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1,3,4,6-Tetracarbonyl Compounds: VI.* Synthesis of 2-Substituted 6-Aryl-3,4-dihydroxy-6-oxo-2,4-hexadienoic Acid Esters and Amides

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Abstract—The Knoevenagel reaction of 5-aryl-2,3-dihydrofuran-2,3-diones with ethyl cyanoacetate or malonodinitrile yields 2-substituted 6-aryl-3,4-dihydroxy-6-oxo-2,4-hexadienoic acid esters or amides which exhibit biological activity. The structure of the products is discussed, taking into account the structure of known 3,4-dihydroxy-6-oxo-2,4-hexadienoic acid esters and 1,6-diaryl-3,4-dihydroxy-2,4-hexadiene-1,6-diones.

Claisen condensation of aryl methyl ketones with diethyl oxalate in the presence of sodium methoxide or ethoxide provides a convenient preparative method of synthesis of 1,6-diaryl-3,4-dihydroxy-2,4-hexadiene-1,6-diones (1,6-diarylhexane-1,3,4,6-tetraones) **I** [2–5]. Compounds **I** usually exist in solution as equilibrium mixtures of two tautomers: open-chain ketoenol form **A** and ring isomer **B** [5–7] (Scheme 1). As concerns such 1,3,4,6-tetracarbonyl compounds as 3,4,6-trioxocarboxylic acid derivatives, 6-aryl-3,4-dihydroxy-6-oxo-2,4-hexadienoic acid esters **II** have been reported [8–12]. Esters **II** exist in solution as two open-chain tautomers **C** and **D** and ring semiacetal tatoumer **E**, the latter prevailing. These compounds are formed by addition of water at the exocyclic double bond of 5-aryl-3-oxo-2,3-dihydro-2-furylideneacetic acid esters **III** [8, 9]. Another route to oxo esters **II** is based on the reaction of 5-aryl-2,3-dihydrofuran-2,3-diones **IV** with ketene acetals [10–12] (Scheme 1).

Prior to our studies, no alternative methods for introduction of an ester group in the synthesis of 1,3,4,6-tetracarbonyl compounds have been known. Such factors as poor yields of the products and limited number of available starting compounds (e.g., reagents like **III**) strongly restrict possible applications of the above reactions to preparation of a wide series of polycarbonyl systems having an ester or amide group.

We previously reported that 5-aryl-2,3-dihydrofuran-2,3-diones **IV** readily react with aryl methyl ketones under mild conditions in the presence of bases, yielding tetraoxo derivatives **I** [5, 7, 13, 14] (Scheme 1). We also found that oxo lactones **IV** are capable of reacting (according to Knoevenagel) with other carbonyl compounds having an active methylene group to afford various 1,3,4,6-tetracarbonyl compounds and their biologically active analogs [14–17]. The present communication reports on the results of our study of the reactions of compounds **IVa**–**IVe** with ethyl cyanoacetate and malonodinitrile in the presence of triethylamine as catalyst with the goal of obtaining 1,3,4,6-tetracarbonyl systems. The reactions were carried out in dioxane at room temperature, and 2-substituted 6-aryl-3,4-dihydroxy-6-oxo-2,4-hexadienoic acid esters or amides **Va**–**Vj** were obtained in satisfactory yields (Scheme 2, Tables 1–3). In some cases, a small amount (2–5%) of the corresponding tetraketone **I** was also isolated.

The spectral parameters of 2,4-hexadienoic acid derivatives **V** are consistent with their structure and with the known data for structurally related 3,4-dihydroxy-1,6-diphenyl-2,4-hexadiene-1,6-dione (**I**, Ar = Ph) [5] and methyl 6-phenyl-3,4-dihydroxy-6-oxo-2,4-hexadienoate (**II**, Alk = Me, Ar = Ph) [8, 9, 11] which were selected as model compounds (Tables 2, 3).

The IR spectra of products **V** (Table 2) contained absorption bands due to stretching vibrations of the amide group (3375–3195 and 1710–1660 cm^{-1}), ester

* For communication V, see [1].

