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2,6,7-Trihydroxy-4,9-dioxodeca-2,5,7-trienoic and 2-Hydroxy-2-(3-hydroxy-4-methyl-2,5-dioxocyclopent-3-en-1-ylidene)acetic Acid Esters: Synthesis and Structural Specificity

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Abstract—Claisen condensation of acetone and butan-2-one with diethyl oxalate in the presence of metallic sodium leads to the formation of ethyl 2,6,7-trihydroxy-4,9-dioxodeca-2,5,7-trienoate and ethyl 2-hydroxy-2-(3-hydroxy-4-methyl-2,5-dioxocyclopent-3-en-1-ylidene)acetate, respectively.

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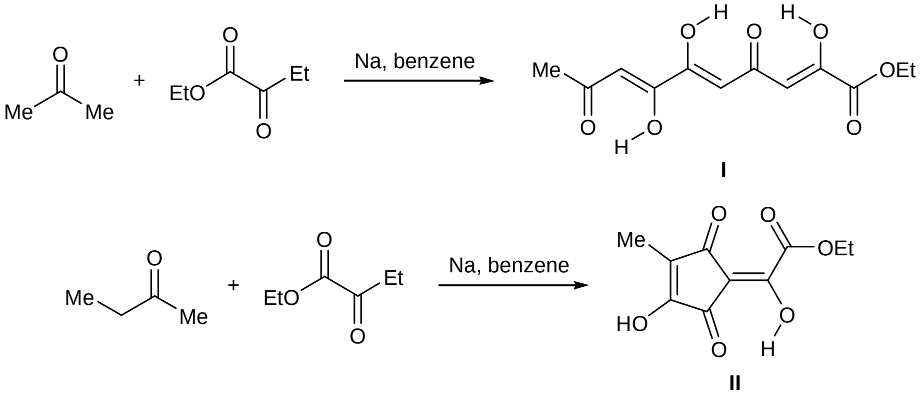
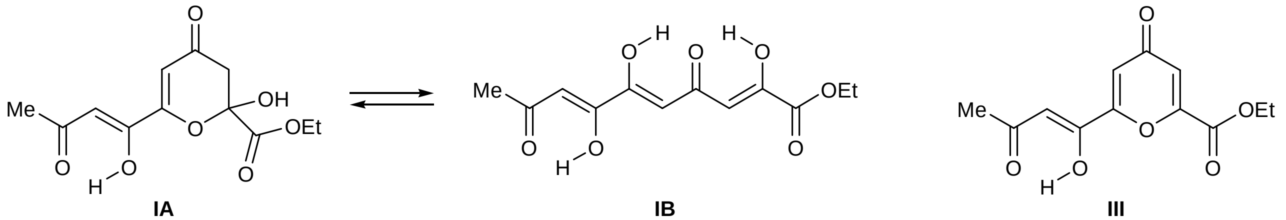
Polyketides possessing a β-triketone fragment are successfully used in organic synthesis, in particular in heterocyclization reactions [1–7]. Among these, accessible compounds are derivatives of chelidonic acid [8–10] and carbonyl compounds based on Meldrum's acid [5–7]. With a view to obtain β-triketones having various carbonyl acceptor moieties and examine their structure and chemical transformations, we synthesized ethyl 2,6,7-trihydroxy-4,9-dioxodeca-2,5,7-trienoate (**I**) and ethyl 2-hydroxy-2-(3-hydroxy-4-methyl-2,5-dioxocyclopent-3-en-1-ylidene)acetate (**II**) by the Claisen condensation of acetone and butan-2-one, respectively, with diethyl oxalate in the presence of metallic sodium in boiling benzene (Scheme 1). It should be noted that reactions of alkyl methyl ketones with diethyl oxalate in the presence of bases are very sensitive to the conditions; depending on the latter, different products can be obtained. For example, we recently isolated eight compounds in such a condensation, and six of them were identified [11].

Compounds **I** and **II** are crystalline substances (**I** is lemon yellow, and **II** is slightly yellowish), which are insoluble in water and readily soluble in common organic solvents. The IR and ^{1}H NMR spectra of **I** are fully consistent with the assumed structure. The IR spectrum of **I** contains a narrow peak at 1728 cm^{-1} due

Scheme 1.



Scheme 2.



