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# Reaction of Reformatsky Reagents with Substituted Alkyl Esters of 2-Oxochromene-3-carboxylic Acid

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**Abstract**—Reformatsky reagents generated from alkyl esters of bromoacetic, α-bromopropionic, α-bromobutyric, and α-bromoisobutyric acids react with alkyl esters of 6,8-dibromo-2-oxochromene-3-carboxylic acid to form alkyl esters of 6,8-dibromo-4-(1-alkoxycarbonylalkyl)-2-oxochromane-3-carboxylic acid.

Proceeding with a search for new ways of functional substitution of heterocycles using organozinc intermediates [1], we studied the reactions of Reformatsky reagents **IIa**–**IId** generated from alkyl esters of bromoacetic, α-bromopropionic, α-bromobutyric, and α-bromoisobutyric acids **Ia**–**Id** with model substrates: methyl and ethyl esters of 6,8-dibromo-2-oxochromene-3-carboxylic acid. The reaction is regiospecific, and the nucleophilic agents attack exclusively the electrophilic $C^4$ atom of the heterocycle to form, via intermediates **IIIa**–**IIIh**, the target products, alkyl esters **IVa**–**IVh** of 6,8-dibromo-4-(1-alkoxycarbonylalkyl)-2-oxochromane-3-carboxylic acids (see table):

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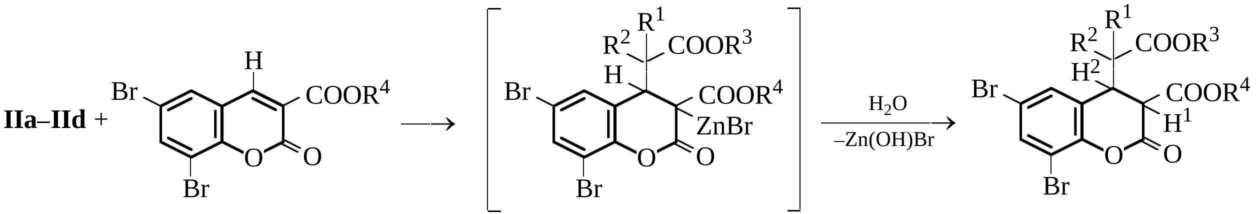
$$\underset{\textbf{Ia–Id}}{R^1R^2CBrCOOR^3} \xrightarrow{Zn} \underset{\textbf{IIa–IId}}{[BrZnCR^1R^2COOR^3]}$$



**IIIa**–**IIIh** **IVa**–**IVh**

**I, II**, $R^1 = R^2 = H$, $R^3 = Me$ (**a**); $R^1 = H$, $R^2 = R^3 = Me$ (**b**); $R^1 = H$, $R^2 = R^3 = Et$ (**c**); $R^1 = R^2 = R^3 = Me$ (**d**). **III, IV**, $R^1 = R^2 = H$, $R^3 = R^4 = Me$ (**a**), Et (**b**); $R^1 = H$, $R^2 = R^3 = R^4 = Me$ (**c**), Et (**d**); $R^1 = H$, $R^2 = R^3 = Et$, $R^4 = Me$ (**e**), Et (**f**); $R^1 = R^2 = R^3 = R^4 = Me$ (**g**), Et (**h**).

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The reaction was performed in low-polarity aprotic solvents (diethyl ether, benzene, ethyl acetate); bromo derivatives **Ia**–**Id** were added to zinc and alkyl 6,8-dibromo-2-oxochromene-3-carboxylate. The reaction success was judged from uniform boiling of the solvent and dissolution of the 2-oxochromene-3-carboxylic acid derivative. The composition and structures of esters **IVa**–**IVh** were proved by elemental analysis and by $^1H$ NMR and IR spectroscopy. The IR spectra contain characteristic absorption bands at 1730–1760 and 1790–1800 cm$^{-1}$ belonging to the exocyclic ester and lactone carbonyl groups, respectively.

Compounds **IVa**–**IVh**, containing chiral centers ($C^3$ and $C^4$ atoms), can exist as stereoisomers **A**–**D**.

