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Reaction of Zinc Enolates Prepared from 2,2-Dibromoindan-1-one or 2,2-Dibromo-1-tetralone and Zinc with 2-Oxochromen-3-carboxylic Acid Derivatives

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Abstract—Zinc enolates obtained from 2,2-dibromoindan-1-one or 2,2-dibromo-1-tetralone and zinc reacted with alkyl esters and amides of 2-oxochromen-3-carboxylic acid giving the corresponding derivatives of 2,1'-dioxospiro(1a,7b-dihydrocyclopropa[*c*]chromen-1,2'-indan)- or 1',2',3',4'-tetrahydro-2,1'-dioxospiro(1a,7b-dihydrocyclopropa[*c*]chromen-1,2'-naphthalene)-1a-carboxylic acids prevailingly in the form of a single geometric isomer.

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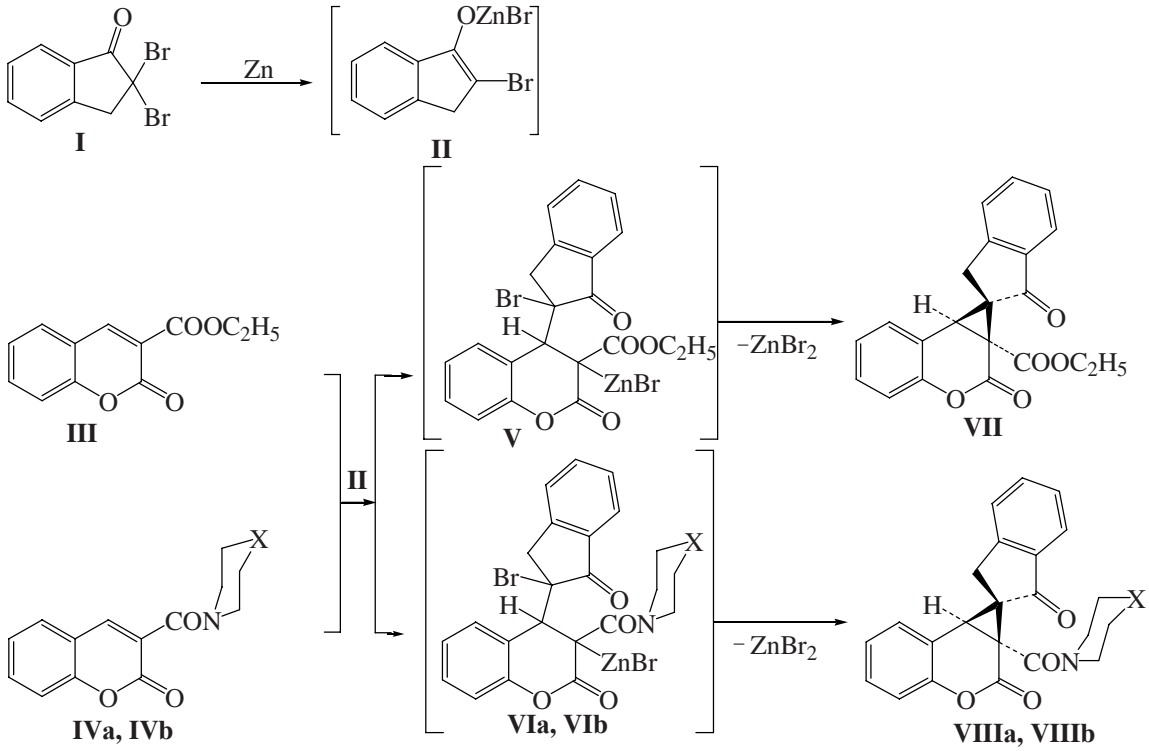
Formerly studying the reaction of bromine-containing zinc enolates obtained from 1-aryl-2,2-dibromoalkanones and zinc with 2-oxochromen-3-carboxylic acid derivatives we isolated cyclopropanation products, 1α-substituted 1-alkyl-1-aroyl-1α,7β-dihydrocyclopropa[*c*]-chromen-2-ones, as a single isomer where the alkyl group and the methine proton were located on different sides of the three-membered ring plane [1]. Planning to prepare

Scheme 1.



