Organic Chemistry

Reaction of 3,3-dichloropentane-2,4-dione with aromatic aldehydes under the conditions of Darzens reaction

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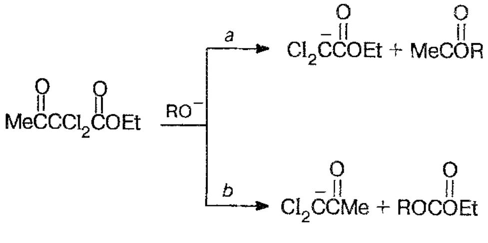
3,3-Dichloropentane-2,4-dione reacts with aromatic aldehydes under the conditions of Darzens reaction to give 4-acetoxy-4-aryl-3,3-dichlorobutan-2-ones, the products of insertion into the σ-C—C bond. The reaction of ethyl dichloroacetylacetate with benzaldehyde yields a derivative of tricyclo[5.1.0.0^{3,5}]octane, rather than 2,6-bis(1'-chlorobenzylidene)-cyclohexane-1,4-dione, as the by-product.

Key words: Darzens reaction, 3,3-dichloropentane-2,4-dione, insertion reaction; 3,3-dichlorobutan-2-one, cyclohexane-1,4-dione, tricyclooctane, X-ray structural investigation.

Aromatic aldehydes react with CH acids of the general formula Hal_2CHY (Y is an electron-withdrawing group) under the conditions of Darzens reaction to give α-chloroepoxides,[1] α-chloroketones,[2] or their mixtures.[3] When β-dicarbonyl compounds are used, the corresponding carbanions can be generated by treatment with sodium alkoxides.[4] However, the yields of target compounds (α-chloroepoxides and α-chloroketones) in the reactions of ethyl 2,2-dichloroacetoacetate (EDCA) with aldehydes[5] in the presence of RONa were rather low, which is caused by the possibility of formation of two types of carbanions from EDCA in competing versions of nucleophilic attack on the two carbonyl groups of EDCA by RO^- (Scheme 1).

Scheme 1



a is the main route, *b* is the side route

It seemed that if 3,3-dichloropentane-2,4-dione (**1**), having two equivalent carbonyl groups, is used in the reaction instead of EDCA, one may expect that only one carbanion, namely, the dichloroacetonyl anion, would be generated and, therefore, only one reaction route would be realized. Nevertheless, in the previous

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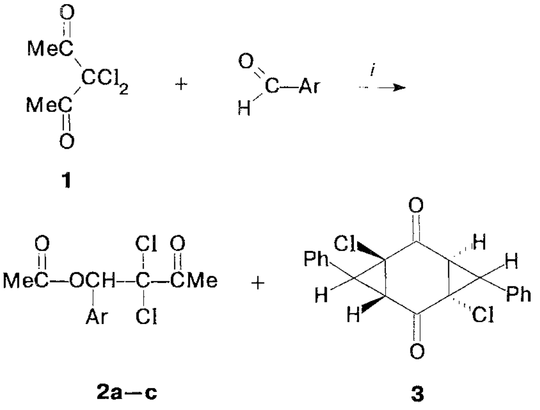
Table 1. Characteristics of 4-acetoxy-4-aryl-3,3-dichlorobutan-2-ones (**2a—c**) synthesized

Compound	Yield (%)	B.p./°C (*p*/Torr) M.p./°C	Found/Calculated (%)			Molecular formula
			C	H	Cl	
2a*	53	121—122	45.21 45.03	3.49 3.43	22.31 22.15	$C_{12}H_{11}Cl_2NO_5$
2b	33	122—130 (0.06) 38—40	52.79 52.39	4.44 4.40	25.85 25.77	$C_{12}H_{12}Cl_2O_3$
2c	11	140—150 (0.02)	51.21 51.18	4.67 4.58	23.35 23.24	$C_{13}H_{14}Cl_2O_4$

* Found (%): N 4.41. Calculated (%): N 4.37.