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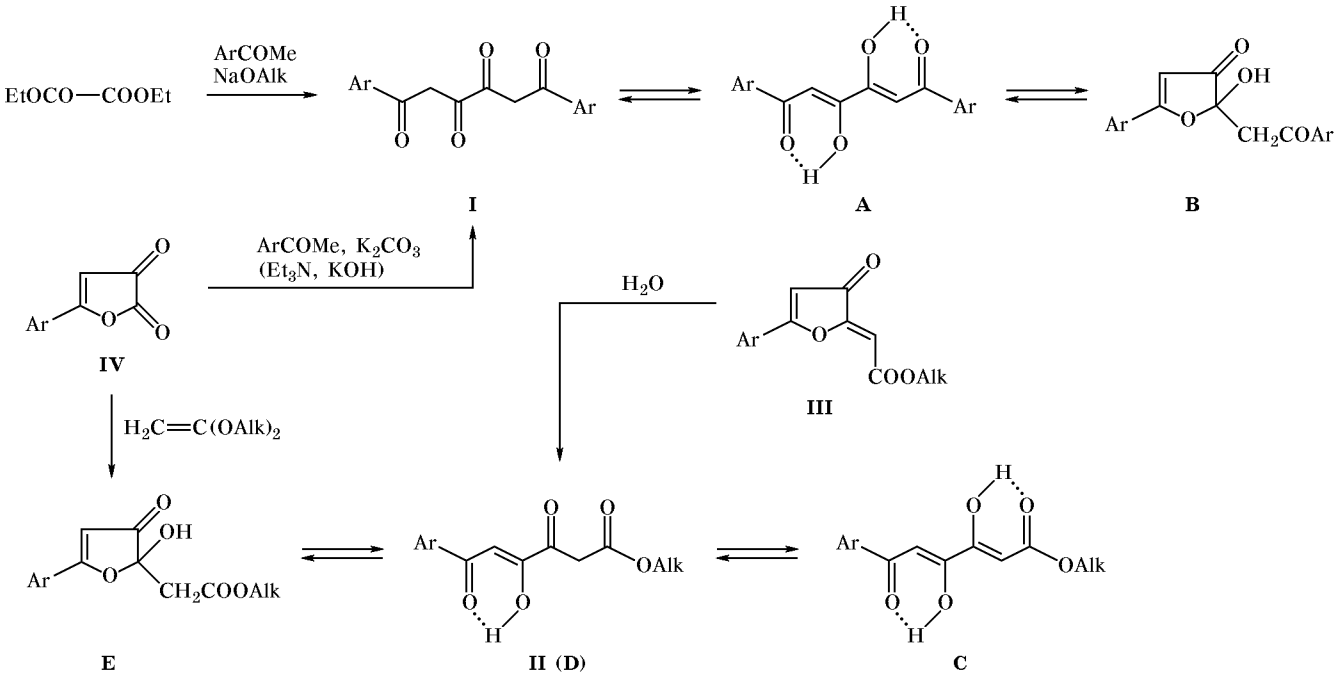
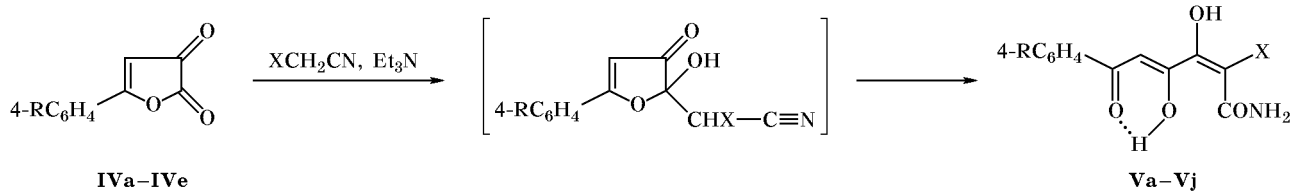
Scheme 1.



Scheme 2.



IVa, **Va**, **Vf**, R = H; **IVb**, **Vb**, **Vg**, R = Me; **IVc**, **Vc**, **Vh**, R = Br; **IVd**, **Vd**, **Vi**, R = Cl; **IVe, Ve**, **Vj**, R = F; **Va**–**Ve**, X = CO_2Et; **Vf**–**Vj**, X = CN.