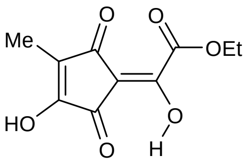
IA **IB** **III**

to stretching vibrations of the ester carbonyl group, a weak broad band in the region 3360–3488 cm^{-1} due to stretching vibrations of the hydroxy groups involved in intramolecular hydrogen bonds, and a very strong broad band at 1572–1638 cm^{-1}, which corresponds to the enolized carbonyl groups (C^2–OH, C^6–OH, and C^7–OH) constituting H-chelate rings. In the ^{1}H NMR spectrum of **I** in $CDCl_3$ we observed closely located singlets at δ 6.32, 6.35, and 6.37 ppm from the CH= protons in the three enol moieties, as well as three broadened downfield signals from the enol hydroxy protons at δ 13.40, 13.52, and 14.63 ppm. These data indicate enolization of all carbonyl groups in molecule **I**, except for the ester carbonyl, and formation of strong intramolecular hydrogen bonds (three H-chelate rings).

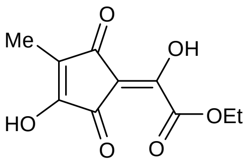
The ^{1}H NMR spectrum of ester **I** in DMSO-d_6 (22°C) contains additional signals which considerably complicate the spectral pattern. For instance, protons in the ester ethyl group give rise to three sets of signals, while signals from methyl protons in the acetyl fragment are doubled in pairs (more downfield pair signals are characterized by much lower intensity). Singlets from at least three methine protons are present (each of these is also tripled), and two doublets from two coupled geminal protons (CH_2 group) are observed. Signals from water were also detected in the ^{1}H NMR spectrum of **I** in DMSO-d_6. Raising the temperature to 50 and then to 70°C leads to reduction in the intensity and disappearance of signals belonging to the C^{3}H, C^{5}H, and C^{8}H methine protons.

We succeeded in satisfactorily identifying signals corresponding to two ring–chain tautomers **IA** and **IB**, as well as to tautomers with non-enolized β-dicarbonyl fragments and dehydration product, ethyl 6-(1-hydroxy-3-oxobut-1-en-1-yl)-4-oxo-4*H*-pyran-2-carboxylate (**III**) (Scheme 2).

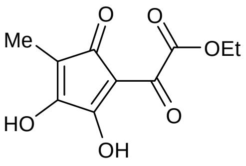
The IR spectrum of a crystalline sample of compound **II** was fairly informative. It contained two narrow peaks at 1752 and 1736 cm^{-1} belonging to stretching vibrations of the ester carbonyl and carbonyl group in the cyclopentene ring (not involved in H-bonding), respectively. The strong broad band in the region 3260–3155 cm^{-1} was assigned to stretching vibrations of the hydroxy group involved in intramolecular hydrogen bond and hydroxy group conjugated with the double bond. The enolized carbonyl group =C–OH gave rise to the most intense broadened band at 1630–1655 cm^{-1}. We can conclude that ester **II** molecule in crystal contains two unassociated (high-frequency) carbonyl groups and an H-chelate ring. These data do not contradict structures **IIA–IID** among seven possible tautomers **IIA**–**IIG**. Structure **IIE** should give rise to absorption of three carbonyl groups with a frequency of no less than 1680 cm^{-1}, while tautomers **IIF** and **IIG** have only one unassociated carbonyl group in the five-membered ring [12], i.e., their spectral patterns should differ from that