Scheme 2



Ar = 4-$O_2NC_6H_4$ (**a**); Ph (**b**); 4-$MeOC_6H_4$ (**c**).

i. RONa, ether

studies we showed that the reaction of compound **1** with aldehydes occurs in an unusual way yielding products of insertion[6,7] and derivatives of tricyclo[5.1.0.$0^{3,5}$]octane.[7]

In this work we present detailed data concerning the reaction of diketone **1** with aromatic aldehydes in the presence of powdered sodium alkoxide. The ratio between the alkoxide (MeONa or EtONa) and the reactants (diketone **1** and ArCHO) or the nature of solvent have practically no effect on the yields of the final products. The insertion products, *viz.*, 4-acetoxy-4-aryl-3,3-dichlorobutan-2-ones (**2a—c**) (Table 1), were obtained in all cases, and in the reaction of benzaldehyde with diketone **1**, 2,6-dioxo-4,8-diphenyl-1,5-dichlorotricyclo[5.1.0.$0^{3,5}$]octane (**3**) was also isolated (Scheme 2).

The structures of compounds **2a—c** were unambiguously determined by spectral (IR, NMR) methods (Tables 1 and 2). The ^{1}H NMR spectra of butanones **2a—c** exhibit singlets of the two nonequivalent methyl groups at ~2.0 and 2.5 ppm. The ^{13}C NMR spectra also exhibit two signals at 168 ppm (COO) and 194 ppm (CO). The carbonyl groups are responsible for absorption bands at 1730 and 1760 cm^{-1} in the IR spectra. Formation of 2,4-dinitrophenylhydrazone from **2b** is chemical evidence of the presence of the keto group in molecules **2a—c**.

It should be noted that, according to the ^{1}H NMR data, the hydrazone obtained exists in DMF-d_7 as a mixture of two isomers (*syn* and *anti*), whereas in CD_3CN, there is either only one isomer or rapid interconversion of the *syn* and *anti* forms.

The structure of tricyclic compound **3** was unambiguously confirmed by its X-ray structural study (Fig. 1, Tables 3 and 4).

The conformation of the central six-membered ring in molecule **3** is planar (within 0.002 Å). The dihedral angle between the plane of this ring and the plane of the cyclopropane ring is 77.3°. The conformation of the tricyclic system may be described as a "long chair". The phenyl groups at the C(4) and C(4′) atoms occupy equatorial positions. The conformation of the

Table 2. Spectral (IR and ^{1}H and ^{13}C NMR) data of compounds **2a—c**

Compound	IR (ν/cm^{-1})	^{1}H NMR (δ, *J*/Hz) (solvent)	^{13}C NMR, δ (solvent)
2a	715, 795, 865, 935, 1230, 1350, 1380, 1465, 1525, 1610, 1730, 1760, 3090, 3120	2.10 (s, 3 H, MeCO); 2.60 (s, 3 H, MeCOO); 6.46 (s, 1 H, CH); 8.16 (d, 2 H,C_6H_4, ^3J = 10); 7.76 (d, 2 H, C_6H_4, ^3J = 10); (CD_3OD)	200.07 (CH_3); 23.97(Me); 75.18 (CH) 87.46 (CCl_2); 147.97, 140.30, 130.23, 122.69, (C_6H_4); 168.11 (COO) 194.05 (C=O); (DMSO-d_6)
2b	710, 775, 795, 940, 1035, 1050, 1200, 1230, 1370, 1460, 1615, 1730, 1760, 3045, 3065	1.96 (s, 3 H, MeCO); 2.40 (s, 3 H, MeCOO); 6.25 (s, 1 H, CH); 7.00—7.60 (m, 5 H, Ph) (CCl_4)	21.3 (Me); 25.2 (Me); 77.34 (CH); 89.3 (CCl_4); 130.0, 128.7, 130.3, 134.9 (Ph); 168.3 (COO); 194.7 (C=O); (CCl_4, external standard C_6D_6+HMDS)
2c	745, 805, 840, 935, 1045, 1190, 1230, 1265, 1430, 1520, 1610, 1735, 1760 2970, 3015	2.00 (s, 3 H, MeCO); 2.46 (s, 3 H, MeCOO); 3.73 (s, 3 H, MeO); 6.31 (s, 1 H, CH); 7.08 (d, 2 H, C_6H_4, ^3J = 9); 6.71 (d, 2 H, C_6H_4,^3J = 9)	19.45 (Me); 23.77 (Me); 54.52 (Me); 75.94 (CH); 88.32 (CCl_2); 112.78, 125.16, 130.06, 159.96 (C_6H_4); 168.12 (COO); 194.77 (C=O) (CD_3CN)