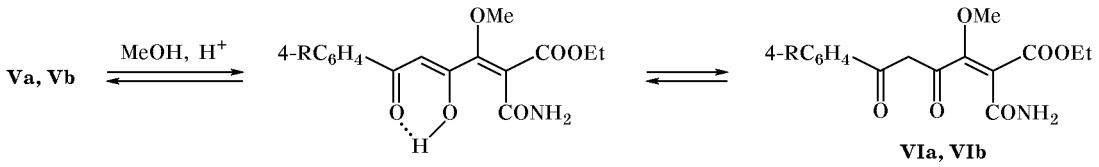
carbonyl (1718–1703 cm^{-1}; compounds **Va**–**Ve**), and cyano group (2229–2208 cm^{-1}; **Vf**–**Vj**). Also, a broad low-frequency band was observed in the region 1665–1580 cm^{-1}. This band corresponds to C=O stretching vibrations of the β-dicarbonyl fragment which has a six-membered H-chelate structure due to intramolecular hydrogen bond like OH···O=C [5, 18]. An analogous band at 1612–1568 cm^{-1} was observed in the IR spectra of 1,3,4,6-tetraketones **I** [5]. The presence of an enol hydroxy group was proved by the color test: a characteristic cherry-red color appeared on treatment of compounds **V** with a 10% solution of iron(III) chloride in ethanol.

We failed to reveal the hydroxy group of the keto-enol moiety (C^3OH) of compounds **V** by spectral methods, but it gives rise to the corresponding methyl ether on treatment with methanol in the presence of hydrochloric acid. By heating of compounds **Va** and **Vb** in boiling methanol containing hydrochloric acid we obtained ethyl 6-aryl-2-carbamoyl-4-hydroxy-3-methoxy-6-oxo-2,4-hexadienoates **VIa** and **VIb** in preparative yields (Scheme 3, Tables 1–3). As expected, enol ethers **VI**, unlike initial enols **V**, give a negative color test with a 10% solution of iron(III) chloride in ethanol.

In the IR spectrum of crystalline compound **VIa** (Table 2) we observed a broad absorption band at 1665–1637 cm^{-1} due to stretching vibrations of the β-dicarbonyl fragment; its position suggests formation of H-chelate ring. The position of bands from the ester and amide groups changes insignificantly, as compared with the corresponding bands of **Va**.

The 5-H signal in the ^1H NMR spectra of esters and amides **V** in DMSO-d_6 (Table 3) appears at δ 6.75–6.92 ppm, which is consistent with the data for model 6-aryl-3,4-dihydroxy-6-oxo-2,4-hexadienoic

Scheme 3.



VI, R = H (**a**), Me (**b**).

acid esters **II** (δ 6.81–6.95 ppm). The corresponding signal (2-H or 5-H) in the spectra of 1,3,4,6-tetraketones **A** is observed in a weaker field, at δ 7.05–7.24 ppm (Δδ ~0.3 ppm) [5], owing to the deshielding effect of the second benzene ring. The relatively downfield position of signal from the CH proton of the enolized aroylacetyl moiety in **V** conforms to the known data for structurally related acylpyruvic acids and their esters, amides, and other derivatives [16–20]. The lack of signals from CH_2 and another CH groups indicates the absence of tautomeric forms having the structure of 2-substituted 6-aryl-3-hydroxy-4,6-dioxo-2-hexenamides and (5-aryl-2-hydroxy-3-oxo-2,3-dihydro-2-furyl)acetamides.

On the other hand, the ^{1}H NMR spectra of keto esters **VI** differ from the spectra of initial compounds **V**: the former display no C^5H signal. Instead, a singlet from the C^5H_2 group appears at δ 3.66 (**VIa**) and 3.58 ppm (**VIb**), which corresponds to the β-dicarbonyl tautomer. We can conclude that crystalline compounds **VI** exist as keto–enol tautomers and that in DMSO solution β-diketone form prevails. Factors responsible for stabilization of different tautomeric forms in crystal and in solution are now not clear. It should be noted that addition of trifluoroacetic acid to solutions of **V** and **VI** in DMSO-d_6 almost does not change the position of proton signals in the ^{1}H NMR spectra.

