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Reaction of Methyl 3,4-Dihydroxy-6-oxo-2,4-alkadienoates with 2-Aminophenol

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Abstract—Methyl [(3*Z*)-2-hydroxy-3-(2-oxoalkylidene)-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]acetates were prepared by reacting methyl 3,4-dihydroxy-6-oxo-2,4-alkadienoates with 2-aminophenol.

Keywords: 1,3,4,6-tetracarbonyl compounds, 3,4-dihydroxy-6-oxo-2,4-alkadienoic acid esters, 2-aminophenol, (3,4-dihydro-2*H*-1,4-benzoxazin-2-yl)acetic acid esters, [2*H*-1,4-benzoxazin-3(4*H*)-ylidene]acetic acid esters

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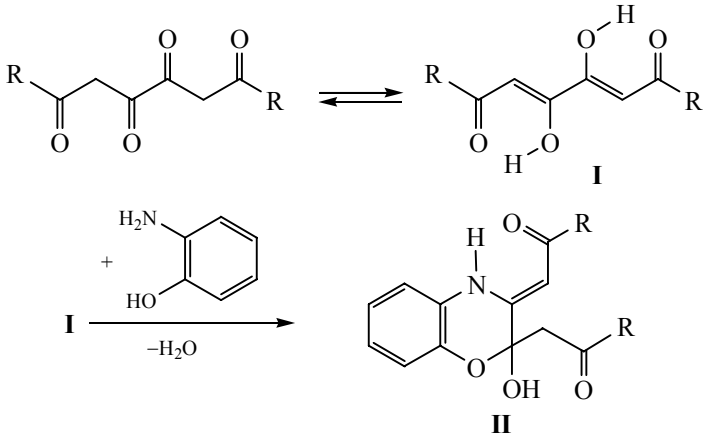
Reaction of 1,3,4,6-tetracarbonyl compounds **I** (R = OAlk, *t*-Bu) [1, 2] with 2-aminophenol has been known to result in the formation of stable *O*,*O*-acetals, 2,2'-(2-hydroxy-2*H*-1,4-benzoxazin-2-yl-3-ylidene) diacetates **II** (R = OAlk) [3] or 2-hydroxy-3-pivaloylmethylene-2-pivaloylmethyl-3,4-dihydrobenzo[*b*]-1,4-oxazines **II** (R = *t*-Bu) [4] (Scheme 1).

Data on the reactions of 3,4-dihydroxy-6-oxo-2,4-alkadienoic acid [5] with 2-aminophenol are absent.

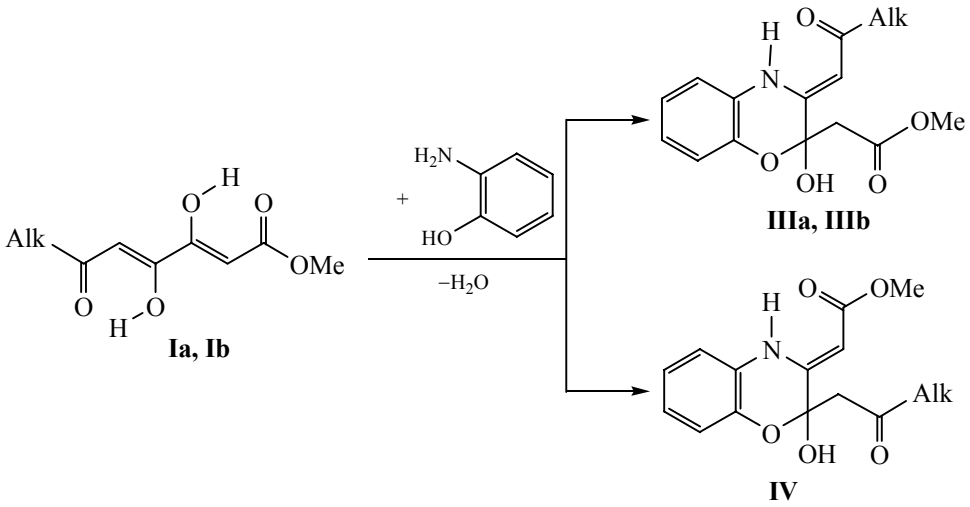
In the present work the interaction of 3,4-dihydroxy-6-oxo-2,4-octa(nona)dienoic acid methyl esters **Ia** and **Ib** with 2-aminophenol was investigated. It was found that the reaction of methyl 3,4-dihydroxy-6-oxo-2,4-alkadienoates **Ia** and **Ib** with 2-aminophenol

