244. Alkoxycarbonyl- and Carboxylate-Group Migrations in the Benzilic Acid Rearrangement of Ethyl Cyclopropane-2,3-dioxopropionate[1])

by **Hans Dahn**[2]), **Lê H. Dao**[3]) and **Rannoo Hunma**

Institut de chimie organique de l'Université de Lausanne, 2, rue de la Barre, CH-1005 Lausanne

(6.X.82)

Summary

In alkaline medium $C_3H_5-CO-C(OH)_2-COOEt$ (**1b**) is transformed into $C_3H_5-C(OH)(COOH)_2$ (**2a**). Labelling experiments show that the cyclopropyl group is not shifted, but only ROOC and/or ^-O_2C groups. GC./MS. and NMR. analysis after incomplete reaction show that both ROOC- and ^-O_2C-groups migrate; at higher pH (*ca.* 14) the ester group rearrangement seems to be more important than at pH *ca.* 9–10.

α,β-Dioxocarboxylic esters form rather stable hydrates in the presence of water; these can be attacked by sufficiently basic nucleophiles, *e.g.* OH^-, at three different positions *(Scheme)*: **A**: at C(1), leading to hydrolysis of the ester group; **B**: at C(2), leading to hydrate-anions which undergo a benzilic acid type rearrangement *via* migration of a ROOC or ^-O_2C group; **C**: at C(3), forming a bishydrate-anion which can be cleaved in a *retro*-aldol-type reaction. Path **C** prevails if the substituent R at C(3) is electron-attracting, *e.g.* aryl of CF_3, favouring the hydration of the *β*-carbonyl group, whereas paths **A** and **B** are used when the hydration of the *β*-carbonyl group is diminished by electron donation (R = alkyl) or by steric effects (R = mesityl) [2]. The balance between paths **A** and **B** depends upon pH: at high pH (*ca.* 14) the hydrate at C(2) is transformed into its anion triggering the migration of COOR′ (**B**), whereas at pH *ca.* 10 the ester group is hydrolysed first, followed by migration of the ^-OOC group [3].

The cyclopropyl group is considerably electron-releasing without important steric constraint, but is at the same time a good migrating group in the benzilic acid rearrangement [4]; so we were interested to see how it influences the balance between reaction paths **A**, **B** and **C**.

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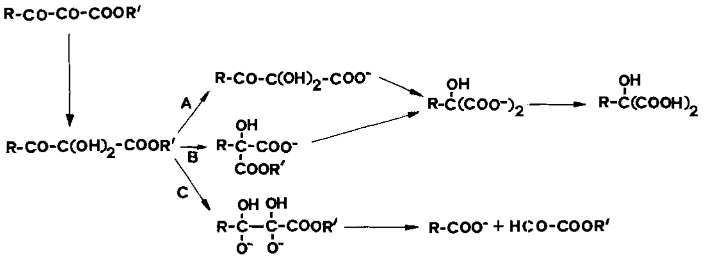
[1]) Reductones and Tricarbonyl Compounds, Part 30. Part 29: [1].

[2]) Author to whom correspondence should be addressed.

[3]) Present address: INRS-Energie, Université du Québec, C.P. 1020, Varennes, Qué., Canada JOL 2PO.

0018-019X/82/8/2458-06$01.00/0

Scheme



We prepared $C_3H_5{-}CO{-}CO{-}COOEt$ (**1b**), a yellow oil, according to [5]; the ^{13}C-labelled substrate [3-^{13}C]-**1b** (**1b***) was prepared in the same way, starting from $C_3H_5{-}^{13}COOH$ [6]. In aqueous solution **1b** is colourless, owing to hydration of the α-carbonyl group; this is borne out by the NMR. spectra: in $CDCl_3$ **1b*** shows in the ^{13}C-NMR. two (labelled) carbonyl signals for C(2), indicating an equilibrium mixture of unhydrated and hydrated **1b**, and correspondingly in the H-NMR. two sets of ethyl protons, but only one $^{13}C(2)$ and one set of ethyl-H signals in D_2O-solution. In the MS. of the mixture the appearance of fragments *m/z* 97 ($C_3H_5{-}CO{-}CO$) and 115 ($C_3H_5{-}CO{-}C(OH)_2$) supports hydration.

