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Chemistry of 1,5-Diketones: I. Halogenation of Aryl-Substituted Pent-2-ene-1,5-diones, Pentane-1,5-diones, and Their Fused Analogs

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Abstract—Halogenation of 3-(4-methoxyphenyl)-1,5-diphenylpent-2-ene-1,5-dione, 3-(4-methoxyphenyl)-1,5-diphenylpentane-1,5-dione, and 2-[1-(4-methoxyphenyl)-3-oxo-3-phenylpropyl)-1,2,3,4-tetrahydronaphthalen-1-one with bromine, chlorine, and dichloro(phenyl)-λ^3-iodane leads to formation of the corresponding monobromo-, dichloro-, or trichloro-substituted 1,5-diketones, depending on the conditions. Halogenation of the aliphatic chain and methoxyphenyl substituent can be accompanied by heterocyclization to give pyrylium salts.

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Among numerous chemical transformations of cyclic and semicyclic 1,5-diketones, their heterocyclizations in reactions with nucleophiles have been studied most thoroughly [1, 2]. The halogenation of phenyl-substituted pent-2-ene-1,5-dione, pentane-1,5-dione, and 2-(3-oxopropyl)tetrahydronaphthalen-1-one with chlorine and bromine was reported in [3–6]. Introduction of a halogen atom into diketone molecules opens new facilities in synthesizing functionalized dicarbonyl and heterocyclic compounds [2, 7].

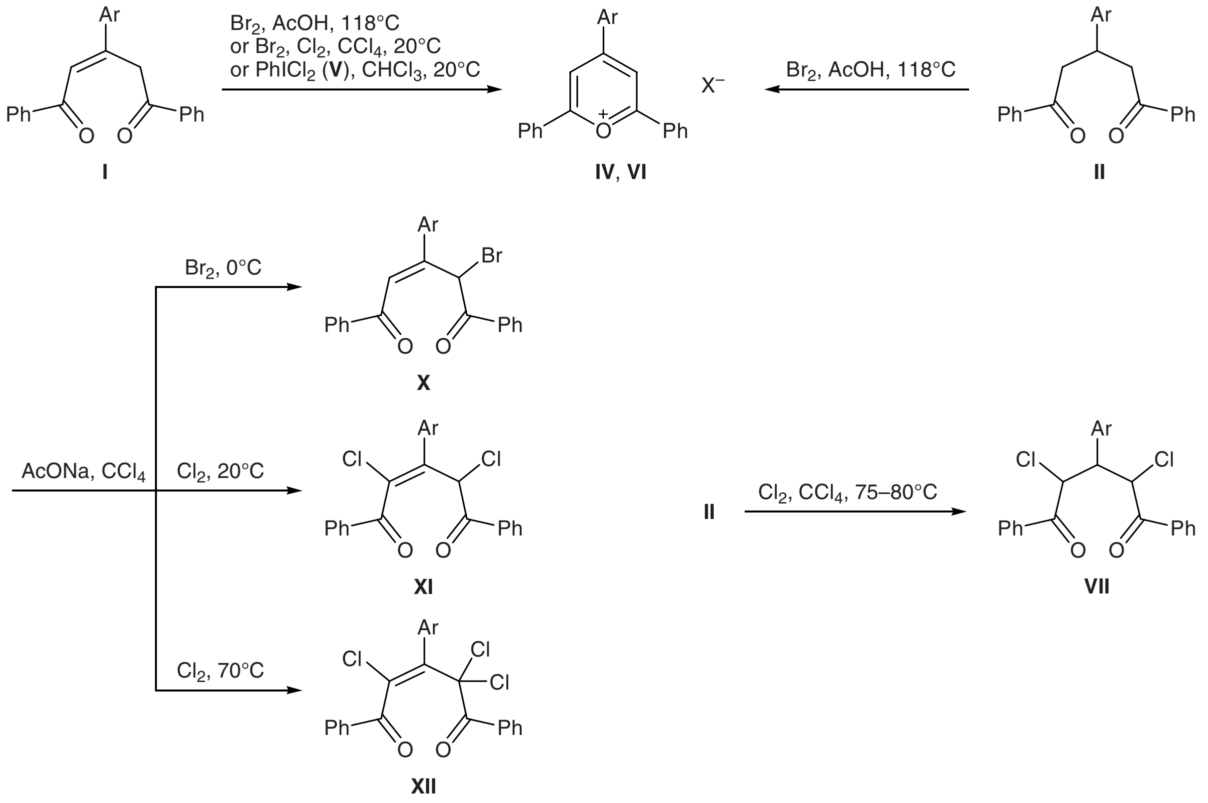
In continuation of our systematic studies on halogenation of dioxo compounds, in the present work we examined reactions of 3-(4-methoxyphenyl)-1,5-diphenylpent-2-ene-1,5-dione (**I**), 3-(4-methoxyphenyl)-1,5-diphenylpentane-1,5-dione (**II**), and 2-[1-(4-methoxyphenyl)-3-oxo-3-phenylpropyl]-1,2,3,4-tetrahydronaphthalen-1-one (**III**) with chlorine, bromine, and dichloro(phenyl)-λ^3-iodane with a view to find out how the substituent nature, degree of saturation, conjugation pattern, and reaction conditions affect the direction of transformation of 1,5-diketones.