Scheme 1.



R = OAlk, *t*-Bu (**I, II**).

Scheme 2.



Alk = Et (**Ia, IIIa, IV**), Alk = *n*-Pr (**Ib, IIIb**).

proceeded under reflux in ethyl acetate to give methyl [(3*Z*)-2-hydroxy-3-(2-oxoalkylidene)-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]acetates **IIIa** and **IIIb** in the yield of 26 and 64%, respectively.

In the case of ester **Ia** along with the target product **IIIa** regioisomeric (2*Z*)-[2-hydroxy-2-(2-oxobutyl)-2*H*-1,4-benzoxazin-3(4*H*)-ylidene]acetate **IV** formed, whose isolation was unsuccessful. According to NMR, the ratio of regioisomers **IIIa** and **IV** in the reaction mixture was 38 : 62 (Scheme 2).

Compounds **IIIa** and **IIIb** were colorless crystalline substances insoluble in water and well soluble in organic solvents. The structures of the prepared benzoxazines were confirmed by NMR (^{1}H, ^{13}C, ^{1}H–^{13}C HMBC, ^{1}H–^{1}H NOESY), IR spectra and elemental analysis data.

In the ^{1}H–^{13}C HMBC NMR spectra of compounds **IIIa** and **IIIb** the cross peaks of the following signals were observed: C^{2a} atom (202.58–203.21 ppm), protons of the methylene group of alkyl group $C^{3a}H_2$ (2.42–2.49 ppm) and methine proton $C^{1a}H$ (5.46–5.49 ppm), as well as proton $C^{1a}H$ (5.46–5.49 ppm) and C^3 atom (149.65–149.83 ppm) that confirmed the presence of (alkanoyl)methylene fragment in the position C^3 of the benzoxazine ring. In addition, the coupling of atom C^{2b} (171.40–171.48 ppm) with methyl protons $C^{3b}H_3$ (3.82–3.85 ppm) and geminal protons $C^{1b}H_2$ (2.88–2.90 and 3.00–3.02 ppm, AB-system, *J* 15.5–15.7 Hz), which interacted with C^2 carbon atom (94.11–95.29 ppm), confirmed the presence of the (methoxycarbonyl)methyl fragment in the position *2* of the benzoxazine ring.

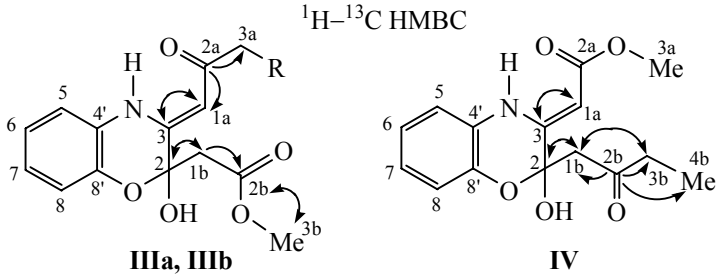
In the ^{1}H–^{1}H NOESY NMR spectra of compounds **IIIa** and **IIIb** the correlation of the signals of methine proton $C^{1a}H$ and methylene protons $C^{3a}H_2$ of the alkyl moiety was revealed together with the correlation of the signals of methine proton $C^{1a}H$ and germinal protons $C^{1b}H_2$, that also proved the (*Z*)-configuration of the prepared compounds.