In stereoisomer **A**, the nonhydrogen substituents at the $C^3$ and $C^4$ atoms occupy axial positions ($C^3_a$, $C^4_a$). The positions of the substituents in the other isomers are as follows: (**B**) $C^3_a$, $C^4_e$; (**C**) $C^3_e$, $C^4_a$; and (**D**) $C^3_e$, $C^4_e$.

The $^1H$ NMR spectra of **IVa** and **IVc**–**IVh** contain a single set of proton signals, suggesting formation of a single diastereomer (see table).

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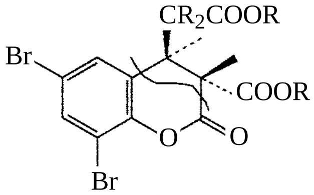
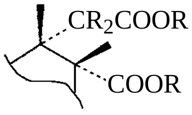
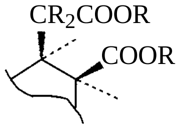


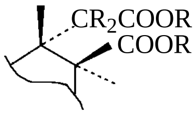
**A**



**B**



**C**

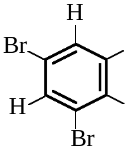


**D**

Yields, melting points, $^1$H NMR spectra, and elemental analyses of alkyl esters **IVa**–**IVh** of 6,8-dibromo-4-(1-alkoxycarbonylalkyl)-2-oxochromane-3-carboxylic acids

| Comp. no. | Yield, % | mp, °C | Solvent | $^1$H NMR spectrum, δ, ppm | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | H$^1$, H$^2$ | R$^1$ | R$^2$ | R$^3$ | R$^4$ | a |
| **IVa** | 56 | 133–134 | CDCl$_3$ | ~3.86 m | 2.56 d (CH$_2$) | | 3.60 s (Me) | | 7.35 s,<br>7.63 s |
| **IVb** | 83 | 84–85 | CDCl$_3$ | ~3.80 m | 2.60–3.40 m (CH$_2$) | | 3.60 s (Me) | 1.10 t,<br>4.10 q (Et) | 7.30 s,<br>7.60 s |
| **IVc** | 47 | 196–197 | CDCl$_3$–DMSO, 1 : 1 | 4.01 s,<br>3.76 d | 2.45–2.80 m (H) | 1.10 d (Me) | 3.60 s (Me) | | 7.43 s,<br>7.66 s |
| **IVd** | 81 | 185–186 | DMSO | 3.98 s,<br>3.72 d | 2.70 m (H) | 1.14 d (Me) | 3.66 s (Me) | 1.10 t,<br>4.10 q (Et) | 7.53 s,<br>7.72 s |
| **IVe** | 77 | 91–92 | DMSO | 4.14 s,<br>3.75 d | 2.54–2.60 m (H) | 1.40–1.50 m, 1.65–1.75, 0.84 t (Et) | 3.95–4.15 m,<br>1.10 t (Et) | 3.62 s (Me) | 7.70 s,<br>7.91 s |
| **IVf** | 50 | 51–52 | CDCl$_3$ | 3.65 s,<br>~3.48 m | 2.10–2.60 m (H) | 1.30–1.80 m, 0.84 d (Et) | 3.70–4.20 m, 0.94 d, 1.04 d (Et) | | 7.20 s,<br>7.60 s |
| **IVg** | 56 | 127–128 | DMSO | 4.20 s,<br>3.73 s | 1.08 s, 1.13 s (Me) | | 3.60 s (Me) | | 7.56 s,<br>7.90 s |
| **IVh** | 82 | 115–116 | DMSO | 4.00 s,<br>3.73 s | 1.16 s, 1.19 s (Me) | | 3.65 s (Me) | 1.10 t,<br>4.09 q (Et) | 7.42 s,<br>7.75 s |

