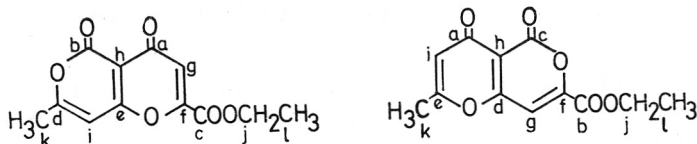
	—COO—C—CH ₃	—CH ₃	—COO—CH ₂ —C	H-3	H-8
II	1.39 (t)	2.33	4.43 (q)	7.09 (s)	6.28
III	1.40 (t)	2.38	4.45 (q)	6.27	7.22 (s)

¹³C NMR Spectra

A difficulty arose in the interpretation of ¹³C NMR spectra. The assignment of chemical shift values to specific carbon atoms must be considered at this time to be tentative.

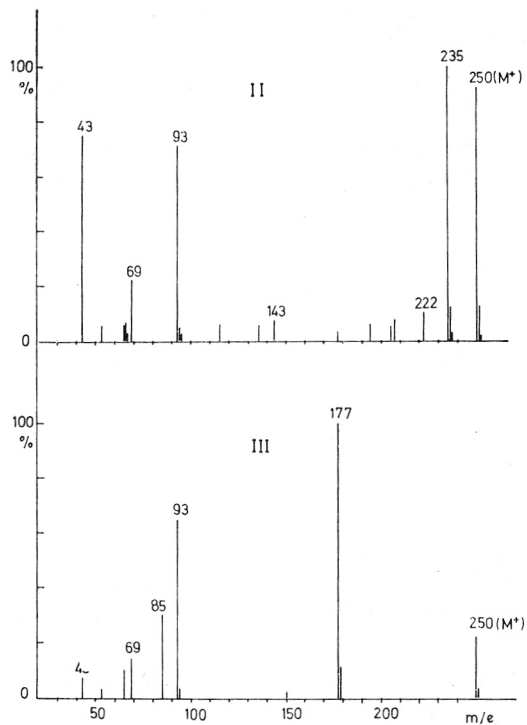
In Table III carbon resonances are listed along with the tentative assignments for compounds II and III¹⁵⁻¹⁷.

TABLE III
 ^{13}C NMR Data, δ ppm

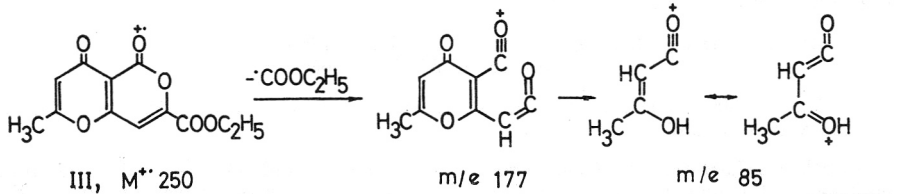
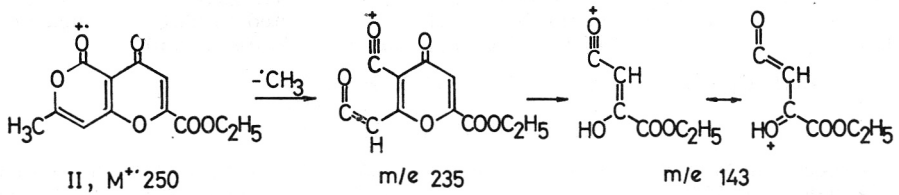
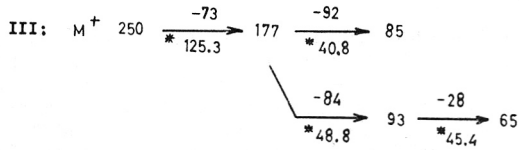
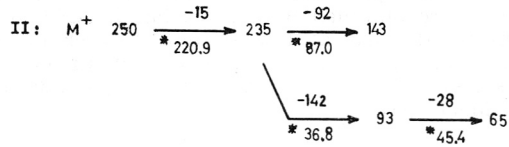


	II	III
a	174.3	173.4
b	169.8	167.7
c	168.9	164.5
d	159.3	158.4
e	157.4	152.1
f	151.1	133.7
g	120.3	116.7
h	106.8	109.6
i	98.8	104.6
j	63.4	63.4
k	20.6	19.6
l	13.9	14.1

Mass Spectra



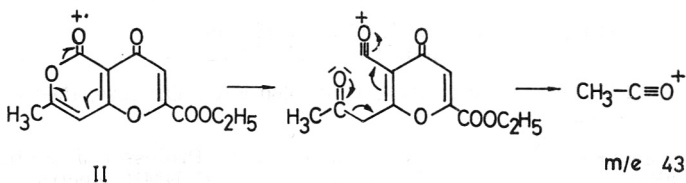
A supporting evidence for structures II and III was found in the mass spectra, a number of the metastable ions showing further similarity in the fragmentation process.



(ref.18-20)

A conspicuous feature of the mass spectra is the ion of mass 43 (acetyl fragment).

Bearing in mind that acetyl fragment is very intensive only in the presence of a favourable structure for its formation the larger peak of m/e 43 suggests structure II as shown in the following Scheme¹⁸⁻²⁰.