Treated with 2N NaOH at RT., **1b** yielded 85% of cyclopropanetartronic acid **2a**. GC./MS. analysis of the methyl esters of the extracted products showed that **2a** was the only acid formed. We did not find glyoxylic acid in the mixture, thus excluding path **C** *(Scheme)*. The diacid **2a** was characterized by its spectra and analysis, by transformation into the dimethyl ester **2c**, and by decarboxylation with hot hydrochloric acid to cyclopropaneglycolic acid (**3**)[4].

$$C_3H_5{-}CO{-}C(OH)_2{-}COOR \xrightarrow[2)\,H^+]{1)\,OH^-} C_3H_5{-}C(OH)(COOR)COOR' \longrightarrow$$

1a R = H
b R = Et
c R = Me

2a R = R' = H
b R = Et; R' = H
c R = R' = Me
d R = Et; R' = Me

$$\rightarrow C_3H_5{-}CHOH{-}COOH \qquad C_3H_5{-}CO{-}COOR \qquad CH_3{-}CO{-}C(OH)_2{-}COOEt$$

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4a R = H
b R = Et
c R = Me

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When the same experiment was performed with **1b*** and the product **2a*** analyzed by ^{13}C-NMR., the label was found exclusively at C(2), proving that the cyclopropyl group had not moved; consequently it was the ROOC- (and/or $^-$OOC-) group that had been shifted. If the cyclopropyl group had migrated, the label would have appeared in a carboxyl group of **2a**.

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[4]) Compound **3** was also formed directly from **1b** by heating with hydrochloric acid, though presumably, as in previous cases [7], *via* a different mechanism [8].

The transformation of **1b** to **2a** comprises rearrangement and ester hydrolysis. At pH *ca.* 14 both reactions are rapid; the transformation of **1b** to **2a** is complete after 5 min at 40° *(Table 2)*. In order to determine the first reaction, *i.e.* whether the ROOC- or the $^{-}O_2C$-group migrates, we interrupted a run after 30 s at 0° in 1 N NaOD/D_2O by neutralization with D_2SO_4, and analysed the mixture by ^{1}H-NMR. Of course it would be difficult to determine simultaneously all five possible constituents (**1a**, **1b**, **2a**, **2b** and ethanol); however the δ of the β-H-atoms of the cyclopropyl group show a difference between the unrearranged structure **1** (1.2 to 1.0 ppm) and the rearranged structure **2** (0.2 to 0.5 ppm) which allows estimation of the overall rearrangement. On the other hand one can estimate the degree of ester hydrolysis by using the difference of OCH_2-signals between ethanol (δ *ca.* 3.65 in aqueous solution) and ethyl esters (δ *ca.* 4.3). After the short reaction time we found 73% rearrangement and 41% hydrolysis, indicating that at pH *ca.* 14 the rearrangement is slightly more rapid than the hydrolysis and that at least part of the reaction proceeds *via* migration of an ester group.

Table 1. *First-order rate constants of the rearrangement of* **1b** (UV. measurements; aqueous KOH/KCl at 40.0° ± 0.1°; μ = 1.0)

pH meas.	$10^2[HO^-]$[a])	$10^3 \cdot k_{obs}(s^{-1})$	pH meas.	$10^2[HO^-]$[a])	$10^3 \cdot k_{obs}(s^{-1})$
12.08	1.20	14.6	12.54	3.47	35.3
12.17	1.48	14.9	12.61	4.07	37.2
12.17	1.48	15.7	12.76	5.75	45.1

[a]) Calculated from pH.