X = CH_2 (**a**), O (**b**).

† Deceased.

new types of cyclopropanated chromenes containing a spiro carbon we investigated reactions of zinc enolates **II** and **X** obtained from 2,2-dibromoindan-1-one (**I**) or 2,2-dibromo-1-tetralone (**IX**) and zinc with alkyl esters **IIIa** and **IIIb** and amides **IVa, IVb**, and **XII** of 2-oxochromen-3-carboxylic acid.

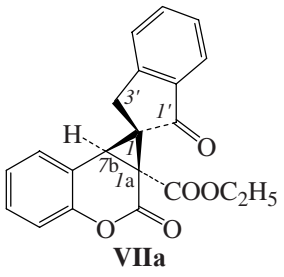
The experiments demonstrated that zinc enolate **II** reacted with ethyl **III** and secondary amides **IVa** and **IVb** of 2-oxochromen-3-carboxylic acid along Scheme 1.

Zinc enolate **II** in a mixture ether–ethyl acetate attacked with its soft nucleophilic center substrates **III**, **IVa**, and **IVb** at the position C^4 of heterocycles leading to the formation of intermediates **V, VIa**, and **VIb** which under the conditions of the reaction underwent spontaneous cyclization providing the final reaction products: ethyl ester **VII** and secondary amides **VIIIa** and **VIIIb** of 2,1'-dioxospiro(1a,7b-dihydrocyclopropa-[*c*]chromen-1,2'-indan)-1a-carboxylic acid.

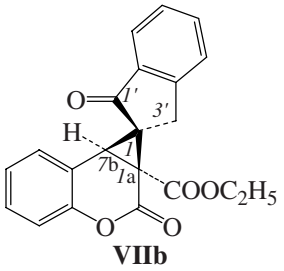
The composition and structure of compounds **VII**, **VIIIa** and **VIIIb** were confirmed by elemental analyses, ^{1}H NMR and IR spectra. The IR spectrum of compound **VII** contains characteristic absorption bands (ν, cm^{-1}) of keto (1725), ester (1745), and lactone (1755) groups. In the ^{1}H NMR spectrum appears a characteristic singlet of methine proton at 3.71 ppm. After one recrystallization from methanol we isolated a mixture of two isomers of the target compound **VII** in a 3:1 ratio; the signal of methine proton belonging to minor isomer was observed at 3.55 ppm. In the IR spectra of compounds **VIIIa** and **VIIIb** appear characteristic absorption bands (ν, cm^{-1}) of carbonyls from amide (1660), keto (1725–1730), and lactone (1755–1760) groups. In the ^{1}H NMR spectrum appear characteristic singlets of methine proton at 3.71 ppm. A single set of signals evidences that compounds **VIIIa** and **VIIIb** were isolated as a unique geometric isomer, and the identical chemical shifts of the methine protons in compounds **VIIIa** and **VIIIb** and the major isomer of compound **VII** suggest the similarity of their geometric structure.

To confirm the structure and to establish the spatial arrangement of the reaction products we investigated the mixture of isomers **VIIa** and **VIIb** by means of ^{1}H and ^{13}C NMR spectroscopy including 2D experiments COSY, NOESY, HSQC, HMBC.

The stereoconfiguration of the cyclopropane fragment was proved by the nuclear Overhauser effect. In the spectrum 2D NOESY of the prevailing isomer **VIIa** the H^{7b} proton had a cross-peak only with the aromatic proton