Unsaturated diketone **I** and its saturated analog **II** failed to undergo bromination on heating with bromine in boiling acetic acid (Scheme 1); instead, heterocyclization of these substrates occurred to give pyrylium bromide **IV**, in keeping with published data for the corresponding triphenyl-substituted diketones [2, 8]. Heteroaromatization of diketone **I** to pyrylium salts **IV** and **VI** was also observed under mild conditions, i.e., by the action of bromine or chlorine in carbon tetrachloride at 0–20°C or of dichloro(phenyl)-λ^3-iodane (**V**) in chloroform at room temperature. Saturated diketone **II** remained unchanged on treatment with chlorine or bromine under analogous conditions. The reaction of 1,5-diketone **II** with chlorine in carbon tetrachloride at 75–80°C (reaction time 30 h) gave dichloropentanedione **VII**.

We succeeded in obtaining monobromo- and di- and trichloropentenediones **X**–**XII** only by treatment of compound **I** with bromine and chlorine, respectively, in carbon tetrachloride in the presence of sodium acetate as reagent suppressing salt formation. Bromodiketone **X** was formed at 0°C, and dichlorodiketone **XI**, at 20°C. Introduction of three chlorine atoms into the substrate molecule required elevated temperature (70°C).

No chlorination of diketone **III** occurred in carbon tetrachloride, benzene, and acetic acid; this is consistent with published data on the chlorination of acyclic 1,5-diketones [6, 9]. Compound **III** readily reacted with bromine at room temperature to give a mixture of 2-bromo-2-[2-bromo-1-(4-methoxyphenyl)-3-oxo-3-phenylpropyl]-1,2,3,4-tetrahydronaphthalen-1-one and 2-bromo-2-[2-bromo-1-(3-bromo-4-methoxyphenyl)-3-oxo-3-phenylpropyl]-1,2,3,4-tetrahydronaphthalen-1-one [6]. Although (dichloro-λ^3-iodanyl)benzene is known to act as effective electrophilic chlorinating agent in polar solvents and is successfully used to

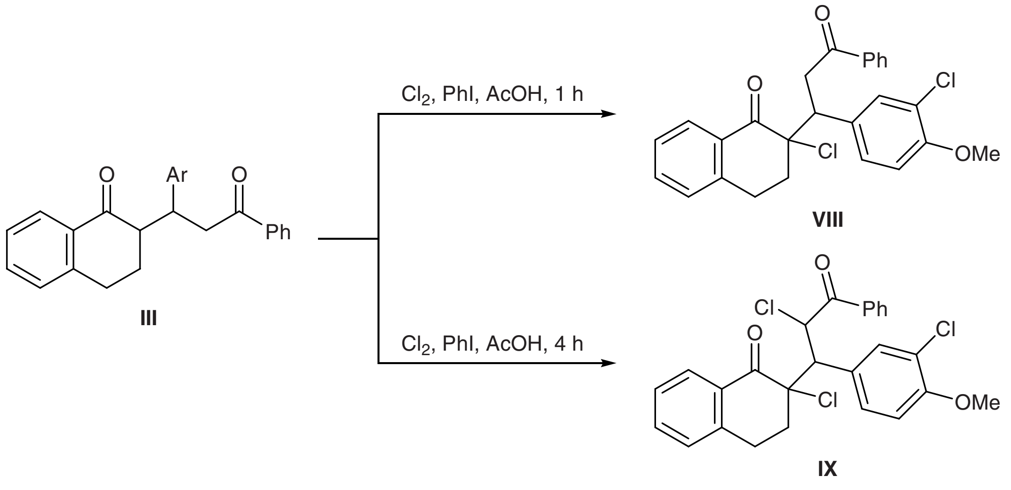
Scheme 1.



