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The Reaction of Aldehydes with Dichloroacetate

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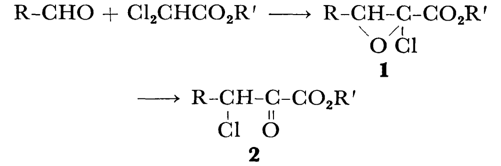
Base-catalyzed condensation of aldehydes with dichloroacetic ester has been reported by several workers.[1-3] Martynov and Titov[1] described that the condensation of benzaldehyde with methyl dichloroacetate in the presence of sodium methoxide afforded methyl 2-chloro-2,3-epoxy-3-phenylpropionate (**1**, $R=C_6H_5$, $R'=CH_3$). McDonald and Schwab,[2] on the contrary, assigned the structure of methyl chlorophenylpyruvate (**2**, $R=C_6H_5$, $R'=CH_3$) instead of **1** to the product of the above reaction suggesting that an anionotropic rearrangement of the intermediate **1** to form **2** has occurred. We also were unsuccessful in isolating aromatic homologs of **1** by the same reaction but obtained the corresponding arylpyruvic esters.[3] Meanwhile, the base-catalyzed cyclization of α,α-dichloro-β-hydroxyalkanecarboxylic esters to yield α-chloroglycidic esters (**1**) has been reported by Castro *et al.* recently.[4] Hence the success of the isolation of intermediate glycidates in these reactions seems largely dependent on their stability. In our attempt to prepare several alkyl-substituted chloropyruvates (**2**, R=alkyl) by the title reaction a mixture of **1** and **2** was formed in the varying ratios of the products depending on the conditions, *e.g.* temperature. In this paper we wish to report the Darzens type condensation of aliphatic aldehydes with dichloroacetic ester to afford **1** and the acid-catalyzed transformation of **1** and **2**.



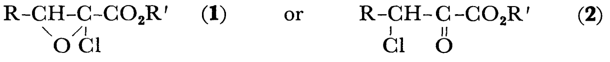
$$\mathrm{R\text{-}CHO + Cl_2CHCO_2R' \longrightarrow R\text{-}\underset{\diagdown O \diagup\,Cl}{CH\text{-}C}\text{-}CO_2R'}\quad \mathbf{1}$$

$$\longrightarrow \mathrm{R\text{-}\underset{\overset{|}{Cl}}{CH}\text{-}\underset{\overset{\|}{O}}{C}\text{-}CO_2R'}\quad \mathbf{2}$$

Structural assignments are based on IR spectra, NMR spectra, and analyses. Yields, physical properties, and analyses of the products are summarized in Table 1.

Heptanal, octanal, and nonanal gave only the rearranged products (**2**) in the present reaction, while the aldehydes such as acetaldehyde, propionaldehyde, isobutyraldehyde, and 2-phenylpro-

TABLE 1. PRODUCTS FROM THE REACTION OF ALIPHATIC ALDEHYDES



$$\mathrm{R\text{-}\underset{\diagdown O \diagup\,Cl}{CH\text{-}C}\text{-}CO_2R'}\ (\mathbf{1}) \quad \text{or} \quad \mathrm{R\text{-}\underset{\overset{|}{Cl}}{CH}\text{-}\underset{\overset{\|}{O}}{C}\text{-}CO_2R'}\ (\mathbf{2})$$

Compound[a]	Product		Yield, %	Bp, °C/mmHg	Found, %		Calcd, %	
	R	R'			C	H	C	H
1a	CH_3	CH_3	31.6	75—78/16	39.78	4.39	39.88	4.69
1b	C_2H_5	CH_3	31.6	93—95/24	43.78	5.79	43.78	5.51
1c	C_2H_5	C_2H_5	24.5	94—98/18	46.78	6.26	47.07	6.21
1d and **2a**	n-C_3H_7	C_2H_5	34.8[b]	96—97/12	50.09	6.84	49.88	6.80
1e	$(CH_3)_2CH$	CH_3	67.9	92—93/16	46.94	6.40	47.07	6.21
1f	$(CH_3)_2CH$	C_2H_5	32.6	104—106/20.5	49.74	7.04	49.88	6.80
1g	$CH_3(C_6H_5)CH$	CH_3	45.3	125—127/2	59.72	5.14	59.88	5.44
2b	n-C_6H_{13}	C_2H_5	45.5	134—136/13	56.29	8.37	56.28	8.16
2c	n-C_7H_{15}	C_2H_5	53.3	123—125/4	58.22	8.74	57.94	8.51
2d	n-C_8H_{17}	C_2H_5	50.3	125—128/3	59.20	9.01	59.42	8.82

a) Compounds excepting **1f** are new.