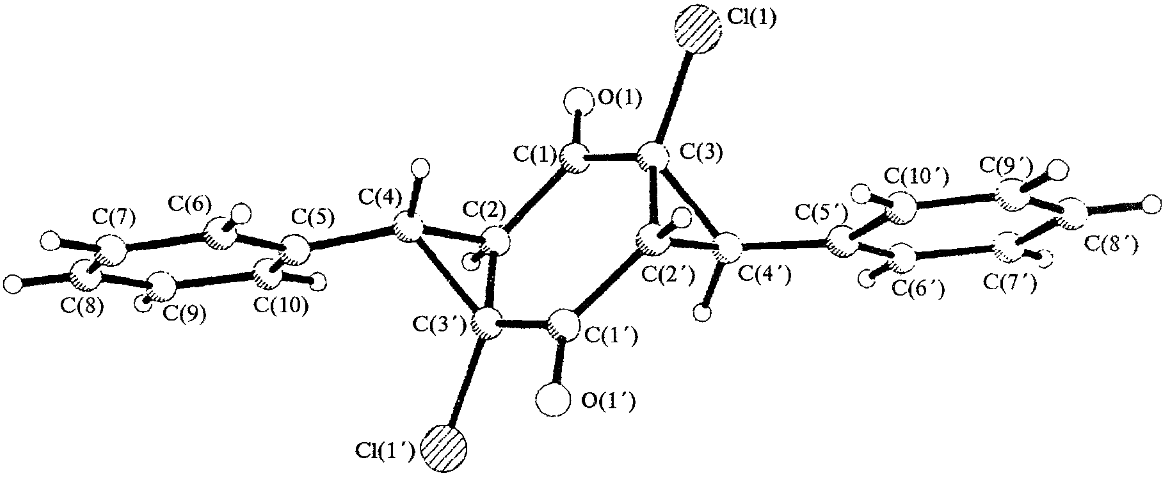


Fig. 1. Geometry of molecule **3** in the crystal.

Table 3. Selected geometric parameters of the structure of **3** (bond lengths (d/Å) and angles (ω/deg))

Bond	d	Bond	d
C(1)—O(1)	1.19(2)	C(2)—C(4)	1.54(2)
C(1)—C(2)	1.51(2)	C(3)—Cl(1)	1.87(1)
C(1)—C(3)	1.46(2)	C(3)—C(4′)	1.58(2)
C(2)—C(3′)	1.44(2)	C(4)—C(5)	1.50(2)

Angle	ω	Angle	ω
O(1)C(1)C(2)	121(1)	C(1)C(3)C(2′)	127(1)
O(1)C(1)C(3)	130(1)	C(1)C(3)C(4′)	116(1)
C(2)C(1)C(3)	109(1)	C(2′)C(3)C(4′)	61(1)
C(1)C(2)C(3′)	125(1)	C(2)C(4)C(3′)	55(1)
C(1)C(2)C(4)	115(1)	C(2)C(4)C(5)	120(1)
C(3′)C(2)C(4)	64(1)	C(3′)C(4)C(5)	117(1)
Cl(1)C(3)C(1)	108(1)	C(4)C(5)C(6)	131(2)
Cl(1)C(3)C(2′)	119(1)	C(4)C(5)C(10)	115(2)
Cl(1)C(3)C(4′)	120(1)	C(6)C(5)C(10)	114(2)

