

Study of Reaction of Reformatsky Reagent Prepared from Methyl Bromocyclopentanecarboxylate and Zinc with 2-Oxochromen- and 6-Bromo-2-oxochromen-3-carboxylic Acids *N*-Arylamides

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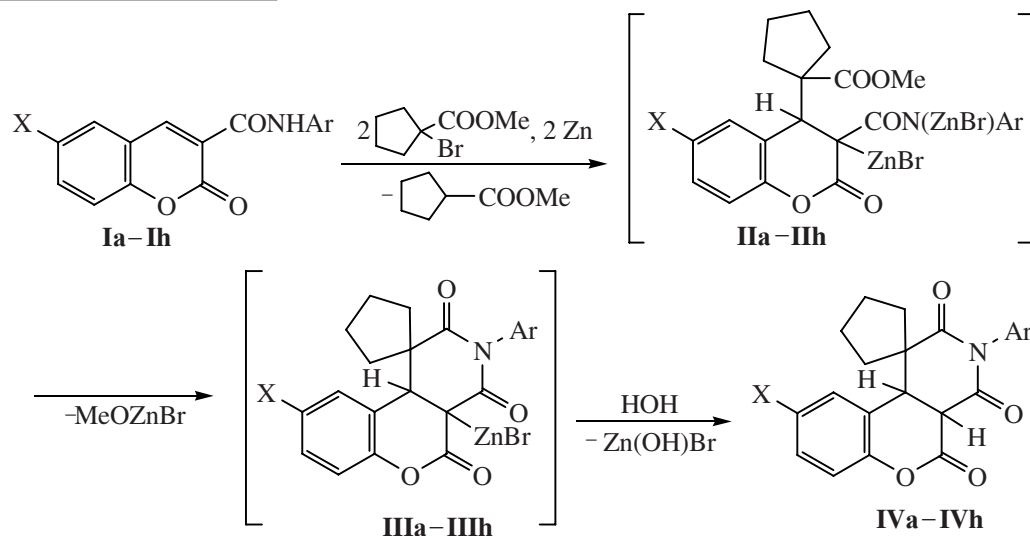
Abstract—Reformatsky reagent prepared from methyl 1-bromocyclopentanecarboxylate and zinc reacted with 2-oxochromen- and 6-bromo-2-oxochromen-3-carboxylic acids *N*-arylamides yielding 3-aryl-1,1-tetramethylene- and 3-aryl-9-bromo-1,1-tetramethylene-2,3,4,4a,5,10b-hexahydro-1*H*-chromeno[3,4-*c*]pyridine-2,4,5-triones as single diastereomers.

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We formerly established that classic Reformatsky reagents reacted with 2-oxochromen-3-carboxylic acids *N*-arylamides providing products of cyclization of the reaction intermediates, substituted 4a,10b-dihydro-1*H*-chromeno[3,4-*c*]pyridine-2,4,5-triones [1].

In the present study we investigated the reactions of organozinc reagent generated from methyl 1-bromocyclopentanecarboxylate and zinc with 2-oxo-chromen- and 6-bromo-2-oxochromen-3-carboxylic acids *N*-arylamides **Ia–Ih**.

It was established that in the first stage the Reformatsky reagent added at the C⁴ atom of electrophilic substrates **Ia–Ih** giving intermediates **IIa–IIh** that by a nucleophilic attack of the amide nitrogen on the carbonyl carbon of the ester group converted into intermediate substances **IIIa–IIIh**. The latter on hydrolysis provide the final products, 3-aryl-1,1-tetramethylene- (**IVa–IVd**) or 3-aryl-9-bromo-1,1-tetramethylene- (**IVe–IVh**) -2,3,4,4a,5,10b-hexahydro-1*H*-chromeno[3,4-*c*]pyridine-2,4,5-triones.