The structure of compound **IV** was confirmed by the presence of the cross peaks of methylene protons $C^{1b}H_2$ (2.75 and 3.22 ppm, AB-system, *J* 15.9 Hz) with the signals of atoms C^2 (95.55 ppm) and C^{3b} (38.83 ppm) in the NMR spectrum of the reaction mixture, which indicated the presence of an ethyl group in the acyl fragment and its localization at atom C^2 of the benzoxazine ring. The presence of the ketone group in the structure of the fragment was proved by the occurrence of the correlations between deshielded atom C^{2b} (211.86 ppm) and methylene protons $C^{1b}H_2$ as well as protons $C^{3b}H_2$ (2.56 ppm) and $C^{4b}H_3$ (1.13 ppm). The cross peak of C^3 carbon atom (150.58 ppm) with methine proton $C^{1a}H$ (5.00 ppm) confirmed the presence of the ylidene fragment at C^3 atom.

In the ^{1}H–^{1}H NOESY NMR spectrum of the reaction mixture besides the signals of compound **IIIa** there was a cross peak of the singlet of methine proton $C^{1a}H$ of compound **IV** with the signals of germinal protons $C^{1b}H_2$. The absence of a cross peak of proton

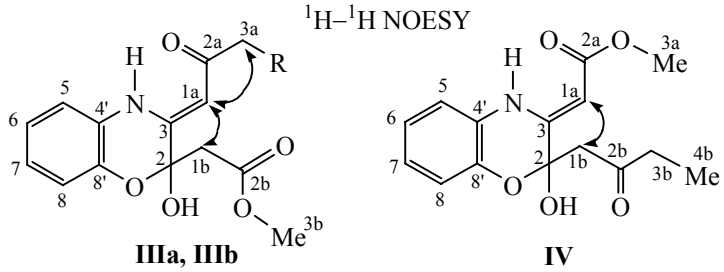
Scheme 3.