Table 2. *Relative NMR. peak intensities* (in % of total) *of starting material and products during alkaline rearrangement and ester hydrolysis of* **1b** (40°; for conditions see text)

pH 9.6				pH *ca.* 14			
t[min]	**1b,a**	EtOH	**2a,b**	t[min]	**1b,a**	EtOH	**2a,b**
5	86	14	0	5	0	53	47
30	57	40	3	110	0	53	48
72	43	52	5				
205	35	58	8				
4320	0	51	49				

At lower pH (sat. aq. $KHCO_3$-solution, or 1:1 mixture of sat. aq. $KHCO_3$- and K_2CO_3-solutions, pH *ca.* 10) **1b** reacts considerably slower than in N NaOH; in $KHCO_3$-solution after 4 h at 60° 36% of **2a** was isolated[5]). In order to establish the relation of ester hydrolysis to rearrangement for the lower pH too, the reaction was followed in aq. $KHCO_3/K_2CO_3$ (1:1, pH *ca.* 10) by ^{1}H-NMR. using the

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[5]) After treatment at this pH, varying amounts of cyclopropaneglyoxylic acid (**4a**) were found, formed by parallel and/or subsequent reactions. **4a** is stable under the conditions applied.

differences indicated above to estimate the degree of total rearrangement and total hydrolysis. *Table 2* shows that at this pH hydrolysis is faster than rearrangement, as had been found for related substrates [3]. In an experiment in $KHCO_3$-solution the mixture of the acidic products formed, analysed by GC./MS. of the methyl esters, contained small amounts of **1a** (ester hydrolysis without rearrangement) and **2b** (rearrangement without hydrolysis) together with the main product **2a** (rearrangement plus hydrolysis); this shows that both reaction paths **A** and **B** are followed. As the rearrangement requires proton abstraction from the relatively acidic[6]) $C(OH)_2$-group, it is understandable that the rearrangement is lagging when the pH is too low. We conclude that at relatively low pH too the ester and the carboxylate group can both be shifted.

Proof that at the lower pH the rearrangement proceeds by EtOOC- and/or $^-$OOC-group migration and not by shift of a cyclopropyl group was furnished by the use of ^{13}C-label at C(3). Starting with **1b***, the acid derivatives **2a*** as well as **2b***, transformed into the methyl esters **2c*** and **2d*** by diazomethane and analysed by GC./MS., showed the label to be exclusively in the position next to the cyclopropyl group (fragment *m/z* $C_3H_5{}^{13}CO^+$). In conclusion we can state that neither scission by attack on C(3) (path **C**, *Scheme*), nor cyclopropyl group migration have been observed with **1b**, but only ROOC- and $^-$OOC-group shifts.

The rearrangement of **1b** is slower than the same reaction of $CH_3{-}CO{-}C(OH)_2{-}COOEt$ (**5**) [3]; we made some preliminary rate measurements in dilute KOH/KCl-mixtures, at different OH^--concentrations between pH 12 and 12.7 *(Table 1)*, by following in the UV. the decrease of the carbonyl group at C(3); checks by GC./MS. had shown that **2** is the only reaction product, *i.e.* a reaction forming **4** does not take place. The reaction velocity shows a general increase with increasing $[OH^-]$; for this pH-range the overall rate data give a second-order rate constant of $k_{\text{rearr.}} = ca.\ 0.9\ \text{M}^{-1}\text{s}^{-1}$; in the same pH range **5** showed $k_{\text{rearr.}} = 4.4\ \text{M}^{-1}\text{s}^{-1}$ [3]. The cyclopropyl group is better electron-donating than the methyl group, thus diminishing the electron deficiency at the carbonyl group at C(3) and slowing down the rearrangement.

We thank the *Swiss National Science Foundation* for financial support.

Experimental Part

General remarks: see [10]. ^{1}H-NMR.: *Bruker WP-80* (chemical shifts (δ) in ppm from TMS as internal reference). – ^{13}C-NMR.: *Bruker WP-60 (FT)* working at 15.08 MHz (chemical shifts (δ) in ppm from TMS; in aqueous solution dioxane ($\delta = 67.4$) was used as internal reference). GC./MS. analysis were performed on a *Finnigan 1020* with a 20 m *OV-101* capillary column.