As might be expected, the main fragmentation pathway of esters and amides **V** and **VI**, as well as of model compounds **I** (Ar = Ph) [21] and **II** (Alk = Me, Ar = Ph), under electron impact is elimination of the aroylacetyl fragment (ion **F**, *m*/*z* 146 and 147) and aroyl and phenyl ions (**G** and **H**, Scheme 4). The

Table 1. Yields, melting points, and elemental analyses of 2,3-disubstituted 6-aryl-4-hydroxy-6-oxo-2,4-hexadienoic acid esters and amides **Va**–**Vj**, **VIa**, and **VIb**

Comp. no.	Yield, %	mp,[a] °C	Found, %			Formula	Calculated, %		
			C	H	N (Hlg)		C	H	N (Hlg)
Va	92	223–224	59.29	5.12	4.37	$C_{15}H_{15}NO_6$	59.01	4.95	4.59
Vb	53	220–221	60.53	5.10	4.58	$C_{16}H_{17}NO_6$	60.18	5.37	4.39
Vc	59	225–226	47.22	3.80	3.87 (20.51)	$C_{15}H_{14}BrNO_6$	46.90	3.67	3.65 (20.80)
Vd	49	227–228	52.84	4.38	4.41 (10.02)	$C_{15}H_{14}SlNO_6$	53.03	4.15	4.12 (10.43)
Ve	32	212–213	55.45	4.49	4.16	$C_{15}H_{14}FNO_6$	55.73	4.37	4.33
Vf	71	234–235	60.65	4.13	10.57	$C_{13}H_{10}N_2O_4$	60.47	3.90	10.85
Vg	68	233–234	61.53	4.67	9.90	$C_{14}H_{12}N_2O_4$	61.76	4.44	10.29
Vh	82	274–275	46.57	3.07	8.62 (23.49)	$C_{13}H_9BrN_2O_4$	46.31	2.69	8.31 (23.70)
Vi	61	261–262	53.64	3.26	9.34 (11.83)	$C_{13}H_9ClN_2O_4$	53.35	3.10	9.57 (12.11)
Vj	52	253–254	56.70	3.45	9.87	$C_{13}H_9FN_2O_4$	56.53	3.28	10.14
VIa	90	211–212	60.47	5.71	4.56	$C_{16}H_{17}NO_6$	60.18	5.37	4.39
VIb	61	215–216	60.92	6.03	4.34	$C_{17}H_{19}NO_6$	61.25	5.75	4.20

[a] With decomposition.

Table 2. IR spectra of model compounds **I** and **II** and esters and amides **V** and **VI**

Comp. no.	IR spectrum, ν, cm^{-1}
I[a]	1605–1585 (CO, chelat.) [5]
II[b]	3085–3070 (OH), 1712 (CO_2Me), 1665 (CO), 1590–1580, 1555
Va	3332 ($CONH_2$), 1718 (CO_2Et), 1672 ($CONH_2$), 1640–1620, 1596 (CO, chelat.)
Vb	3323 ($CONH_2$), 1710 (CO_2Et), 1672 ($CONH_2$), 1635–1620, 1605 (CO, chelat.)
Vc	3330 ($CONH_2$), 1712 (CO_2Et), 1670 ($CONH_2$), 1645–1630, 1580 (CO, chelat.)
Vd	3375 ($CONH_2$), 1703 (CO_2Et), 1660 ($CONH_2$), 1638, 1622, 1585 (CO, chelat.)
Ve	3340 ($CONH_2$), 1707 (CO_2Et), 1690 ($CONH_2$, C=C), 1650–1620 (CO, chelat.)
Vg	3240–3225 ($CONH_2$), 2208 (C≡N), 1706, 1680 ($CONH_2$, C=C), 1652, 1625, 1602, 1585 (CO, chelat.)
Vi	3225–3195 ($CONH_2$), 2229 (C≡N), 1710 (C=C, $CONH_2$), 1656, 1587 (CO, chelat.)
Vj	3360–3345 ($CONH_2$), 3145–3130 (CH), 2229 (C≡N), 1719, 1701 (C=C, $CONH_2$), 1665–1635, 1593 (CO, chelat.)
VIa	3460 ($CONH_2$), 1722 (CO_2Et), 1704 ($CONH_2$, C=C), 1665–1637 (CO, chelat.)