^1H–^{13}C HMBC



IIIa, IIIb **IV**

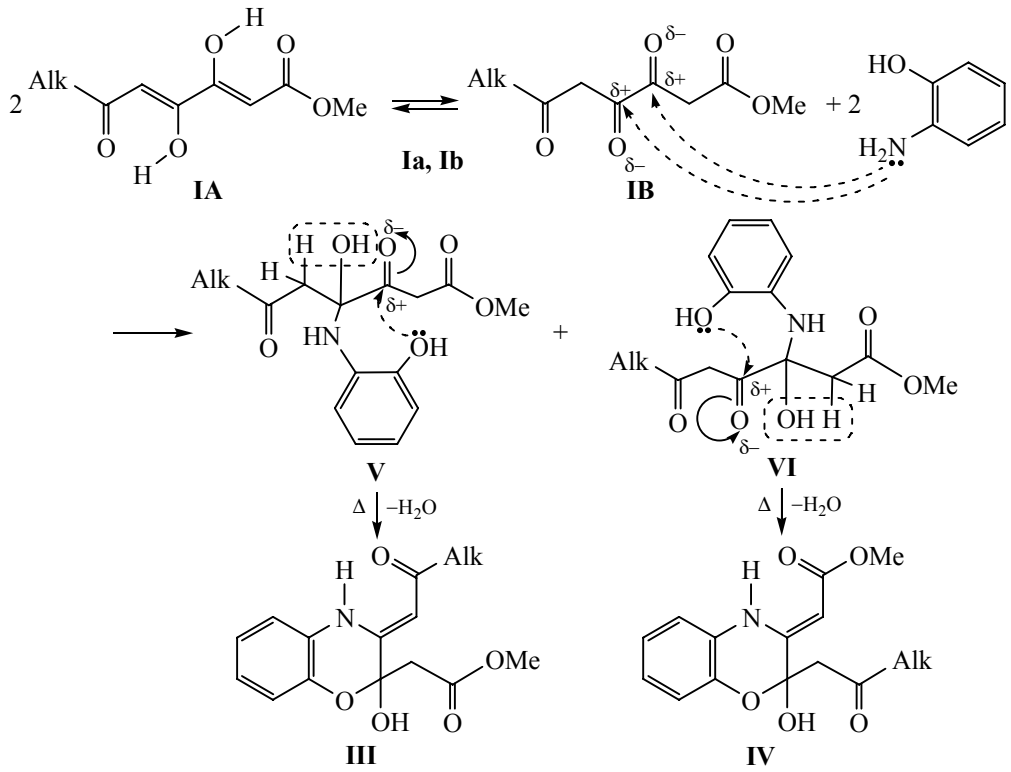
^1H–^1H NOESY



IIIa, IIIb **IV**

R = Me (**IIIa**); R = Et (**IIIb**).

Scheme 4.



IA **Ia, Ib** **IB** **V** **VI** **III** **IV**

Alk = Et (**Ia, IIIa, IV–VI**); Alk = *n*-Pr (**Ib**, **IIIb, V**).

$C^{1a}H$ with ethyl group protons confirmed the (*Z*)-configuration of compound **IV** (Scheme 3).

According to the NMR spectroscopy data, the ratio of isomers **IIIa** and **IV** did not change, when deuterated chloroform was replaced by DMSO-d_6 or temperature was increased from 25 to 55°C.

The structure of compounds **III** and **IV** was also proved by IR spectroscopic data. Thus, in the spectra

of compounds **IIIa** and **IIIb** the absorption bands of amino (3180–3188 cm^{-1}) and carbonyl (1597–1598 cm^{-1}) groups of the (alkyl)carbonyl fragment were observed as well as the absorption bands of acetal hydroxyl (3054–3057 cm^{-1}) and ester carbonyl group (1746–1749 cm^{-1}). Low absorption frequency of NH and carbonyl groups of AlkCO-fragment evidenced the presence of NH-chelate in the structure of (alkyl)-carbonyl fragment that did not contradict the literature data on the *O*,*O*-acetals **II** of similar structure [3, 4].

In the IR spectrum of a mixture of compounds **IIIa** and **IV** there were the absorption bands of amino group (3379 cm^{-1}), acetal OH-group (3294 cm^{-1}), ester carbonyl groups (1662 cm^{-1}), and EtCO (1624 cm^{-1}) functionalities. Low-frequency absorption of the ester carbonyl group in the spectra of related compounds **II** (R^1=R^2=OAlk) has been observed in the similar area (1653–1669 cm^{-1}) [3].

The suggested mechanism of the reaction of **Ia** and **Ib** with 2-aminophenol is presented in Scheme 4.

Most probably the reaction started with nucleophilic addition of the amino group of aminophenol to the carbonyl groups $C^{3(4)}$ of oxo form **IB** with the formation of intermediates **A** and **B** followed by heterocyclization at the hydroxy group of the phenol. Elimination of water led to the formation of compounds **III** and **IV**. It is worthy to note that the prepared *O*,*O*-acetals **III** and **IV** are resistant to dehydration.

EXPERIMENTAL

IR spectra were recorded on a Bruker Alpha IR Fourier spectrometer (adapter NPVO, ZnSe) for compounds **IIIa** and **IV** and on a Spectrum Two Perkin Elmer spectrophotometer for compound **IIIb**. ^{1}H, ^{13}C, HMBC, and NOESY NMR spectra were registered on a Bruker AVANCE II (400 MHz) spectrometer for solutions in deuterated chloroform and DMSO-d_6, internal reference TMS. The reaction progress and the purity of the prepared compounds were monitored by means of TLC on Silufol UV-254 plates eluting with a mixture hexane–acetone, 3 : 1. Starting compounds **Ia** and **Ib** were prepared by the known procedure [5].