Table 4. Coordinates of nonhydrogen atoms in the structure of **3** and their equivalent isotropic thermal factors

$$B_{\mathrm{iso}}^{\mathrm{equiv}} = \frac{4}{3}\sum_{i=1}^{3}\sum_{j=1}^{3}(a_i a_j)B(i,j) \quad (\text{Å}^2)$$

Atom	x	y	z	B
Cl(1)	0.0175(7)	0.3338(2)	−0.0934(6)	5.0(3)
O(1)	−0.209(2)	0.091(1)	−0.252(1)	3.3(6)
C(1)	−0.118(2)	0.059(2)	−0.142(2)	3.8(7)
C(2)	−0.144(1)	−0.077(1)	−0.071(1)	1.6(4)
C(3)	0.034(2)	0.128(1)	−0.058(2)	3.6(7)
C(4)	−0.190(2)	−0.041(2)	0.047(2)	2.5(5)
C(5)	−0.317(2)	−0.132(2)	0.067(2)	2.3(5)
C(6)	−0.349(2)	−0.089(2)	0.178(2)	4.7(7)
C(7)	−0.467(2)	−0.153(2)	0.210(2)	4.0(7)
C(8)	−0.560(2)	−0.270(2)	0.132(2)	3.9(7)
C(9)	−0.532(2)	−0.313(2)	0.018(2)	3.7(7)
C(10)	−0.415(2)	−0.248(2)	−0.009(2)	4.2(7)

C(2)C(4)C(5)C(10) fragment is eclipsed (the torsion angle is −8.1°). This conformation is probably stabilized by the steric interactions between the Cl atom and the benzene ring. Unfortunately, due to the low accuracy of the determination of geometrical parameters, a more detailed discussion of the features of spatial structure of molecule **3** is impossible.

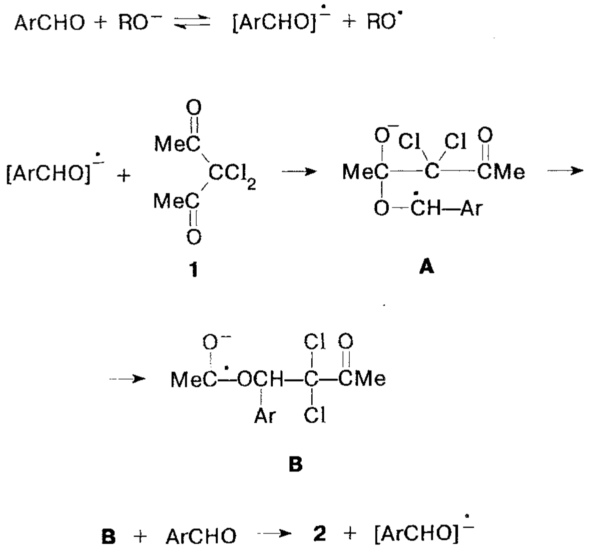
The formation of products **2** and **3** is apparently caused by the fact that the reaction of **1** with aldehydes occurs according to two pathways. One of these involves homolytic cleavage of the C(2)—C(3) bond in radical anion **A** (Scheme 3) produced by the reaction of the radical anion derived from the aromatic aldehyde with diketone **1**. This reaction might be a chain process in which the alkoxide anion acts only as the initiator. Further transformations involve rearrangement of intermediate **A** to radical anion **B** and the reaction of the latter with ArCHO to give products **2a—c** with the generation of a new radical anion of the aromatic aldehyde, which continues the chain.

This scheme is supported by the following facts: the yields of compounds **2a—c** (see Table 1) increase on going from anisaldehyde to *p*-nitrobenzaldehyde, which is matched by the ease of the formation of the radical anions of aromatic aldehydes, and when the reaction is carried out in the resonator of an ESR spectrometer, the resonance signal of a free radical is detected.