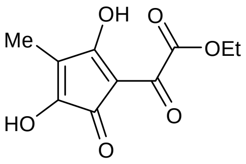
IIA



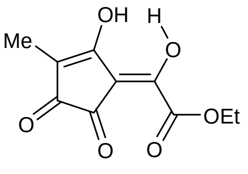
IIB



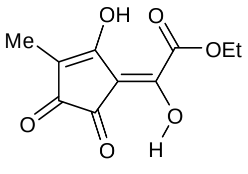
IIC



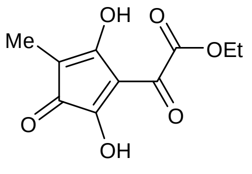
IID



IIE



IIF

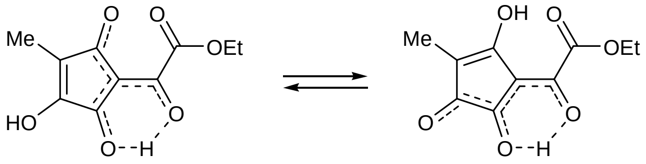


IIG

observed experimentally. Unfortunately, the ^1H NMR and mass spectra did not allow us to unambiguously determine the tautomeric structure of ester **II**. Tautomers **IIE**–**IIG** seem to be much less probable, for signals from the hydroxy protons in the ^1H NMR spectrum ($CDCl_3$) are strongly nonequivalent (the difference in the chemical shifts is as large as 2.35 ppm), and only one of these protons is involved in intramolecular H-bonding. Among the most probable tautomeric forms **IIA**–**IID**, the first two (**IIA** and **IIB**) are *Z* and *E* isomers, while structures **IIC** and **IID** are regioisomeric, and they cannot be distinguished from the corresponding tautomers **IIA** and **IIB**.

Our results led us to conclude that the structure of ester **II** may be represented as resonance-stabilized structures shown in Scheme 3: both these include an H-chelate ring conjugated with the cyclic β-dicarbonyl fragment and a partially delocalized double bond. The H-chelate rings therein are characterized by different degrees of proton tunneling; therefore, absorption of one more carbonyl group (in addition to the ester carbonyl) and unassociated hydroxy group appears in the spectra.

Scheme 3.



II

EXPERIMENTAL

The IR spectra of esters **I** and **II** were recorded in KBr on a Specord M-80 spectrometer. The ^1H NMR spectra were measured on a Bruker DRX-500 instrument (500.13 MHz) relative to tetramethylsilane as internal reference. The mass spectra were obtained on a Finnigan MAT INCOS 50 spectrometer with direct sample admission into the ion source. The purity of compounds **I** and **II** was checked by TLC on Silufol UV-254 plates using benzene–diethyl ether–acetone (10:9:1) as eluent; spots were visualized by treatment with iodine vapor.

Ethyl 2,6,7-trihydroxy-4,9-dioxodeca-2,5,7-trienoate (I). Metallic sodium, 0.69 g (30 mmol), was added in small pieces under stirring and cooling to a mixture of 1.4 ml (20 mmol) of acetone and 2.8 ml (20 mmol) of diethyl oxalate in 30 ml of benzene. The mixture was heated for 2.5–3 h under reflux, the solvent was distilled off, the residue was thoroughly ground with 20–30 ml of ice water, and 10–15 ml of 15% hydrochloric acid was added under stirring. After 3–5 h, the precipitate was filtered off, dried, and recrystallized from ethyl acetate. Yield 0.73 g (27%), mp 137–138°C (decomp., from ethyl acetate); published data: mp 144°C (monohydrate, mp 119°C) [9], 140–141°C [10]. IR spectrum, ν, cm^{-1}: 3360–3488 (OH_{as}), 3108, 2980 (CH=), 1728 (CO, ester), 1572–1638 ($=C–OH_{as}$), 1382 (δCH=, in-plane.), 1272, 1184, 1124, 1108, 1092, 1026, 980, 854, 804, 780, 732 (δCH=, out-of-plane), 556. ^1H NMR spectrum, δ, ppm: in $CDCl_3$: 1.38 t (3H, $C\mathbf{H}_3CH_2O$), 2.28 s (3H, CH_3), 4.37 q (2H, OCH_2), 6.32 s (1H, 3-H), 6.35 s (1H, 8-H), 6.37 s (1H, 5-H), 13.40 br.s (1H, 2-OH), 13.52 br.s (1H, 6-OH), 14.63 br.s (1H, 7-OH); in DMSO-d_6: 1.23 t (3H, $C\mathbf{H}_3CH_2O$), 1.25 t (3H, $C\mathbf{H}_3CH_2O$), 1.32 t (3H, $C\mathbf{H}_3CH_2O$), 2.12 s (3H, CH_3), 2.16 s (3H, CH_3), 2.27 s (3H, CH_3), 2.30 s (3H, CH_3), 2.87 d and 2.93 d (2H, CH_2), 3.30 br.s (2H, H_2O), 4.21 q (2H, OCH_2), 4.26 q (2H, OCH_2), 4.37 q (2H, OCH_2), 5.50 s (1H, CH), 5.86 s (1H, CH), 5.90 s (1H, CH), 6.03 s (1H, CH), 6.28 s (1H, CH), 6.40 s (1H, CH), 6.42 s (1H, CH), 6.97 s (1H, CH), 7.03 s (1H, CH), 7.62 br.s (1H, OH), 7.95 br.s (1H, OH), 8.70 br.s (1H, OH), 11.65 br.s (1H, OH). Mass spectrum, *m/z* (I_{rel}, %; ion peaks with $I_{rel.} > 1\%$ are given): 270 (9) $[M]^+$, 252 (3) $[M – H_2O]^+$, 227 (1) $[M – CH_3CO]^+$, 210 (1) $[M – H_2O – CH_2CO]^+$, 197 (5) $[M – CO_2Et]^+$, 186 (7), 185 (16) $[M – CH_3CO – CH_2CO]^+$, 179 (4), 158 (8), 157 (15) $[M – CH_3CO – CH_2CO – CO]^+$, 155 (11), 147 (2), 143 (3) $[M – CH_3CO – 2CH_2CO]^+$, 139 (3), 137 (3), 129 (2), 127 (3) $[M – COCH_2COCO_2Et]^+$, 117 (3), 115 (3), 113 (10) $[CH_3COCH_2COCO]^+$, 111 (29) (cyclopentane-1,2,4-trione $[C_5H_3O_3]^+$), 109 (1), 89 (2), 87 (2), 86 (2), 85 (48) $[CH_3COCH_2CO]^+$, 84 (17), 71 (2), 69 (37) $[O{\equiv}C–CH{=}C{=}O]^+$, 67 (2), 66 (2), 55 (9), 53 (3), 45 (4), 44 (13), 43 (100) $[CH_3CO]^+$, 42 (12). Found, %: C 53.61; H 5.36. *M* 270.23. $C_{12}H_{14}O_7$. Calculated, %: C 53.33; H 5.22.