Syntheses. – *Cyclopropyl methyl [2-^{13}C]ketone* (method: [11]). A solution of methyllithium (150 mmol) in 100 ml dry ether was added dropwise under an atmosphere of dry N_2 to a solution of 8.0 g (92 mmol) of cyclopropane[^{13}C] acid (90% ^{13}C, prepared from cyclopropylmagnesium bromide and $^{13}CO_2$, following [6]) in 100 ml dry ether. The mixture was decomposed by the addition of a sat. aq. solution of NH_4Cl, the ethereal layer washed and dried and the ether evaporated. The oily residue was

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[6]) The hydrates of simple aliphatic aldehydes and ketones show pK_a *ca.* 13, which drops to *ca.* 10 in the presence of electron-attracting groups like CF_3 [9].

distilled at 110–112°/740 Torr to give 4.7 g (61%); the IR. and ^{1}H-NMR. spectra were identical with those of a non-labelled authentic sample of cyclopropyl methyl ketone.

Ethyl cyclopropane-3-oxo[3-^{13}C]propionate was prepared from 4.5 g cyclopropyl methyl [2-^{13}C]-ketone (53 mmol), 2.0 g $NaNH_2$ and 11 g diethyl carbonate (93 mmol) in 60 ml dry ether, heated 3 h under reflux, following [5]. Yield: 3.4 g (42%) of b.p. 65–67°/2 Torr. – ^{1}H-NMR.: (labelled, $CDCl_3$): 4.15 (*qa*, 2 H); 3.55 (*d*, 2 H); 2.0 (*m*, 1 H); 1.25 (*t*, 3 H); 0.7–1.1 (*m*, 4 H). – ^{13}C-NMR. (labelled, $CDCl_3$ as solvent and internal reference): 202.5 (C(3), labelled); 179.4 (C(1)); 61.3 (CH_2 ester); 50.0 (*d*, $^{1}J(C,C) = 50$ Hz, C(2)); 20.6 (*d*, $^{1}J(C,C) = 60$ Hz, cyclopropyl-C(1)); 14.3 (CH_3); 11.8 (cyclopropyl-C(2)). – MS. (non-labelled; 70 eV): 156 (3); 128 (19); 111 (7); 69 (100).

Ethyl cyclopropane-2,3-dioxo[3-^{13}C]propionate (**1b***). A mixture of 3.0 g (19 mmol) ethyl cyclopropane-3-oxo[3-^{13}C]propionate and 2.1 g selenium dioxide (19 mmol) in 50 ml dioxane was heated under reflux for 2.5 h. After filtering through neutral alumina and eluting with CH_2Cl_2 the solvents were removed *in vacuo* and the residue distilled at 64–67°/2 Torr: 2.0 g (61%) of a yellow liquid; on contact with water it forms a hydrate. – UV. (dioxane): 250 (3200), 420 (27); (ethanol): 288 (109). – ^{1}H-NMR. (CCl_4): 4.38 (2 *qa*, 2 H); 2.67 (*m*, 1 H); 1.38 (*m*, 3 H); 0.9–1.3 (*m*, 4 H). – ^{13}C-NMR. (D_2O): 208.8 (C(3), labelled); 172.3 (C(1)); 82.1 (C(2)hydrated); 59.4, 15.2 (ethyl); 18.7, 4.0 (cyclopropyl). – ^{13}C-NMR. ($CDCl_3$): 203.4, 197.5 (C(3) of hydrated and unhydrated forms, labelled). – MS. of **1b*** (labelled, 70 eV): 171 (1, M^{+}); 143 (9, $M-CO$); 142 (1); 98 (0.3, $M-CO_2C_2H_5$); 70 (100, $C_3H_5{}^{13}CO$); 69 (17); 41 (39, C_3H_5).