EXPERIMENTAL

The melting points were determined on a Kofler heating microscope and Büchi apparatus and are uncorrected. The ir spectra were recorded with a Perkin-Elmer Infracord Model 137 spectrophotometer using KBr pellets and uv spectra with a Perkin-Elmer Model 124 spectrophotometer in CHCl_3 . The ^1H NMR spectra were recorded with a Varian A-60 spectrometer in CDCl_3 with TMS as internal standard. The ^{13}C NMR spectra were obtained with a Varian XL-100-15 spectrometer in the Fourier transform mode. Because of low solubility of compound II a mixture of CDCl_3 , CD_3SOCD_3 , and CF_3COOH was used as solvent. In the case of compound III CDCl_3 was used as solvent. TMS was used as internal standard. Mass spectra were taken with a Varian MAT CH7.

Cyclization of 2,4-Dioxo-4-(4-hydroxy-6-methyl-2-pyrone-3-yl) Butyric Acid Ethyl Ester in Glacial Acetic Acid

2-Ethoxycarbonyl-7-methyl-4H,5H-pyrone/4,3-b/pyrone (II) and 7-Ethoxycarbonyl-2-methyl-4H,5H-pyrone/4,3-b/pyrone (III). — 4 g (15 mmol) of compound I was refluxed in 150 ml of acetic acid for 10–12 hrs and then concentrated to 30–40 ml. After standing overnight at room temperature 0.5 g (13%) of isomer II was obtained. The filtrate was treated with Et_2O to precipitate 2.1 g (56.4%) of isomer III. The crude product II was crystallized from acetic acid giving white crystals, m. p. 228–231 °C. Crystallization (acetic acid-ether) of isomer III gave white crystals too, m. p. 160–170 °C. For analysis the isomer III was subjected to TLC on silica plates with chloroform (»Merck« Silica Gel 60 F₂₅₄, layer thickness 2 mm).

Anal. $\text{C}_{12}\text{H}_{10}\text{O}_6$ (250.20) calc'd.: C 57.60 H 4.03%
 (II) found: C 57.48 H 4.10%
 (III) found: C 57.54 H 4.47%

II: Ir spectrum: 1760, 1740, 1660 ν (C=O); 1640, 1550 ν (C=C); 1260, 1175 ν (C—O) cm^{-1} .
 III: Ir spectrum: 1765, 1730, 1670 ν (C=O); 1650, 1560 ν (C=C); 1275 ν (C—O) cm^{-1} .

7-Methyl-4H,5H-pyrone/4,3-b/pyrone-2-carboxylic acid (IV). — 0.5 g (2 mmol) of compound II was treated with 10 ml conc. HCl at room temperature for 3 days. The product was filtered, washed with water and crystallized from diluted ethanol giving white crystals m. p. > 250° C (dec.).

Anal. $\text{C}_{10}\text{H}_6\text{O}_6$ (222.15) calc'd.: C 54.06 H 2.72%
 found: C 54.00 H 2.98%

Ir spectrum: ~ 3000 (OH); 1775, 1755, 1740, 1655 ν (C=O); 1630, 1555 ν (C=C); 1240, 1225, 1175 ν (C—O) cm^{-1} .

2-Methyl-4H,5H-pyrone/4,3-b/pyrone-7-carboxylic acid (V). — 0.5 g (2 mmol) of compound III was treated with conc. HCl at room temperature for 10–15 days. The white crystals of acid V were obtained m. p. > 235 °C (dec.).

Anal. $\text{C}_{10}\text{H}_6\text{O}_6$ (222.15) calc'd.: C 54.06 H 2.72%
 found: C 53.87 H 2.98%

Ir spectrum: ~ 2600, ~ 1900 (OH); 1750, 1700, 1650 ν (C=O); 1630, 1550 ν (C=C); ~ 1250 ν (C—O) cm^{-1} .

3-Carboxy-6-methyl-4-pyrone-2-pyruvic acid (VI). — 0.5 g (2 mmol) of compound III was heated with dil. HCl (1 : 1) for 5–10 min. It was cooled and left to stand at room temperature for 3–5 days, yielding white crystals m. p. > 240 °C (dec.).

Anal. $\text{C}_{10}\text{H}_8\text{O}_7$ (240.16) calc'd.: C 50.01 H 3.36%
 found: C 50.15 H 3.52%

Ir spectrum: ~ 3590, 2450, ~ 1900 (OH); 1740, 1660 ν (C=O); 1620, 1560 ν (C=C); 1280, 1220, 1130 ν (C—O) cm^{-1} .

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SAŽETAK

Određivanje struktura izomernih pironopirona sintetiziranih iz etilestera [2,4-dioks-4-(4-hidroksi-6-metil-2-piron-3-il)] maslačne kiseline

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Ciklizacijom etilestera [2,4-dioks-4-(4-hidroksi-6-metil-2-piron-3-il)] maslačne kiseline u ledenoj octenoj kiselini ili anhidridu octene kiseline dobivena su dva izomerna pironopirona. Strukture novih spojeva razmatrane su na temelju njihovih ir, uv, ^1H NMR, ^{13}C NMR i masenih spektara, te na osnovu kemijskih reakcija.

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