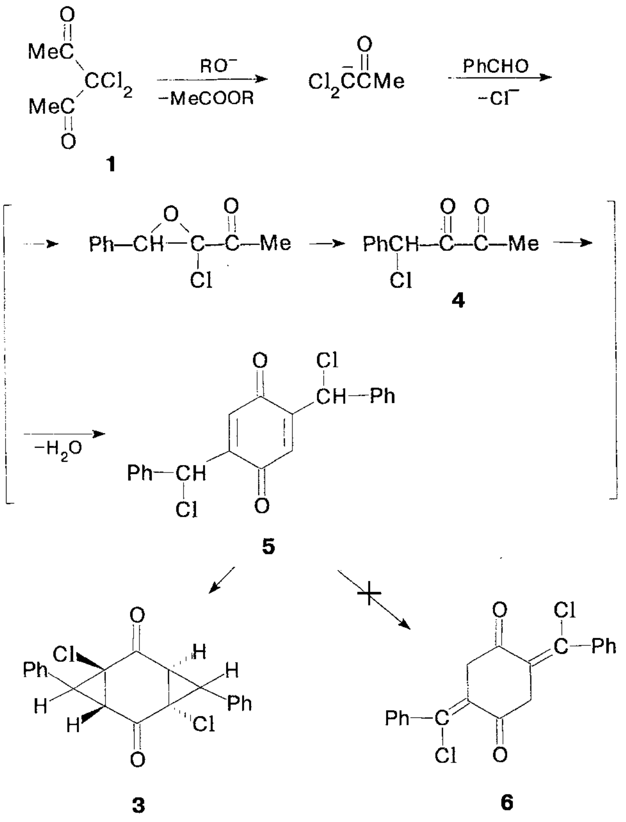
The second (side) reaction pathway is heterolytic cleavage of the C(2)—C(3) bond (or the equivalent C(3)—C(4) bond) in diketone **1** through the action of RO^- to give dichloroacetonyl anion, whose interaction with benzaldehyde yields the normal product of the Darzens reaction, *viz.*, 1-chloro-1-phenylbutane-2,3-dione (**4**). Cyclocondensation of the latter in the presence of the base affords tricyclooctane **3** (Scheme 4).

If the dichloroacetonyl anion can be generated by the reaction of aldehyde with both EDCA[5] and diketone, one should expect that the reaction involving diketone **1**, would give 2,5-bis(chlorobenzylidene)cyclohexane-

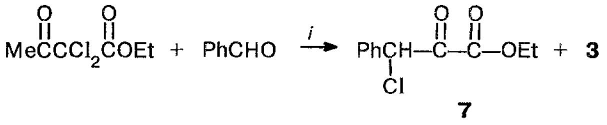
Scheme 3



Scheme 4



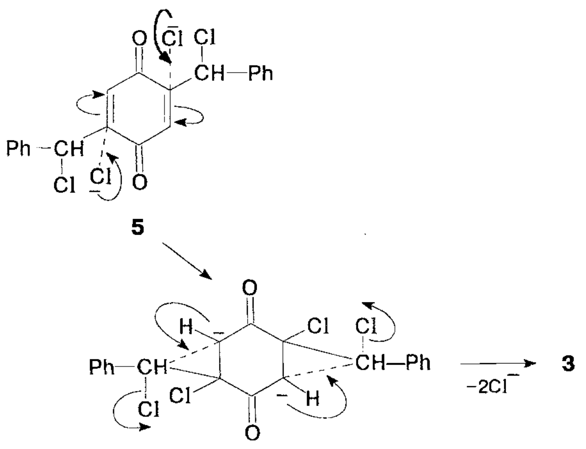
1,4-dione (**6**), described by A. Takeda *et al.*,[5] rather than tricyclooctane **3**, as a minor product; and compound **6** differs from compound **3** in melting point and the ^{1}H NMR spectrum. The repeated study of the reaction of EDCA with benzaldehyde carried out by us confirmed that ethyl 3-chloro-3-phenyl-2-oxopropionate (**7**) is its major product (*cf.* with the data of Ref. 5). However, the compound isolated as the minor product corresponds in its spectral characteristics to tricyclooctane **3**, rather than to cyclohexanedione **6**.



i. EtONa, ether

It is likely that the reaction of EDCA or diketone **1** with aldehydes does not involve mere isomerization of the quinone intermediate **5** to compound **6**, as has been suggested by A. Takeda *et al.*[5] Instead, a two-step process occurs that begins with the attack on the C(2) and C(5) atoms of quinone **5** by the chloride anion and ends with intramolecular cyclization (Scheme 5).