| Comp. no. | Found, % | | Formula | Calculated | |
|---|---|---|---|---|---|
| | C | H | | C | H |
| **IVa** | 38.41 | 2.69 | $C_{14}H_{12}Br_2O_6$ | 38.56 | 2.77 |
| **IVb** | 39.90 | 3.05 | $C_{15}H_{14}Br_2O_6$ | 40.03 | 3.14 |
| **IVc** | 39.95 | 3.02 | $C_{15}H_{14}Br_2O_6$ | 40.03 | 3.14 |
| **IVd** | 41.30 | 3.39 | $C_{16}H_{16}Br_2O_6$ | 41.41 | 3.48 |
| **IVe** | 42.58 | 3.71 | $C_{17}H_{18}Br_2O_6$ | 42.71 | 3.79 |
| **IVf** | 43.81 | 4.10 | $C_{18}H_{20}Br_2O_6$ | 43.93 | 4.10 |
| **IVg** | 41.26 | 3.45 | $C_{16}H_{16}Br_2O_6$ | 41.41 | 3.48 |
| **IVh** | 42.50 | 3.78 | $C_{17}H_{18}Br_2O_6$ | 42.71 | 3.79 |

[a] 

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An additional important feature of the $^1$H NMR spectra at **IVa**–**IVh** is that the H$^1$ signal at 3.65–4.20 ppm is a singlet, i.e., the coupling constant $J_{H^1H^2}$ is negligibly small ($J$ < 2 Hz).

To interpret the results obtained, we calculated the geometries (bond lengths, bond angles, dihedral angles) of the molecules of **IVa**, **IVb**, **IVd**, and **IVg** by the semiempirical SCF MO LCAO method in the

MNDO [2], AM1 [3], and MNDO-PM3 [4] approximations. As follows from the comparison of the calculated (in all the approximations used) enthalpies of formation, stereoisomers of type **A** should be the most stable. Isomers of type **D** of compounds **IVb**, **IVd**, and **IVg** in the course of geometry optimization transformed into more stable isomers **A**.

Stereoisomers **A**–**D** of **IV** differ in the dihedral angles $H^1C^3C^4H^2$; for these angles, the calculations give the values of 83.9° ± 6.2°, 57.3° ± 3.6°, –52.6° ± 5.2°, and –158.4° ± 12.9° for isomers **A**, **B**, **C**, and **D,** respectively. We estimated the vicinal coupling constants $J_{HH}$ in these isomers using the Karplus equation with the Bothner-Bye parameters [5] and obtained the values in the ranges 2.0–2.4, 4.3–5.9, 4.5–5.6, and 9.6–12.8 Hz for isomers **A**, **B**, **C**, and **D**, respectively. Thus, the coupling constant $J_{H^1H^2}$ is small only for isomers **A**. The spectroscopic data in combination with the results of the quantum-chemical calculations suggest that molecules of compounds **IV** exist as diastereomers **A** with axial orientation of the alkoxycarbonyl and alkoxycarbonylalkyl substituents at $C^3$ and $C^4$.

## EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer (neat samples). The $^1$H NMR spectra (solutions in $CDCl_3$ and DMSO-$d_6$) were taken on Bruker (400 MHz for **IVe**, 500 MHz for **IVd** and **IVh**) and RYa-2310 (60 MHz, for **IVa**–**IVc**, **IVf**, and **IVg**) spectrometers.

The quantum-chemical calculations were performed with MOPAC 7.00 program package [6].

**Alkyl esters of 6,8-dibromo-4-(1-alkoxycarbonylalkyl)-2-oxochromane-3-carboxylic acid IVa–IVh.** A 0.026-mol portion of alkyl α-bromoalkanoate was added dropwise with stirring to a mixture of 4 g of finely cut zinc chips and 0.013 mol of an alkyl ester of 6,8-dibromo-2-oxochromene-3-carboxylic acid in 4 ml of diethyl ether and 15 ml of benzene. The mixture was heated to initiate the reaction, after which the reaction occurred spontaneously. After the reaction completion, the mixture was heated for an additional 15 min on a water bath, cooled, hydrolyzed with 5% HCl, treated with benzene, and dried over $Na_2SO_4$; the solvents were removed, and the residue was recrystallized three times from methanol.

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