VIIa

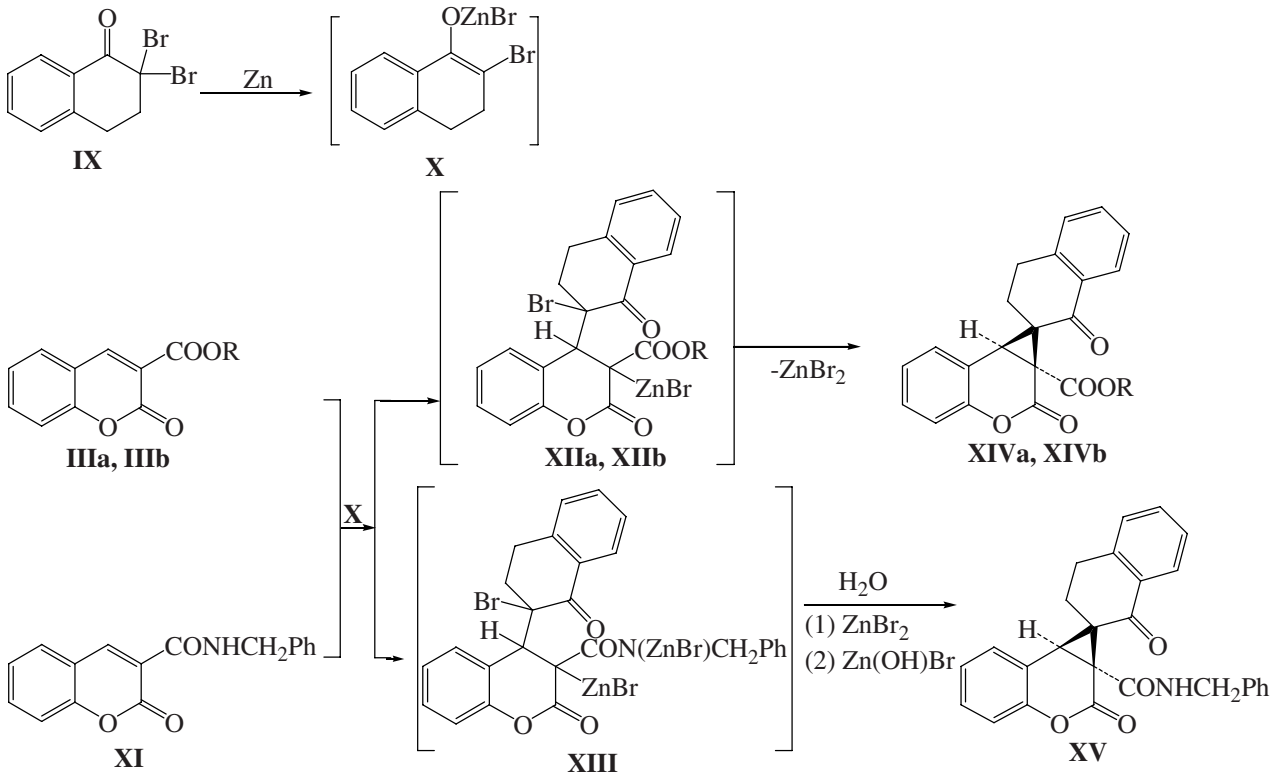


VIIb

H^7, whereas in the minor isomer **VIIb** beside this cross-peak another one was observed with an upfield proton from the *AB* system of the methylene protons at $C^{3'}$. These data suggest a conclusion that in compound **VIIa** the methine proton and the methylene group of the indan fragment are located in *trans*-position to each other, and in compound **VIIb**, in *cis*-position. The partial overlapping of signals prevented the complete assignments of resonances in the ^{1}H and ^{13}C NMR spectra of isomers, but the signals of the principal structural fragments were identified based on the analysis of two-dimensional correlation experimenrs HSQC/HMBC. In particular, we assigned the signals of the carbonyl carbon atoms 198.40, 163.45, 160.62 ppm for isomer **VIIa** and 196.29, 166.36, 160.35 ppm for isomer **VIIb**, of carbon atoms in the cyclopropane fragment 43.28, 41.39, 35.75 ppm (**VIIa**) and 43.34, 38.35, 37.65 ppm (**VIIb**), and also of atoms $C^{3'}$ from indan fragment 29.11 and 34.78 ppm for isomers **VIIa** and **VIIb** respectively.