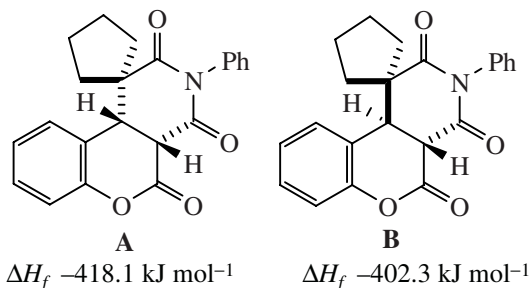
I–IV, X = H, Ar = Ph (**a**), 4-BrC₆H₄ (**b**), 4-MeC₆H₄ (**c**), 4-MeOC₆H₄ (**d**); X = Br, Ar = Ph (**e**), 4-BrC₆H₄ (**f**), 4-MeC₆H₄ (**g**), 4-MeOC₆H₄ (**h**).

[†] Deceased.

The composition and structure of compounds **IVa–IVh** were confirmed by elemental analysis, IR and ^1H NMR spectra. In the IR spectra of compounds **IVa–IVh** appear characteristic absorption bands in the region 1685–1695, 1720–1730 cm^{-1} belonging to carbonyl groups in the imide fragment, and at 1755–1770 cm^{-1} from lactone carbonyls.

^1H NMR spectra show that compounds **IVa–IVh** formed as a single geometrical isomers. The most characteristic feature of ^1H NMR spectra is the presence of two doublet signals in the region 3.65–4.18 and 3.97–4.67 ppm corresponding to protons HC^{10b} and HC^{4a} with a coupling constant 5.6 Hz.

To gain additional information on the structure of compounds synthesized we performed a calculation of 1,1-tetramethylene-3-phenyl-2,3,4,4a,5,10b-hexahydro-1*H*-chromeno[3,4-*c*]pyridine-2,4,5-trione (**IVa**) molecule by semiempirical method SCF MO LCAO in MNDO-PM3 approximation [2]. Compound **IVa** can exist in the form of two diastereomers **A** and **B**.



According to the calculations diastereomer **A** is more stable than diastereomer **B** as follows from the comparison of the enthalpy of formation (ΔH_f).

In the most stable diastereomer **A** the atoms included into the chromen fragment are located virtually in the same plane except C^{4a} deviated from the plane by 0.78 Å. Piperidine fragment forms a chair flattened from one side, and the cyclopentane ring is a distorted envelope.

The calculations show that the dihedral angle $\text{H}-\text{C}^{4a}-\text{C}^{10b}-\text{H}$ in diastereomer **A** is 50.0 and in diastereomer **B** 162.7 deg. The estimated angles values permitted a calculation of the vicinal coupling constant $J_{\text{HC}^{4a}, \text{HC}^{10b}}$ for each diastereomer applying Karplus equation with Bothner-By parameters [3]. Thus calculated coupling constant for diastereomer **A** equaled 5.5 Hz, whereas for diastereomer **B** 12.1 Hz. In the real ^1H NMR spectrum this constant is 5.6 Hz evidencing that compound **IVa** and the other compounds of the synthesized series exist as a single diastereomer of **A** type.

EXPERIMENTAL

IR spectra of individual compounds were recorded from mulls in mineral oil on a spectrophotometer UR-20. ^1H NMR spectra were registered from solutions of compounds **IVa**, **IVc–IVe** in CDCl_3 , of compounds **IVb** and **IVf** in a mixture $\text{CDCl}_3 - \text{DMSO}-d_6$, 1:1, on a spectrometer Tesla BS-567A (100 MHz), from solutions of compounds **IVg** and **IVh** in $\text{DMSO}-d_6$ on a spectrometer Bruker DRX (500 MHz), internal references HMDS and TMS respectively. Quantum-chemical calculations were performed applying a software package MOPAC 7.0 [4].

3-Aryl-1,1-tetramethylene- (IVa–IVd) or 3-aryl-9-bromo-1,1-tetramethylene- (IVe–IVh) 2,3,4,4a,5,10b-hexahydro-1*H*-chromeno[3,4-*c*]pyridine-2,4,5-triones. To 2 g of fine zinc turnings and 8 mmol of 2-oxo- or 6-bromo-2-oxochromen-3-carboxylic acid arylamide in 10 ml of benzene, 5 ml of ethyl ether, and 1 ml of HMPT was added 22 mmol of methyl 1-bromocyclopentanecarboxylate. The mixture was heated till the start of the reaction that then proceeded spontaneously. Then the reaction mixture was heated for 2 h, 3 ml of THF was added, and the heating continued for 2 h more. On cooling the reaction mixture was treated with 5% solution of acetic acid. The organic layer was separated, the water layer was twice extracted with ethyl acetate. The combined organic solutions were washed with water and dried with anhydrous sodium sulfate. On distilling off the solvent the reaction product was twice recrystallized.