IV, X = Br; **VI**, X = Cl; Ar = 4-$MeOC_6H_4$.

introduce chlorine atoms into 1,5-dicarbonyl compounds [9], chlorination of the methoxyphenyl group was observed only in the reaction with diketone **III**. Treatment of **III** with compound **V** in acetic acid gave dichloro derivative **VIII** in 1 h. When the reaction time was increased to 4 h, three chlorine atoms were introduced into the substrate molecule to produce compound **IX** (Scheme 2). Analogous results were obtained by carrying out the chlorination in a simpler way: a solution of diketone **III** in acetic acid in the presence of iodobenzene (PhI-to-**III** molar ratio ~1:3) was saturated with chlorine; in this case, dichloro(phenyl)-λ^3-iodane is generated *in situ*, and iodobenzene acts as chlorine carrier.

Scheme 2.



Halogenation of 1,5-diketones **I–III**

Substrate	Reagent	Solvent	Reaction time, h	Temperature, °C	Product	Yield, %
I	Br_2	AcOH	0.5	118	**IV**	96
I	Br_2	CCl_4	1.0	20	**IV**	88
I	Cl_2	CCl_4	1.0	20	**VI**	86
I	$PhICl_2$ (**V**)	$CHCl_3$	1.0	20	**VI**	81
I	Br_2/AcONa	CCl_4	1.0	0	**X**	63
I	Cl_2/AcONa	CCl_4	2.0	20	**XI**	78
I	Cl_2/AcONa	CCl_4	2.0	70	**XII**	72
II	Br_2	AcOH	1.0	118	**IV**	84
II	Cl_2	CCl_4	30	75–80	**VII**	55
III	**V**	AcOH	1.0	20	**VIII**	59
III	**V**	AcOH	4.0	20	**IX**	57

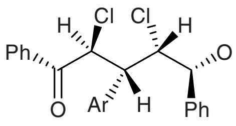
The conditions and results of halogenation of 1,5-diketones **I–III** are collected in table. We can conclude that halogenation of diketones **I–III** under mild conditions (in carbon tetrachloride or acetic acid at room or slightly elevated temperature) is not accompanied by transformation of the substrate skeleton (compounds **VII–XII**); moreover, the double C=C bond in the aliphatic chain of pentenedione **I** remains intact (compounds **X–XII**).

The structure of halogen derivatives **VII–XII** was confirmed by the IR and ^{1}H and ^{13}C NMR data. The position and intensity of IR bands arising from stretching vibrations of conjugated C=O and C=C bonds could provide information on mutual arrangement of these bonds in α,β-unsaturated ketones [10]. The differences between the stretching vibration frequencies of the double C=O and C=C bonds in initial pentenedione **I** (62 cm^{-1}) and bromodiketone **X** (66 cm^{-1}), as well as the intensity ratios of the C=O and C=C bands (0.8 and 0.7, respectively), indicate *cis* configuration of the double C=C bond in molecule **X**. In the IR spectra of di- and trichloro-substituted pentenediones **XI** and **XII**, the corresponding difference is 36 cm^{-1}, and the intensity ratio is equal to 3.6–3.9; therefore, these compounds may be assigned *s-trans* configuration as shown below.

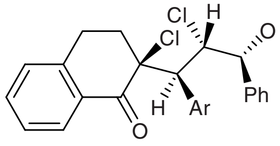
The strong absorption band at 1674 cm^{-1} in the IR spectrum of **III** belongs to stretching vibrations of the C=O groups; in the spectra of chlorinated diketones **VIII** and **IX**, the carbonyl band appears at a higher frequency (1680–1685 cm^{-1}). Introduction of a chlorine atom into the α-position with respect to the carbonyl group in the aliphatic chain increases the carbonyl stretching vibration frequency ($\nu_{C=O}$). In this case, the molecule has an eclipsed conformation with respect to the chlorine and carbonyl oxygen atoms. The presence of a halogen atom in the methoxyphenyl group of diketones **VIII** and **IX** gives rise to two bands in the region 878–838 cm^{-1} due to bending vibrations ($\delta_{C–H}$) of 1,2,4-substituted benzene ring.