The investigation of the isomers mixture by ^{1}H and ^{13}C NMR spectroscopy revealed the chemical shifts of indicator signals for the steroisomers in the ^{1}H and ^{13}C NMR spectra. In the ^{13}C NMR spectra the largest difference in the chemical shifts for isomers was observed for the methylene $C^{3'}$ atom of the indanone fragment ($\Delta\delta$ ~5.7 ppm): therewith the downfield signal belonged to minor isomer **VIIb**. In the ^{1}H NMR spectra the characteristic signals were those of methine proton and methylene fragment protons observed respectively for the major isomer **VIIa** at 3.71 s (1H, $C^{7b}H$), 3.15 d, 2.66 d (2H, $C^{3'}H_2$, *J* 17.7 Hz) and for the minor isomer **VIIb** at 3.55 s (1H, $C^{7b}H$), 3.85 d, 3.50 d (2H, $C^{3'}H_2$, *J* 18.3 Hz). The downfield shift of the protons from the methylene fragment of the minor isomer also confirmed the established configurations of the spiro carbons in compounds **VIIa** and **VIIb** for a similar shift ~0.5–0.6 ppm had been previously observed for the protons of a methyl group of studied earlier substituted amides of 1-aroyl-1-methyl-2-oxo-1a,7b-dihydrocyclopropa[*c*]-chromen-1a-carboxylic acid in going from the structure with the *trans*-position of methine proton and methyl

Scheme 2.



R = CH_3 (**a**), C_2H_5 (**b**).

group to the *cis*-structure [2]. The significant difference in the chemical shifts of the mentioned protons provides a possibility of reliable establishing the stereo configuration of compounds with analogous structure from the ^{1}H NMR spectra.

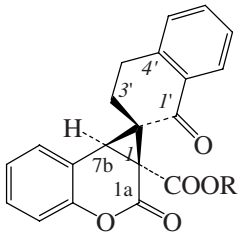
Alkyl esters of 2-oxochromen-3-carboxylic acid **IIIa** and **IIIb** reacted with zinc enolate **X** along Scheme 2 analogous to Scheme 1 providing as a result the corresponding esters of 1',2',3',4'-tetrahydro-2,1'-dioxospiro-(1a,7b-dihydrocyclopropa[*c*]chromen-1,2'-naphthalene)-1a-carboxylic acid **XIVa** and **XIVb**.

The reaction of zinc enolate **X** with 2-oxochromen-3-carboxylic acid benzylamide (**XI**) is complicated by deprotonation of the amide group and by replacement of the hydrogen by ZnBr species in the first stage of the reaction. This process results in considerable reduction of the double bond electrophilicity, and the reaction under common conditions does not yield the expected product. To perfom the reaction the heating of the reaction mixture to 85–90°C was required, and it was achieved by toluene addition. Under these conditions the reaction occurred analogously to the above described processes and resulted in the corresponding cyclopropanation product, 1',2',3',4'-tetrahydro-2,1'-dioxospiro(1a,7b-dihydrocyclopropa[*c*]-chromen-1,2'-naphthalene)-1a-carboxylic acid *N*- benzylamide (**XV**).

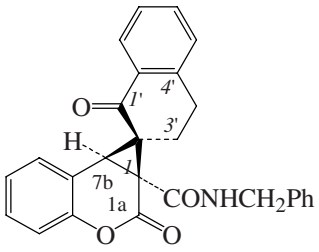
The composition and structure of compounds **XIVa, XIV**b, and **XV** were confirmed by elemental analyses, ^{1}H NMR and IR spectra. In the IR spectra of compounds **XIVa** and **XIV b** appear characteristic absorption bands (ν, cm^{-1}) of carbonyls from keto (1705), ester (1745), and lactone (1750) groups. In the ^{1}H NMR spectrum appear characteristic singlets of methine proton at 3.41–3.42 ppm. In the IR spectrum of compound **XV** appear characteristic absorption bands (ν, cm^{-1}) of carbonyls from amide (1660), keto (1710), and lactone (1750) groups and from *N–H* bond (3360). In the ^{1}H NMR spectrum appears a characteristic singlet of methine proton at 3.80 ppm. A single set of signals evidences that compounds **XIVa, XIVb**, and **XV** were isolated as a unique geometric isomer.

The comparison of the chemical shifts from the methylene protons $C^{3'}H_2$ in compounds obtained allows a conclusion on their spatial arrangement. The downfield shift by ~0.4 ppm in benzylamide **XV** as compared with alkyl esters **XIVa** and **XIVb** permits the assignment to

these compounds of structures shown on the previous page.