1,1-Tetramethylene-3-phenyl-2,3,4,4a,5,10b-hexahydro-1*H*-chromeno[3,4-*c*]pyridine-2,4,5-trione (IVa). Yield 85%, mp 221–222°C (butyl acetate). IR spectrum, cm^{-1} : 1695, 1725, 1770 (CONCO, $\text{CO}_{\text{lactone}}$). ^1H NMR spectrum, δ , ppm: 1.20–2.20 m [8H, $(\text{CH}_2)_4$], 3.66 d (1H, C^{10b}H , J 5.6 Hz), 4.00 d (1H, C^{4a}H , J 5.6 Hz), 6.80 d (J 8 Hz), 7.00–7.35 m (9H, Ar). Found, %: C 73.01; H 5.35; N 3.72. $\text{C}_{22}\text{H}_{19}\text{NO}_4$. Calculated, %: C 73.12; H 5.30; N 3.88.

3-(4-Bromophenyl)-1,1-tetramethylene-2,3,4,4a,5,10b-hexahydro-1*H*-chromeno[3,4-*c*]pyridine-2,4,5-trione (IVb). Yield 94%, mp 222–224°C (toluene). IR spectrum, cm^{-1} : 1685, 1725, 1755 (CONCO, $\text{CO}_{\text{lactone}}$). ^1H NMR spectrum, δ , ppm: 1.18–2.35 m [8H, $(\text{CH}_2)_4$], 3.84 d (1H, C^{10b}H , J 5.6 Hz), 4.18 d (1H, C^{4a}H , J 5.6 Hz), 6.82 d (J 8 Hz), 6.94–7.32 m, 7.43 d (8H, Ar, J 8 Hz). Found, %: C 59.91; H 4.23; Br 17.94; N 3.03. $\text{C}_{22}\text{H}_{18}\text{BrNO}_4$. Calculated, %: C 60.02; H 4.12; Br 18.15; N 3.18.

3-(4-Methylphenyl)-1,1-tetramethylene-2,3,4,4a,5,10b-hexahydro-1H-chromeno[3,4-c]-pyridine-2,4,5-trione (IVc). Yield 83%, mp 210–212°C (benzene). IR spectrum, cm^{-1} : 1685, 1720, 1760 (CONCO, $\text{CO}_{\text{lactone}}$). ^1H NMR spectrum, δ , ppm: 1.15–2.30 m [8H, $(\text{CH}_2)_4$], 2.29 s (3H, CH_3), 3.67 d (1H, C^{10b}H , J 5.6 Hz), 4.01 d (1H, C^{4a}H , J 5.6 Hz), 6.78 d (J 8 Hz), 7.00–7.33 m (8H, Ar). Found, %: C 73.71; H 5.49; N 3.88. $\text{C}_{23}\text{H}_{21}\text{NO}_4$. Calculated, %: C 73.59; H 5.64; N 3.73.

3-(4-Methoxyphenyl)-1,1-tetramethylene-2,3,4,4a,5,10b-hexahydro-1H-chromeno[3,4-c]-pyridine-2,4,5-trione (IVd). Yield 83%, mp 189–190°C (benzene). IR spectrum, cm^{-1} : 1695, 1730, 1770 (CONCO, $\text{CO}_{\text{lactone}}$). ^1H NMR spectrum, δ , ppm: 1.15–2.50 m [8H, $(\text{CH}_2)_4$], 3.67 d (1H, C^{10b}H , J 5.6 Hz), 3.70 s (3H, OCH_3), 4.01 d (1H, C^{4a}H , J 5.6 Hz), 6.79–7.32 m (8H, Ar). Found, %: C 70.46; H 5.34; N 3.67. $\text{C}_{23}\text{H}_{21}\text{NO}_5$. Calculated, %: C 70.58; H 5.41; N 3.58.