b) The presence of two components (**1d** and **2a**) in equal portions was detected, roughly estimated by the comparison of TLC spot areas [Merck Silica Gel G; Acetone—n-Hexane (1 : 5). $R_f=0.76$ (**1d**); 0.36 (**2a**).].

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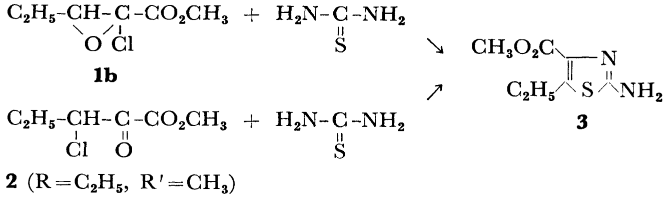
1) V. F. Martynov and M. I. Titov, *Zh. Obshch. Khim.*, **32**, 319 (1962); *Chem. Abstr.*, **57**, 12373c (1962).

2) R. N. McDonald and P. A. Schwab, *J. Org. Chem.*, **29**, 2459 (1964).

3) A. Takeda, S. Wada, and T. Uno, *Mem. School Eng., Okayama Univ.*, **2**, 80 (1967).

4) B. Castro, J. Villieras and N. Ferracutti, *Compt. Rend., (C)*, **267**, 1502 (1968).



pionaldehyde yielded the intermediate α-chloroglycidic esters (**1**) predominantly. It has been occasionally observed that the conversion of **1** to **2** has occurred partly in the reactions of butyraldehyde, and propionaldehyde with dichloroacetate. α-Chloroglycidic esters (**1**) listed in Table 1 were treated with dry hydrogen chloride in ether at 0°C to investigate the facility of the epoxy-carbonyl rearrangement.[5] Methyl 2-chloro-2,3-epoxyvalerate (**1b**) was thus converted readily to methyl 3-chloro-2-oxovalerate (**2**, $R=C_2H_5$, $R'=CH_3$) in 40.0% yield. On the other hand, an attempt to convert methyl 2-chloro-2,3-epoxy-4-methylvalerate (**1e**) in the same manner resulted in the recovery of the unchanged starting material. The treatment of ketones such as acetone, 3-heptanone, and acetophenone with dichloroacetate gave a small amount of product in each case, but we failed to detect any appreciable amount of either epoxyesters or pyruvates. Sodium methoxide was of no use in effecting the epoxy-carbonyl rearrangement of **1b**.

To establish the correlation in chemical properties of **1** and **2**, methyl 2-chloro-2,3-epoxyvalerate (**1b**) was heated under reflux with equimolar amount of thiourea in methanol. It afforded 2-amino-5-ethyl-4-methoxycarbonylthiazole (**3**) in a yield of 72.6%. This compound was prepared alternatively[6] by the reaction of methyl 3-chloro-2-oxovalerate (**2**, $R=C_2H_5$, $R'=CH_3$) with thiourea under the same condition in 71.4% yield.

Experimental[7]

The following experiments are shown as a typical run.

Methyl 2-Chloro-2,3-epoxyvalerate (1b). Dry powdered sodium methoxide (13.5 g, 0.25 mol) was added gradually to a mixture of propionaldehyde (11.6 g, 0.2 mol) and methyl dichloroacetate (28.4 g, 0.2 mol) dissolved in dry ether (100 m*l*) at 0±1°C. The resulting mixture was stirred at room temperature for 3 hr and treated with water. The ethereal extract was washed several times with water and dried ($MgSO_4$). After removal of the solvent it was distilled giving 9.4 g (31.6%) of **1b**: bp 93—95°C/24 mmHg; IR (cm^{-1}, liquid) 1750 (ester C=O); NMR (τ, $CDCl_3$) 6.60 (t, 1H, $J=10$ Hz, $\underset{\diagdown O \diagup}{-CH-CCl}$).