Scheme 5



Experimental*

Melting points were determined on a Boetius hot-stage apparatus. The ^{1}H NMR spectra of compounds **2a—c** and **7** were recorded on a Varian-60 instrument operating at 60 MHz. The ^{13}C NMR spectra of compounds **2a—c**, the ^{1}H and ^{13}C NMR spectra of compound **3**, and the ^{1}H NMR spectrum of compound **4** were recorded on a Bruker MSL-400 instrument operating at 400.13 MHz (for ^{1}H) or 100.6 MHz (for ^{13}C). The IR spectra were measured on a UR-20 spectrophotometer (in vaseline oil).

X-ray structural study of compound 3, $C_{20}H_{14}Cl_2O_2$. The crystals are monoclinic; at 20 °C, a = 9.121(2), b = 8.921(3), c = 10.921(4) Å, β = 113.68(2)°, V = 813.8(5) Å^3, d_{calc} = 1.46 g/cm^3, Z = 2, space group $P2_1/n$ (the molecule is in a partial position in the center of symmetry).

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* Kazan' State University student O. O. Charyev participated in the synthesis of the compounds.

The unit cell parameters and intensities of 2237 reflections were measured on a ENRAF-NONIUS CAD-4 automatic four-circle diffractometer (λMoK_α, graphite monochromator, $\omega/2\theta$-scanning, $2\theta_{max} = 58°$).

The structure was solved by the direct method using the MULTAN program and refined initially in the isotropic approximation, and then in the anisotropic approximation. All of the H atoms were identified from the differential series, and their contributions to structural amplitudes were taken into account in the final cycles of the refinement with fixed positional and isotropic thermal parameters ($B_{iso} = 6$ Å^2). The final value of the residual factor: $R = 0.029$ over 1168 reflections with $F^2 \geq 4\sigma(F)$ (the unit weight scheme was used).

The atomic coordinates are presented in Table 4, the main geometric parameters are listed in Table 3. The geometry of the molecule is shown in Fig. 1.

4-Acetoxy-3,3-dichloro-4-phenylbutan-2-one (2b). At −20 to −15 °C, powdered MeONa (0.1 mol), prepared by dissolution of Na (2.3 g) in 25 mL of anhydrous methanol followed by removal of MeOH *in vacuo*, was added over a period of 30 min to a solution of 3,3-dichloropentane-2,4-dione (16.8 g, 0.1 mol) and benzaldehyde (10.6 g, 0.1 mol) in 100 mL of dry ether stirred in an argon atmosphere. The reaction mixture was stirred at 0 °C for an additional 1.5 h, boiled for 1 h, cooled, and poured in 1.5 L of ice-cooled water. The crystals precipitated were filtered off, washed with ether, dried in air, and recrystallized from DMSO to give 1.6 g (9.1 %) of compound **3**. M.p. 236—237 °C. ^{1}H NMR (DMSO-d_6), δ: 3.59 (d, 2 H, H(4) and H(8)); 4.15 (d, 2 H, H(3) and H(7), $^3J_{H(7)H(8)} = {}^3J_{H(3)H(4)} = 7.26$ Hz); 7.55 (br.s, 10 H, 2 Ph). ^{13}C NMR, δ: 39.2 (d, C(4) and C(8), $^1J_{CH} = 165.0$ Hz); 41.63 (d, C(3) and C(7), $^1J_{CH} = 174.7$ Hz); 55.2 (s, C(1) and C(5)); 132.2, 132.3, 133.2, 135.4 (Ph); 195.7 (s, C(2) and C(6)). IR (ν/cm^{-1}): 680, 700, 760, 865, 945, 1030, 1050, 1110, 1120, 1240, 1295, 1380, 1460, 1470, 1710, 3070.