9-Bromo-1,1-tetramethylene-3-phenyl-2,3,4,4a,5,10b-hexahydro-1H-chromeno[3,4-c]-pyridine-2,4,5-trione (IVe). Yield 85%, mp 237–238°C (ethyl acetate). IR spectrum, cm^{-1} : 1690, 1730, 1765 (CONCO, $\text{CO}_{\text{lactone}}$). ^1H NMR spectrum, δ , ppm: 1.10–2.55 m [8H, $(\text{CH}_2)_4$], 3.65 d (1H, C^{10b}H , J 5.6 Hz), 3.97 d (1H, C^{4a}H , J 5.6 Hz), 6.92 d (J 8 Hz), 7.07–7.52 m (8H, Ar). Found, %: C 60.21; H 4.19; Br 18.03; N 3.01. $\text{C}_{22}\text{H}_{18}\text{BrNO}_4$. Calculated, %: C 60.02; H 4.12; Br 18.15; N 3.18.

9-Bromo-3-(4-bromophenyl)-1,1-tetramethylene-2,3,4,4a,5,10b-hexahydro-1H-chromeno[3,4-c]-pyridine-2,4,5-trione (IVf). Yield 88%, mp 255–257°C (toluene). IR spectrum, cm^{-1} : 1695, 1725, 1770 (CONCO, $\text{CO}_{\text{lactone}}$). ^1H NMR spectrum, δ , ppm: 1.20–2.35 m [8H, $(\text{CH}_2)_4$], 3.85 d (1H, C^{10b}H , J 5.6 Hz), 4.20 d (1H, C^{4a}H , J 5.6 Hz), 6.85–7.55 m (7H, Ar). Found,

%: C 51.06; H 3.45; Br 30.51; N 2.58; $\text{C}_{22}\text{H}_{17}\text{Br}_2\text{NO}_4$. Calculated, %: C 50.90; H 3.30; Br 30.78; N 2.70.

9-Bromo-3-(4-methylphenyl)-1,1-tetramethylene-2,3,4,4a,5,10b-hexahydro-1H-chromeno[3,4-c]-pyridine-2,4,5-trione (IVg). Yield 72%, mp 243–244°C (toluene). IR spectrum, cm^{-1} : 1685, 1725, 1755 (CONCO, $\text{CO}_{\text{lactone}}$). ^1H NMR spectrum, δ , ppm: 1.25–2.40 m [8H, $(\text{CH}_2)_4$], 2.34 s (3H, CH_3), 4.18 d (1H, C^{10b}H , J 5.6 Hz), 4.67 d (1H, C^{4a}H , J 5.6 Hz), 6.92 d, 7.21 d, 7.25 d, 7.64 s, 7.66 d (7H_{arom} , J 8 Hz). Found, %: C 60.96; H 4.55; Br 17.88; N 2.96. $\text{C}_{23}\text{H}_{20}\text{BrNO}_4$. Calculated, %: C 60.81; H 4.44; Br 17.59; N 3.08.

9-Bromo-3-(4-methoxyphenyl)-1,1-tetramethylene-2,3,4,4a,5,10b-hexahydro-1H-chromeno[3,4-c]-pyridine-2,4,5-trione (IVh). Yield 70%, mp 204–205°C (ethyl acetate). IR spectrum, cm^{-1} : 1690, 1725, 1760 (CONCO, $\text{CO}_{\text{lactone}}$). ^1H NMR spectrum ($\text{DMSO}-d_6$), δ , ppm: 1.23–2.41 m [8H, $(\text{CH}_2)_4$], 3.79 s (3H, OCH_3), 4.16 d (1H, C^{10b}H , J 5.6 Hz), 4.66 d (1H, C^{4a}H , J 5.6 Hz), 6.97 d, 6.99 d, 7.21 d, 7.64 s, 7.66 d (7H_{arom} , J 8 Hz). Found, %: C 58.68; H 4.11; Br 17.18; N 3.09. $\text{C}_{23}\text{H}_{20}\text{BrNO}_5$. Calculated, %: C 58.74; H 4.29; Br 16.99; N 2.98.

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