Methyl 2-Chloro-2,3-epoxy-4-methylvalerate (1e). This product was prepared by the condensation of isobutyraldehyde (14.4 g, 0.2 mol) and methyl dichloroacetate (28.4 g, 0.2 mol) in the presence of dry sodium methoxide (13.5 g, 0.25 mol) in dry ether (100 m*l*), yield 24.2 g (67.9%): bp 92—93°C/16 mmHg; IR (cm^{-1}, liquid) 1750 (ester C=O); NMR (τ, $CDCl_3$) 6.99 (d, 1H, $J=15$ Hz, $\underset{\diagdown O \diagup}{-CH-CCl}$).

Ethyl 3-Chloro-2-oxononanoate (2b). To a mixture of heptanal (11.4 g, 0.1 mol) and ethyl dichloroacetate (15.7 g, 0.1 mol) dissolved in anhydrous ether (50 m*l*) dry sodium ethoxide (8.5 g, 0.125 mol) was added at 0±1°C during the course of 1 hr, with stirring. The stirred mixture was allowed to warm up to room temperature and then refluxed for 2 hr. The ethereal layer was washed with water several times cautiously, dired ($MgSO_4$), and concentrated. The residue was distilled to give 10.7 g (45.5%) of **2b**: bp 134—136°C/13 mmHg; IR (cm^{-1}, liquid) 1760 (shoulder, keto C=O) and 1735 (ester C=O); NMR (τ, $CDCl_3$) 5.06 (t, 1H, $J=11.2$ Hz, $-CHCl-\underset{|}{C}=O$).

Methyl 3-Chloro-2-oxovalerate (**2**, $R=C_2H_5$, $R'=CH_3$). Methyl 2-chloro-2,3-epoxyvalerate (5.0 g, 0.03 mol) was treated for 5 hr with the stream of dry hydrogen chloride in dry ether (50 m*l*) at 0°C. The ethereal layer was washed with water, dried ($MgSO_4$), concentrated, and distilled to give 2.0 g (40.0%) of the product: bp 77—79°C/13 mmHg; IR (cm^{-1}, liquid) 1760 (shoulder, keto C=O) and 1735 (ester C=O).

Found: C, 43.39; H, 5.32%. Calcd for $C_6H_9ClO_3$: C, 43.78; H, 5.51%.

2-Amino-5-ethyl-4-methoxycarbonylthiazole (3). *(a) From* ***1b*** *and Thiourea.* A mixed solution of **1b** (3.3 g, 0.02 mol) and thiourea (1.5 g, 0.02 mol) in methanol (15 m*l*) was refluxed for 18 hr. The mixture was diluted with water and was made alkaline with aqueous ammonia to yield 2.7 g (72.6%) of the crude product: mp 131—133°C (from benzene); IR (cm^{-1}, nujol) 3400, 3200, 3100, 1690, 1610, 1555, and 1225.

Found: C, 45.36; H, 5.49; N, 14.65%. Calcd for $C_7H_{10}N_2O_2S$: C, 45.14; H, 5.41; N, 15.05%.

(b) From Methyl 3-Chloro-2-oxovalerate and Thiourea. A mixture of methyl 3-chloro-2-oxovalerate (2.5 g, 0.015 mol) and thiourea (1.1 g, 0.015 mol) dissolved in methanol (12 m*l*) was refluxed for 19 hr. The reaction mixture treated similarly as in (a) gave 2.0 g (71.4 %) of the same product as above: mp 131—133°C.

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[5] M. Mousseron, F. Winternitz, and R. Jacquier, *Compt. Rend.*, **223**, 1014 (1946); *Chem. Abstr.*, **41**, 2008a (1947).

[6] H. Erlenmeyer and Ch. J. Morel, *Helv. Chim. Acta*, **25**, 1073 (1942).

[7] All the boiling points and the melting points are uncorrected. Elementary analyses were carried out by Mr. Eiichiro Amano and Miss Hiroe Nisino of our laboratory. We are indebted to Dr. Akira Suzuki and Mr. Sigezo Simokawa, both of Hokkaido University, Sapporo, for NMR measurements.