The ethereal filtrate was washed with water several times and dried with $MgSO_4$. After removal of the ether, the residue was distilled in an oil-pump vacuum to yield compound **2b** (see Table 1).

The reaction of 3,3-dichloropentane-2,4-dione **1** (16.8 g, 0.1 mol), benzaldehyde (10.6 g, 0.1 mol), and MeONa (0.05 mol) carried out in a similar way gave 1.5 g (8.3%) of compound **3** and 8.8 g (32%) of compound **2b**. The use of 0.2 mol of MeONa resulted in 1.7 g (9.6%) of compound **3** and 8.4 g (28%) of compound **2b**.

2,4-Dinitrophenylhydrazone of ketone 2b was obtained in 82 % yield, m.p. 169—173 °C (from ethyl acetate). Found (%): C, 47.59; H, 3.30; Cl, 15.61; N, 11.65. $C_{18}H_{16}Cl_2N_4O_6$. Calculated (%): C, 47.50; H, 3.51; Cl, 16.57; N, 12.30. IR (ν/cm^{-1}); 940, 1045, 1120, 1295, 1320, 1350, 1380, 1460, 1510, 1590, 1620, 1740, 3305. ^{1}H NMR (CD_3CN), δ: 10.93 (br.s, 1 H, NH); 9.00 (d, 1 H, H(3), $^4J_{H(3)H(5)} = 2.6$ Hz); 8.38 (d.d, 1 H, H(5), $^3J_{H(5)H(6)} = 9.6$ Hz); 7.85 (d, 1 H, H(6)); 7.7—7.4 (m, 5 H, Ph); 6.76 (s, 1 H, CH—O); 2.40 (s, 3 H, MeC=O); 2.01 (s, 3 H, MeC=N).

^{1}H NMR (DMF-d_7): 9.06 (d, 1 H, H(3), $^4J_{H(3)H(5)} = 2.4$ Hz) and 9.00 (d, 1 H, H(3), $^4J_{H(3)H(5)} = 2.6$ Hz); 8.77 d.d and 8.52 d.d (1 H, H(5), $^3J_{H(5)H(6)} = 9.5$ Hz); 8.10 d and 7.91 d (1 H, H(6)); 2.54 s and 2.29 s (3 H, Me); 2.18 s and 2.13 s (3 H, Me).

4-Acetoxy-3,3-dichloro-4-(4′-nitrophenyl)butan-2-one (2a) and 4-acetoxy-3,3-dichloro-4-(4′-methoxyphenyl)butan-2-one (2c) were prepared similarly to compound **2b** (see Table 1).

Conducting the reaction in the presence of EtONa or using benzene or a mixture of ether with benzene, instead of ether, had no effect on the result of the reaction.

Reaction of ethyl dichloroacetate with benzaldehyde. The reaction was carried out according to the previously reported procedure.[5] EtONa was added at 0—5 °C to a solution of EDCA (19.9 g, 0.1 mol) and benzaldehyde (10.6 g, 0.1 mol) in 200 mL of anhydrous ether in several portions, and the mixture was boiled for 2 h. The crystals obtained were dried in air and recrystallized from DMSO to give compound **3**, yield 5.6 %, m.p. 237 °C (*cf.*: m.p. 218 °C).[6] A mixed sample with tricyclooctanedione **3** prepared from **1** exhibited no depression of melting point. M.p. 236—237 °C. The ethereal layer was dried with $MgSO_4$, and the solvent was removed *in vacuo*. Recrystallization of the residue afforded compound **7**, yield 37 %, b.p. 110—115 °C (0.01 Torr), *cf.* lit:[8] 110—115 °C (0.01 Torr). ^{1}H NMR (CCl_4), δ: 1.25 (t, 3 H, $OCH_2\underline{CH_3}$); 4.20 (q, 2 H, $O\underline{CH_2}CH_3$); 6.00 (s, 1 H, CHCl); 7.26 (s, 5 H, Ph).

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