In the ^{1}H NMR spectra of compounds **X** and **XI**, the one-proton singlet from 4-H (δ 6.60 and 6.58 ppm, respectively) is displaced downfield relative to the 4-H signal of initial pentenedione **I** (δ 4.86 ppm) owing to deshielding effect of the halogen atom. Likewise, dichloropentanedione **VII** is characterized by downfield shift of the 2-H signal relative to 4-H (δ 6.52 ppm; $\Delta\delta = 0.8$ ppm) and of C^4 relative to C^2 ($\Delta\delta_C =$ 7.56 ppm) in the ^{13}C NMR spectrum. The reason is that the oxygen and chlorine atoms are spatially close to each other; as a result of additional shielding, the carbonyl carbon signals shift upfield. Similar chemical shifts of 4-H, C^4, and C^5 in dichloro diketones **VII**, **XI**, and **XII** suggest eclipsed configuration of the C^4–Cl and C^5=O bonds in their molecules [11].

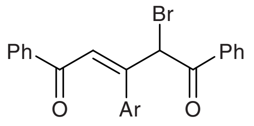
The shape and intensity of signals in the ^{1}H NMR spectra of dichloro diketones **VIII** and **IX** are consistent with the assumed structures. The ^{1}H NMR spectra



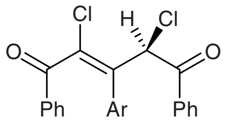
VII



IX



X



XI

of diketones **VIII** and **IX** contained multiplet signals from aromatic and alicyclic protons at δ 6.88–8.29 and 2.04–3.12 ppm, respectively, and a singlet from protons in the methoxy group at δ 3.94 ppm; the latter is displaced downfield relative to the corresponding signal of diketones **I**–**III** and halogenated acyclic diketones **VII** and **X**–**XII**, indicating that the chlorine atom is located in the *ortho* position with respect to the methoxy group.

The facts that the chlorination of compound **I** changes the geometry of the conjugated C=O and C=C bonds and that the *s-cis* configuration of the initial unsaturated diketone is conserved in the bromination process suggest that its transformation follows two concurrent pathways: (1) electrophilic addition of chlorine with subsequent elimination of hydrogen chloride which favors enolization of intermediate pentenediones, and (2) substitutive bromination.

The chlorination of saturated diketones **II** and **III** involves initial enolization, attack by chlorine on the double C=C bond thus formed, and elimination of hydrogen chloride. The presence of an aryl substituent on C^3 favors approach of chlorine molecule from the rear side (with respect to the aryl group) of the enol C=C bond. Attack by the second chlorine molecule on the C=C bond appearing as a result of enolization of the second phenacyl fragment is likely to be determined by electrostatic interaction between electronic orbitals of the chlorine molecule and chlorine atom in the chloro diketone. Therefore, the reaction gives *threo*-dichloropentanedione **VII** in which the last introduced chlorine atom is distant from that introduced first, and it occupies eclipsed position with respect to the carbonyl oxygen atom.

The chlorination of diketone **III** in the presence of iodobenzene involves electrophilic (by the result) replacement of hydrogen atoms in the α-positions with respect to the carbonyl groups and in the *meta* position of the methoxyphenyl substituent (*ortho* position with respect to the methoxy group). The major product is *threo* isomer **IX**. As follows from the results of halogenation of compound **III**, obtained in 1 and 4 h, the chlorination occurs first at the alicyclic carbon atom (C^2) and only then the side-chain carbon atom is involved.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 spectrometer from samples dispersed in mineral oil or hexachlorobutadiene. The ^{1}H and ^{13}C NMR spectra were measured on Varian FT-80A and Bruker MSL-400 instruments from solutions in chloroform-*d* and DMSO-d_6 using TMS as internal reference.

3-(4-Methoxyphenyl)-1,5-diphenylpent-2-ene-1,5-dione (**I**) was synthesized by alkaline hydrolysis of 3-(4-methoxyphenyl)-2,6-diphenylpyrylium perchlorate [12], 3-(4-methoxyphenyl)-1,5-diphenylpentane-1,5-dione (**II**) was prepared according to the procedure described in [1], and 2-[1-(4-methoxyphenyl)-3-oxo-3-phenylpropyl]-1,2,3,4-tetrahydronaphthalen-1-one (**III**) was synthesized by the Michael reaction as reported in [13].

Gaseous chlorine was prepared by treatment with dilute sulfuric acid of a mixture of sodium chloride and manganese dioxide at a ratio of 1:2 and was dried by passing through concentrated sulfuric acid [14].