$C_8H_{10}O_4 \cdot H_2O$ (188.2, unlabelled) Calc. C 51.06 H 6.43% Found C 50.87 H 6.34%

Cyclopropanetartronic acid (**2a**). A solution of 0.84 g (4.9 mmol) of **1b** (unlabelled) in 25 ml 2N NaOH was kept at 25°. After 4 h it was cooled to 0°, acidified to pH *ca.* 2, saturated with NaCl and extracted with ether. The extracts were dried, the solvent evaporated and the residue recrystallized from ether/petroleum ether: 0.70 g (89%) of **2a**, m.p. 136–138°. – ^{1}H-NMR. ((D_6)acetone): 6.9 (br. *s*, 3 H); 1.4–1.8 (*m*, 1 H); 0.3–0.6 (*m*, 4 H). – ^{13}C-NMR. ((D_6)acetone as solvent and internal reference): 171.8 (C(1,3)); 76.6 (C(2)); 21.2, 12.2 (cyclopropyl). – MS. (CI, CH_4, 100° 150 eV): 161 ($M+1$); 143 ($M+1-H_2O$); 125; 115; 99 ($M+1-CO_2-H_2O$); 69 (C_3H_5CO); 57; 41 (C_3H_5).

$C_6H_8O_5$ (160.1) Calc. C 45.01 H 5.04% Found C 44.92 H 5.22%

Dimethyl ester **2c**. The acid **2a** (300 mg) was esterified with an excess ethereal solution of diazomethane, then distilled at 100°/1.5 Torr: 200 mg. – ^{1}H-NMR. (CCl_4): 3.78 (*s*, 6 H); 1.1–1.8 (*m*, 1 H); 0.4–0.7 (*m*, 4 H). – ^{13}C-NMR. ($CDCl_3$): 171.3 (C(1,3)); 76.8 (C(2)); 53.2 (CH_3); 14.4, 2.5 (cyclopropyl). – MS.: 188 (0.1, M^{+}); 170 (2, $M-H_2O$); 147 (3, $M-C_3H_5$); 129 (99, $M-CO_2CH_3$); 101 (8); 69 (100, C_3H_5CO); 59 (19, CO_2Me).

Cyclopropaneglycolic acid (**3**). A) A solution of 200 mg of diacid **2a** in 5 ml conc. HCl was heated 4 h to 70°. Evolved CO_2 was precipitated as $BaCO_3$: 216 mg (87%). The cooled aqueous solution was diluted with water, sat. with NaCl and extracted with ether. The extract was dried ($MgSO_4$), the solvent evaporated and the residue (142 mg, 90%) recrystallized from CCl_4, m.p. 77–78° ([12]: 77.5–78.5°). – ^{1}H-NMR. ((D_6)acetone): 1.4–1.9 (*m*, 1 H); 1.15 (*d*, 1 H); 0.3–0.6 (*m*, 4 H).

Methyl cyclopropaneglyoxylate (**4c**) was prepared following [13]. – UV. (ethanol): 290 (23; unchanged after 3 days in 0.01M aqueous $KHCO_3$ solution). – ^{1}H-NMR. ($CDCl_3$): 3.85 (*s*, 3 H); 2.7 (*m*, 1 H); 1.2 (*m*, 4 H). – ^{13}C-NMR. ($CDCl_3$ as solvent and internal reference): 194.0 (C(2)); 161.9 (C(1)); 52.8 (CH_3); 18.3, 13.7 (cyclopropyl). – MS.: 128 (3.5, M^{+}); 69 (100, C_3H_5CO); 59 (9, COOMe).

Rearrangement of *1b* (and *1b, respectively).** – A) *At pH ca. 14.* A mixture of 175 mg **1b*** and 3 ml 1.3N NaOD in D_2O were kept at 40° in an NMR. tube with dioxane as internal standard. When all label had disappeared from the 210–170 ppm region of the ^{13}C-NMR. spectra and was only visible at 80.5 ppm (2.5 h), the mixture was acidified and extracted with ether, the ether extract dried, esterified with excess diazomethane and the product isolated. GC. showed only one signal, identical with that of authentic **2c**. – ^{13}C-NMR. ($CDCl_3$): 171.7; 77.1 (labelled); 53.5; 14.3; 4.8 (no label in any position except C(2)). – MS.: 189 (0.1); 171 (0.6); 148 (1.1); 130 (59); 102 (6); 70 (100); 59 (15).