[a] Ar = Ph. [b] Alk = Me, Ar = Ph.

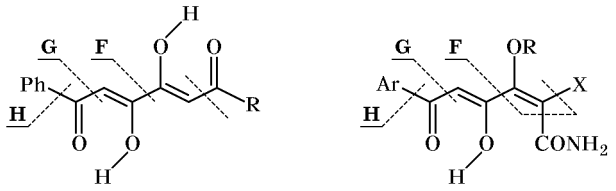
Table 3. ^1H NMR spectra of model compounds **I** and **II** and esters and amides **V** and **VI** in DMSO-d_6

Comp. no.	Chemical shifts δ, ppm
I[a, b]	3.48 d and 3.95 d (2H, CH_2, J = 14.0 Hz, **B**, 53%), 6.35 s (1H, 4-H, **B**), 7.15–8.05 m (12H, 2-H, 5-H, **A**; $2C_6H_5$, **A** and **B**), 7.07 s (2H, 2-H, 5-H, **A**, 100%), 7.25–8.08 m (10H, $2C_6H_5$), 15.27 br.s (2H, OH) [5]
II[b, c]	2.76 d and 2.88 d (2H, CH_2, J = 15.0 Hz, **E**, 49%) (2.70 d and 3.05 d; **E**, 68% [11]), 3.66 s (3H, CO_2Me, **D**, 35%) (9% of **D** [11]), 3.69 s (3H, CO_2Me, **E**), 3.78 s (3H, CO_2Me, **C**, 16%) (22% of **C** [11]), 3.89 s (2H, CH_2, **D**), 5.95 s (1H, 4-H, **E**), 6.82 s (1H, 5-H, **C**, **D**), 7.12 s (1H, 2-H, **C**), 7.33–7.75 m (1H, 2-OH, **E**; 5H, C_6H_5, **C**–**E**)
Va	1.22 t (3H, CH_2**Me**); 4.18 q (2H, C**H**$_2$Me); 6.83 s (1H, 5-H); 7.55 m, 7.67 m, and 7.98 m (5H, C_6H_5); 8.83 s and 10.08 s (2H, NH_2)
Vb	1.24 t (3H, CH_2**Me**), 2.42 s (3H, Me), 4.20 q (2H, C**H**$_2$Me), 6.80 s (1H, 5-H), 7.36 d and 7.90 d (4H, C_6H_4), 8.84 s and 10.09 s (2H, NH_2)
Vc	1.22 t (3H, CH_2**Me**), 4.15 q (2H, C**H**$_2$Me), 6.75 s (1H, 5-H), 7.62 d and 7.90 d (4H, C_6H_4), 8.87 s and 10.05 s (2H, NH_2)
Vd	1.28 t (3H, CH_2**Me**), 4.20 q (2H, C**H**$_2$Me), 6.80 s (1H, 5-H), 7.53 d and 8.02 d (4H, C_6H_4), 8.82 s and 10.15 s (2H, NH_2)
Ve	1.25 t (3H, CH_2**Me**), 4.21 q (2H, C**H**$_2$Me), 6.79 s (1H, 5-H), 7.32 m and 8.07 m (4H, C_6H_4), 8.75 s and 10.04 s (2H, NH_2)
Vf	6.90 s (1H, 5-H); 7.55 m, 7.67 m, and 8.00 m (5H, C_6H_5); 10.18 s (2H, $2NH_2$)
Vg	2.72 s (3H, Me), 6.92 s (1H, 5-H), 7.35 d and 7.90 d (4H, C_6H_4), 10.33 s (2H, NH_2)
Vh	6.88 s (1H, 5-H), 7.64–8.00 m (4H, C_6H_4), 10.28 s (2H, NH_2)
Vi	6.89 s (1H, 5-H), 7.57, 8.02 m (4H, C_6H_4), 10.19 s (2H, NH_2)
Vj	6.88 s (1H, 5-H), 7.33, 8.09 m (4H, C_6H_4), 10.14 s (2H, NH_2)
VIa	1.21 t (3H, CH_2**Me**), 3.15 s (3H, OMe), 3.66 s (2H, CH_2), 4.15 q (2H, C**H**$_2$Me), 7.42–8.02 m (5H, C_6H_5), 8.51 s and 9.45 s (2H, NH_2)
VIb	1.25 t (3H, CH_2**Me**), 2.36 s (3H, Me), 3.16 s (3H, OMe), 3.49 d and 3.64 d (2H, CH_2), 4.15 q (2H, C**H**$_2$Me), 7.28 d and 7.81 d (4H, C_6H_4), 8.32 s and 9.34 s (2H, NH_2)