XIVa, XIVb



XV

EXPERIMENTAL

IR spectra of individual compounds were recorded from mulls in mineral oil on spectrophotometer UR-20. ^{1}H NMR spectra were registered from solutions in $CDCl_3$ on spectrometrs Tesla BS-576 A, operating frequency 100 MHz (compounds **VII, VIIIa, VIIIb, XIVa, XIVb**), and Mercury Plus-300 (300 MHz) (compound **XV**). 1D- and 2D-NMR spectra for solution in $CDCl_3$ of isomers mixture of compound **VII** were measured on a spectrometer Bruker DRX-400 [400 (^{1}H) and 100 MHz (^{13}C)]. Internal reference TMS.

Ethyl 2,1'-dioxospiro(1a,7b-dihydrocyclopropa-[*c*]chromen-1,2'-indan)-1a-carboxylate (VII). To 0.9 g of fine zinc turnings in 8 ml of ether and 5 ml of ethyl acetate was added 0.013 mol of 2,2-dibromoindan-1-one and 0.01 mol of ethyl ether. The mixture was boiled till zinc nearly completely dissolved and 40 min afterwards, then the solution was cooled and hydrolyzed with a solution of acetic acid. The reaction products were extracted into ether, the extract was dried with Na_2SO_4, the solvents were distilled off, and the residue was recrystallized from methanol. After one recrystallization from methanol the fraction of the major isomer was 73%. Yield 2.54 g (67%), mp 134–135°C. IR spectrum, ν, cm^{-1}: 1725, 1745, 1755. ^{1}H NMR spectrum, δ, ppm (**VIIa**): 1.33 t (3H, $OCH_2C\underline{H}_3$, *J* 7 Hz), 2.66 d (1H, CH_2, *J* 18 Hz), 3.15 d (1H, CH_2, *J* 18 Hz), 3.71 s (1H, CH), 4.31 q (2H, $OC\underline{H}_2CH_3$, *J* 7 Hz), 7.02–7.78 m (8H, $2C_6H_4$); (**VIIb**): 3.50 d (1H, CH_2, *J* 18 Hz), 3.55 C (1H, CH), 3.85 d (1H, CH_2, *J* 18 Hz). Found, %: C 72.30; H 4.53. $C_{21}H_{16}O_5$. Calculated, %: C 72.41; H 4.63.

Secondary amides of 2,1'-dioxospiro(1a,7b-dihydrocyclopropa[*c*]chromen-1,2'-indan)-1a-carboxylic acid VIIIa and VIIIb were obtained analogously to compound **VII**.

1a-Piperidinocarbonylspiro(1a,7b-dihydrocyclopropa[*c*]chromen-1,2'-indan)-2,1'-dione (VIIIa). Yield 2.09 g (54%), mp 230–231°C. IR spectrum, ν, cm^{-1}: 1660, 1730, 1760. ^{1}H NMR spectrum, δ, ppm: 1.20–1.68 m (6H, $C_5H_{10}N$), 2.76 d (1H, CH_2, *J* 18.0 Hz), 3.15 d (1H, CH_2, *J* 18.0 Hz), 2.80–3.89 m (4H, $C_5H_{10}N$), 3.71 s (1H, CH), 7.10–7.87 m (8H, $2C_6H_4$). Found, %: C 74.28; H 5.39; N 3.51. $C_{24}H_{21}NO_4$. Calculated, %: C 74.40; H 5.46; N 3.62.

1a-Morpholinocarbonylspiro(1a,7b-dihydrocyclopropa[*c*]chromen-1,2'-indan)-2,1'-dione (VIIIb). Yield 1.82 g (47%), mp 234–235°C. IR spectrum, ν, cm^{-1}: 1660, 1725, 1755. ^{1}H NMR spectrum, δ, ppm: 2.70 d (1H, CH_2, *J* 18.0 Hz), 3.09 d (1H, CH_2, *J* 18.0 Hz), 3.71 s (1H, CH), 2.70–4.00 m (8H, C_4H_8NO), 7.02–7.82 m (8H, $2C_6H_4$). Found, %: C 70.82; H 4.84; N 3.49. $C_{23}H_{19}NO_5$. Calculated, %: C 70.94; H 4.92; N 3.60.