B) *In $KHCO_3$ solution.* – *a)* A mixture of 1.0 g **1b** and 30 ml sat. aq. $KHCO_3$-solution was heated for 4 h at 60°. The cooled mixture was acidified and extracted with ether, the extract dried, the solvent evaporated and the residue recrystallized from acetone/petroleum ether: 0.31 g (36%) of **2a**.

b) A mixture of 250 mg **1b*** and 3 ml of a sat. $KDCO_3$-solution in D_2O was kept at 40°. In the ^{13}C-NMR. spectrum signals at 185.3 and 79.9 ppm appeared, indicating formation of the anion of **2a**, and a signal at 81 ppm, typical for the anion of **2b**, appeared, then diminished again. When no more changes in the 210–190 ppm region of the ^{13}C-NMR. spectrum were observable (7 h), the mixture was cooled. After extraction of neutral products with ether the aq. phase was acidified and extracted with ether, the ethereal extract was dried, the ether evaporated and the residue (123 mg) esterified with excess diazomethane and analysed by GC./MS. It consisted essentially of 3 compounds. *1)* **4c***; MS.: 129 (15); 70 (100, $C_3H_5{}^{13}CO$); 59 (8). *2)* **2c***; MS.: 171 (0.5); 148 (0.9); 130 (40, M^* – COOMe); 70 (100, $C_3H_5{}^{13}CO$); 59 (15). *3)* **2d***; MS.: 203 (0.1, M^{*+}); 144 (M^* – COOMe); 130 (40, M^* – COOEt); 70 (100, $C_3H_5{}^{13}CO$); 59 (15, COOMe). – The ^{13}C-NMR. spectra of the mixture *1–3* ($CDCl_3$) showed signals at 208.2 (C(3) of **1c***); 194.0 (C(2) of **4c***); 175.3 (COOR); 76.6 (C(2) of **2c,d***); 53.1 (Me); 20.1, 16.2, 13.7 (C_3H_5 and CH_3).

c) In a parallel experiment (with unlabelled **1b**), interrupted after 3.5 h at 45°, GC./MS. analysis showed, in addition to the signals of **4c**, **2c** (main component) and **2d**, a minor peak of **1c**. – MS.: 156 (0.6, M^+); 128 (13, M – CO); 97 (0.6, M – COOMe); 69 (100, C_3H_5CO); 59 (15, COOMe).

Kinetics. – A) *By UV.-spectrophotometry* at 290 nm in thermostatted cuvettes at 40.0°±0.1° in a modified *Beckman DU* spectrophotometer. Aqueous stock solutions: *a)* 2M KOH; *b)* 2M KCl; *c)* 0.020M **1b**. For measurements: 1.5 ml of *c* were mixed with 1.5 ml of mixtures of $a+b$ (all solutions prethermostatted); pH-measurements inside the cuvette. After 10 s mixing the absorption measurements were started. Each individual run was linear in first order over at least 3 half-lives. Results see *Table 1.*

B) *By ¹H-NMR. measurements* at 40°. 30 mg of **1b** were mixed with 0.5 ml of either *a)* a sat. solution of $KHCO_3/K_2CO_3$ 1:1 in H_2O (pH *ca.* 10); or *b)* aq. 2N NaOH. Internal standards: CH_3COONa (1.92 ppm) or acetone (2.20 ppm). The pH of the solutions was measured before and after the run. The following signals were followed (determined independently): for **1** (**a** and **b**), 1.18–1.10 (CH_2 of $C_3H_5C{=}O$); for **2** (**a** and **b**), 0.50–0.20 (CH_2 of $C_3H_5{-}C{-}OH$); for ethyl esters (**1b** and **2b**), 4.28 (*qa*, OCH_2); for ethanol, 3.65 (*qa*). Results see *Table 2.*

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