[a] Ar = Ph. [b] In $CDCl_3$. [c] Alk = Me, Ar = Ph.

molecular ion peaks in the mass spectra of **I**, **II**, and **VI** have low intensity, Compounds **V** give no molecular ion peaks, but they readily lose water with formation of $[M-H_2O]^+$ ions (–18). A similar pattern is typical of tetraketones **I** [21].

Scheme 4.



I, II **V, VI**

Thus, 5-aryl-2,3-dihydrofuran-2,3-diones **IV** readily react with ethyl cyanoacetate and malonodinitrile in the presence of triethylamine, affording addition products at the lactone carbonyl group of the heteroring. The resulting semiacetals undergo ring opening at the C^2-O bond, and mild hydrolysis of the cyano group (in the presence of water) leads to formation of compounds **V**. Nucleophilic addition of CH acids at the lactone carbonyl group of furandiones **IV** is not surprising: analogous examples have been well known and described in detail [5, 7, 12, 14–17, 22, 23].

Esters and amides **V** exhibit bacteriostatic activity with respect to *Staphylococcus aureus* P-209 and *Escherichia coli* M_{17} [24, 25]; they also show a pronounced analgetic and antitumor activity.

EXPERIMENTAL

The IR spectra were taken on UR-20 and Specord M-80 spectrometers in mineral oil. The ^1H NMR spectra were obtained on RYa-2310 (60 MHz), Bruker AC-300 (300.13 MHz), and Bruker DRX-500 spectrometers (500.13 MHz) using DMSO-d_6 and $CDCl_3$ as solvents and TMS or HMDS as internal reference. The mass spectra (70 eV) were recorded on a Kratos MS-30 instrument with direct sample admission into the ion source; emission current 1000 mA, vaporizer temperature 100–150°C. The purity of the products was checked by TLC on Silufol UV-254 plates in the system benzene–diethyl ether–acetone (10 : 9 : 1); development with iodine vapor.

Initial 5-aryl-2,3-dihydrofuran-2,3-diones **IVa**–**IVe** were synthesized by dehydration of the corresponding aroylpyruvic acids by the action of acetic anhydride [5, 26] or acetyl chloride under similar conditions. Model 3,4-dihydroxy-1,6-diphenyl-2,4-hexadiene-1,6-dione (**I**, Ar = Ph) was obtained by the Claisen condensation of acetophenone with diethyl oxalate in the presence of MeONa [2, 4]. Methyl 3,4-dihydroxy-6-oxo-6-phenyl-2,4-hexadienoate (**II**, Alk = Me, Ar = Ph) was synthesized as described in [8, 9].

2-Substituted 6-aryl-3,4-dihydroxy-6-oxo-2,4-hexadienoic acid esters and amides Va–Vi (*general procedure***).** To a solution of 10 mmol of 5-aryl-2,3-dihydrofuran-2,3-dione **IVa**–**IVe** in 40–50 ml of dioxane we added 10 mmol of ethyl cyanoacetate or malonodinitrile and 0.4 ml of triethylamine. After 24 h, the precipitate was filtered off, washed with ethanol, and recrystallized from dimethylformamide. Compounds **Va**–**Vj** were isolated as light yellow substances poorly soluble in most organic solvents.

Ethyl 6-aryl-2-carbamoyl-4-hydroxy-3-methoxy-6-oxo-2,4-hexadienoates VIa and VIb. A mixture of 5 mmol of compound **Va** or **Vb**, 100 ml of methanol, and 6 ml of hydrochloric acid was refluxed for 1 h. The precipitate was filtered off and recrystallized from methanol. Products **VIa** and **VIb** were isolated as colorless crystalline substances.

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