4-(4-Methoxyphenyl)-2,6-diphenylpyrylium bromide (IV). *a.* A solution of 2.1 g (13 mmol, 0.7 ml) of bromine in 10 ml of acetic acid was added under stirring at 20°C to a solution of 3.2 g (9 mmol) of diketone **I** in 40 ml of glacial acetic acid. The mixture was heated for 0.5 h at 118°C, cooled, and poured into 150 ml of diethyl ether. The crystalline product was filtered off and dried. Yield 3.7 g (96%), yellow crystals; the product was characterized as 3-(4-methoxyphenyl)-2,6-diphenylpyrylium tetrafluoroborate [12].

b. A solution of 2.1 g (13 mmol) of bromine in 25 ml of carbon tetrachloride was added at 20°C to a suspension of 3.2 g (9 mmol) of diketone **I** in 30 ml of carbon tetrachloride. The mixture was stirred for 1 h at 20°C, washed with water, dried over magnesium sulfate, and evaporated. The crystals were filtered off and dried. Yield 3.4 g (88%).

c. A solution of 2.7 g (17 mmol) of bromine in 10 ml of acetic acid was added to a solution of 4.8 g (12 mmol) of diketone **II** in 50 ml of glacial acetic acid. The mixture was heated for 1 h at 118°C and evaporated, and the residue was treated with 150 ml of diethyl ether. The crystals were filtered off and dried. Yield 4.4 g (84%).

4-(4-Methoxyphenyl)-2,6-diphenylpyrylium chloride (VI). *a.* A solution of 7.0 g (22 mmol) of pentenedione **I** in 70 ml of carbon tetrachloride was saturated with chlorine for 2 h at 20°C. The precipitate was filtered off, washed with diethyl ether, and dried. Yield 7.3 g (86%); the product was characterized as 3-(4-methoxyphenyl)-2,6-diphenylpyrylium tetrafluoroborate [12].

b. A mixture of 3.5 g (11 mmol) of diketone **I**, 6.0 g (22 mmol) of dichloro(phenyl)-λ^3-iodane [15], and

40 ml of chloroform was stirred for 1 h at 20°C. The mixture was evaporated, the residue was treated with 150 ml of diethyl ether, and the precipitate was filtered off, washed with diethyl ether, and dried. Yield 3.3 g (81%).

2,4-Dichloro-3-(4-methoxyphenyl)-1,5-diphenylpentane-1,5-dione (VII). Chlorine was passed over a period of 30 h through a solution of 3.6 g (10 mmol) of diketone **II** in 30 ml of carbon tetrachloride, heated to 75–80°C. The solvent was distilled off under reduced pressure, and the crystalline product was filtered off, washed with ethanol, and dried. Yield 2.3 g (55%), colorless crystals, mp 124.5–125°C. IR spectrum, ν, cm^{-1}: 1680, 1673, 823, 750, 706. ^1H NMR spectrum (400 MHz, DMSO-d_6, 20°C), δ, ppm: 6.52 d (1H, 4-H), 5.72 d (1H, 2-H), 4.27 d.d (1H, 3-H), 3.85 s (3H, CH_3). ^{13}C NMR spectrum (400 MHz, $CDCl_3$, 20°C), δ_C, ppm: 191.60 (C^5), 191.11 (C^1), 63.90 (C^4), 56.34 (C^2), 54.91 (CH_3), 49.38 (C^3). Found, %: C 64.34; H 4.80; Cl 16.71. $C_{24}H_{20}Cl_2O_3$. Calculated, %: C 67.45; H 4.72; Cl 16.59.

2-Chloro-2-[1-(3-chloro-4-methoxyphenyl)-3-oxo-3-phenylpropyl]-1,2,3,4-tetrahydronaphthalen-1-one (VIII). A mixture of 5 g (13 mmol) of diketone **III**, 0.5 g (2.5 mmol) of iodobenzene, and 80 ml of acetic acid was saturated with chlorine over a period of 1 h. The crystals were filtered off and washed with ethanol. Yield 3.5 g (59%), colorless crystals, mp 190–191.5°C (from EtOH–$CHCl_3$, 1:1). IR spectrum, ν, cm^{-1}: 1680, 878, 860, 840, 800, 786, 767, 690. ^1H NMR spectrum (400 MHz, DMSO-d_6, 20°C), δ, ppm: 8.20–6.88 m (H_{arom}), 3.94 s (3H, CH_3), 3.12–2.04 m ($H_{alicycl}$). Found, %: C 68.39; H 4.44; Cl 16.01. $C_{26}H_{22}Cl_2O_3$. Calculated, %: C 68.88; H 4.89; Cl 15.64.