Ethyl 2-hydroxy-2-(3-hydroxy-4-methyl-2,5-dioxocyclopent-3-en-1-ylidene)acetate (II) was synthesized in a similar way from 0.9 ml (10 mmol) of butan-2-one, 2.8 ml (20 mmol) of diethyl oxalate, and 0.46 g (20 mmol) of metallic sodium in 30 ml of benzene. Yield 0.97 g (43%), mp 163–164°C (from ethyl acetate); published data [13]: mp 160–162°C. IR spectrum, ν, cm^{-1}: 3260–3155 (OH_{as}), 2996 (CH=), 1752 (CO, ester), 1736 (CO, free), 1670, 1630–1655 ($=C–OH_{as}$), 1442, 1392 (δCH=, in-plane), 1374, 1356, 1348, 1232, 1168, 1092, 1022, 894, 804 (CH=, out-of-plane), 686, 536. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.42 t (3H, $OCH_2C\mathbf{H}_3$), 1.97 s (3H, CH_3), 4.42 q (2H, OCH_2), 7.45 br.s (1H, OH), 9.80 br.s (1H, OH). Mass spectrum, m/z (I_{rel}, %; ion peaks with $I_{rel.} > 5\%$ are given): 226 (10) $[M]^+$, 198 (8) $[M - CO]^+$, 170 (8) $[M - 2CO]^+$, 154 (9), 153 (100) $[M - CO_2Et]^+$, 152 (10), 126 (8), 125 (10) $[M - CO_2Et - CO]^+$, 124 (13) $[M - CO_2Et - CO - H]^+$, 107 (14), 101 (8), 97 (8) $[M - CO_2Et - 2CO]^+$, 96 (15) $[M - CO_2Et - 2CO - H]^+$, 83 (49) $[CH_2COCH{=}C{=}O]^+$, 79 (5), 69 (43) $[O{\equiv}C{-}CH{=}C{=}O]^+$, 68 (11), 67 (7), 57 (6), 56 (10), 55 (37), 53 (18), 51 (6), 44 (13), 43 (12), 41 (17), 40 (16), 39 (20), 38 (5). Found, %: C 52.87; H 4.68. M 226.18. $C_{10}H_{10}O_6$. Calculated, %: C 53.10; H 4.46.

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