Alkyl 1',2',3',4'-tetrahydro-2,1'-dioxospiro(1a,7b-dihydrocyclopropa[*c*]chromen-1,2'-naphthalene)-1a-carboxylates XIVa, and XIVb. To 1.5 g of fine zinc turnings in 8 ml of ether and 5 ml of ethyl acetate was added 0.013 mol of 2,2-dibromo-1-tetralone in 10 ml of ethyl acetate. The mixture was heated till the reaction started, and then it proceeded spontaneously. On completion of the reaction the mixture was boiled for 10 min. Then to the reaction mixture was added 0.01 mol of alkyl 2-oxochromen-3-carboxylate, and the mixture was boiled for 40 min and on cooling it was hydrolyzed with acetic acid solution. The reaction products were extracted into ether, the extract was dried with Na_2SO_4, the solvents were distilled off, and the residue was recrystallized from methanol.

Methyl 1',2',3',4'-tetrahydro-2,1'-dioxospiro(1a,7b-dihydrocyclopropa[*c*]chromen-1,2'-naphthalene)-1a-carboxylate (XIVa). Yield 2.05 g (59%), mp 199–200°C. IR spectrum, ν, cm^{-1}: 1705, 1745, 1750. ^{1}H NMR spectrum, δ, ppm: 1.70–2.07 m (2H, $C^{3'}H_2$), 2.58–3.35 m (2H, $C^{4'}H_2$), 3.41 s (1H, CH), 3.84 s (3H, CH_3), 6.85–7.42 m, 7.69 d (8H, $2C_6H_4$). Found, %: C 72.32; H 4.55. $C_{21}H_{16}O_5$. Calculated, %: C 72.41; H 4.63.

Ethyl 1',2',3',4'-tetrahydro-2,1'-dioxospiro(1a,7b-dihydrocyclopropa[*c*]chromen-1,2'-naphthalene)-1a-carboxylate (XIVb). Yield 2.28 g (63%), mp 216–217°C. IR spectrum, ν, cm^{-1}: 1705, 1745, 1750. ^{1}H NMR spectrum, δ, ppm: 1.39 t (3H, $C\underline{H}_3CH_2$, *J* 6.5 Hz), 1.70–2.20 m (2H, $C^{3'}H_2$), 2.65–3.40 m (2H, $C^{4'}H_2$), 3.42 s (1H, CH), 4.33 q (2H, $CH_3C\underline{H}_2$, *J* 6.5 Hz), 6.80–7.50 m, 7.74 d (8H, $2C_6H_4$). Found, %: C 72.81; H 4.93. $C_{22}H_{18}O_5$. Calculated, %: C 72.92; H 5.01.

1',2',3',4'-Tetrahydro-2,1'-dioxospiro(1a,7b-dihydrocyclopropa[*c*]chromen-1,2'-naphthalene)-1a-

carboxylic acid *N*-benzylamide (XV) was prepared similarly to compounds **IXa** and **IXb** but a double amount of zinc enolate was used, and in the second stage of the reaction 15 ml of toluene was added. Yield 1.78 g (42%), mp 201–202°C. IR spectrum, ν, cm^{-1}: 1660, 1710, 1750, 3360. ^1H NMR spectrum, δ, ppm: 2.17–2.43 m (2H, $C^{3'}H_2$), 2.89–3.31 m (2H, $C^{4'}H_2$), 3.80 s (1H, CH), 4.46 d.d (2H, $C\underline{H}_2Ph$, *J* 15, *J* 6.0 Hz), 4.61 d.d (2H, $C\underline{H}_2Ph$, *J* 15, *J* 6.0 Hz), 6.96–7.48 m, 7.77 d (13H, $2C_6H_4$, C_6H_5), 8.62 t (1H, NH, *J* 6.0 Hz). Found, %: C 76.47; H 4.92; N 3.23. $C_{27}H_{21}NO_4$. Calculated, %: C 76.58; H 5.00; N 3.31.

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