2-Chloro-2-[2-chloro-1-(3-chloro-4-methoxyphenyl)-3-oxo-3-phenylpropyl]-1,2,3,4-tetrahydronaphthalen-1-one (IX). A mixture of 5 g (13 mmol) of diketone **III**, 0.5 g (2.5 mmol) of iodobenzene, and 80 ml of acetic acid was saturated with chlorine over a period of 4 h. The crystals were filtered off and washed with ethanol. Yield 3.6 g (57%), colorless crystals, mp 170–171°C (from *i*-PrOH). IR spectrum, ν, cm^{-1}: 1685, 876, 838, 752, 738, 702. ^1H NMR spectrum (400 MHz, DMSO-d_6, 20°C), δ, ppm: 8.29–6.84 m (H_{arom}), 3.94 s (3H, CH_3), 2.88–2.16 m ($H_{alicycl}$). Found, %: C 66.51; H 3.96; Cl 22.28. $C_{26}H_{21}Cl_3O_2$. Calculated, %: C 64.02; H 4.34; Cl 21.80.

4-Bromo-3-(4-methoxyphenyl)-1,5-diphenylpent-2-ene-1,5-dione (X). A solution of 2.1 g (13 mmol) of bromine in 25 ml of carbon tetrachloride was added over a period of 1 h to a suspension of 2.8 g (8 mmol) of diketone **I** and 2.5 g (36 mmol) of sodium acetate in 30 ml of carbon tetrachloride, stirred at 0°C. When the reaction was complete, excess bromine was removed by purging with an inert gas, the mixture was washed with water and dried over $MgSO_4$, the solvent was distilled off, and the crystalline product was filtered off and dried. Yield 2.2 g (63%), yellow crystals, mp 101–102°C. IR spectrum, ν, cm^{-1}: 1718, 1648, 1582, 822, 746, 700. ^1H NMR spectrum (400 MHz, DMSO-d_6, 20°C), δ, ppm: 6.60 s (1H, 4-H), 3.85 s (3H, CH_3). ^{13}C NMR spectrum (400 MHz, $CDCl_3$, 20°C), δ_C, ppm: 191.10 (C^5), 189.32 (C^1), 138.66 (C^3), 123.84 (C^2), 61.71 (C^4), 55.24 (CH_3). Found, %: C 66.10; H 4.21; Br 18.16. $C_{24}H_{19}BrO_3$. Calculated, %: C 66.21; H 4.37; Br 18.39.

2,4-Dichloro-3-(4-methoxyphenyl)-1,5-diphenylpent-2-ene-1,5-dione (XI). A suspension of 2.8 g (8 mmol) of diketone **I** and 2.6 g (32 mmol) of sodium acetate in 30 ml of carbon tetrachloride was saturated with chlorine for 2 h at 20°C. The mixture was filtered, the filtrate was evaporated, and the crystals were filtered off, washed with ethanol, and dried. Yield 2.7 g (78%), pale yellow crystals, mp 122–123°C (from EtOH). IR spectrum, ν, cm^{-1}: 1720, 1675, 1640, 820, 748, 704. ^1H NMR spectrum (400 MHz, DMSO-d_6, 20°C), δ, ppm: 6.58 s (1H, 4-H), 3.83 s (3H, CH_3). ^{13}C NMR spectrum (400 MHz, $CDCl_3$, 20°C), δ_C, ppm: 191.36 (C^5), 189.46 (C^1), 139.34 (C^3), 133.50 (C^2), 63.42 (C^4), 55.30 (CH_3). Found, %: C 66.97; H 4.06; Cl 16.25. $C_{24}H_{18}Cl_2O_3$. Calculated, %: C 67.76; H 4.24; Cl 16.71.

2,4,4-Trichloro-3-(4-methoxyphenyl)-1,5-diphenylpent-2-ene-1,5-dione (XII) was synthesized as desribed above for compound **XI** using 2.8 g (8 mmol) of diketone **I**, 3.3 g (40 mmol) of sodium acetate, and 30 ml of carbon tetrachloride at 70°C (2 h). Yield 2.6 g (72%), colorless crystals, mp 152–153°C (from EtOH). Found, %: C 62.14; H 3.44; Cl 22.98. $C_{24}H_{17}Cl_3O_3$. Calculated, %: C 62.67; H 37.00; Cl 23.18.

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