Methyl [(3*Z*)-2-hydroxy-3-(2-oxobutylidene)-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]acetate (IIIa). 2-Aminophenol (25 mmol, 2.73 g) was added to a solution of compound **Ia** (25 mmol, 5.35 g) in 50 mL of ethyl acetate. The reaction mixture was heated under reflux, and then evaporated. The residue was ground with diethyl ether, dried, and recrystallized from ethanol. Yield 1.89 g (26%), mp 93–95 °C. IR spectrum, ν, cm^{-1}: 3188 (NH), 3057 (OH), 1746 (MeOC=O), 1598 (C=O, chelate), 1500, 1458 (C=C, arom.), 1290, 1276 [δ_{planar}(C–OH), 1177 (C–O–C, ether), 1081 [δ_{planar}(CH, arom.)], 746 [δ(CH, arom.)]. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.16 t (3H, $CH_2C\underline{H}_3$, *J* 7.5 Hz), 2.49 q (2H, $C\underline{H}_2CH_3$, *J* 7.5 Hz), 2.90 d and 3.02 d (2H, $\underline{CH}_2COOCH_3$, *J* 15.7 Hz), 3.85 s (3H, OCH_3), 5.49 s (1H, CH), 6.11 s (1H, OH), 6.80–7.10 m (4H, C_6H_4), 12.22 s (1H, NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.16 t (3H, CH_2CH_3, *J* 7.5 Hz), 2.49 q (2H, CH_2CH_3, *J* 7.5 Hz), 2.96 d and 3.16 d (2H, $\underline{CH}_2COOCH_3$, *J* 15.6 Hz), 3.57 s (3H, OCH_3), 5.58 s (1H, CH), 6.80–7.30 m (4H, C_6H_4), 7.78 s (1H, OH), 12.20 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 9.27 (C^{4a}), 36.11 (C^{3a}), 40.06 (C^{1b}), 52.68 (C^{3b}), 90.92 (C^{1a}), 94.29 (C^2), 115.96 (C^6), 117.68 (C^7), 123.32 (C^5), 123.63 (C^8), 126.59 ($C^{4'}$), 141.31 ($C^{8'}$), 149.83 (C^3), 171.57 (C^{2b}), 203.21 (C^{2a}). Found, %: C 62.08; H 6.87; N 4.76. $C_{15}H_{17}NO_5$. Calculated, %: C 61.85; H 5.88; N 4.81. *M* 291.30.

Methyl [(3*Z*)-2-hydroxy-3-(2-oxopentylidene)-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]acetate (IIIb) was prepared similarly. Yield 4.88 g (64%), mp 78–79°C. IR spectrum, ν, cm^{-1}: 3180 (NH), 3054 (OH), 1749 (MeOC=O), 1597 (C=O, chelate), 1498, 1455 (C=C, arom.), 1292, 1274 [δ_{planar}(C–OH)], 1175 (C–O–C, ester), 1076 [δ_{planar}(CH, arom.)], 868 [δ(CH, arom.)]. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.97 t (3H, $CH_2CH_2\underline{CH}_3$, *J* 7.5 Hz), 1.68 m (2H, $CH_2\underline{CH}_2CH_3$), 2.42 t (2H, $\underline{CH}_2CH_2CH_3$, *J* 7.5 Hz), 2.88 d and 3.00 d (2H, $\underline{CH}_2COOCH_3$, *J* 15.5 Hz), 3.82 s (3H, OCH_3), 5.46 s (1H, CH), 6.12 s (1H, OH), 6.89–6.99 m (4H, C_6H_4), 12.25 s (1H, NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.90 t (3H, $CH_2CH_2\underline{CH}_3$, *J* 7.5 Hz), 1.57 m (2H, $CH_2\underline{CH}_2CH_3$), 2.34 t (2H, $\underline{CH}_2CH_2CH_3$, *J* 7.5 Hz), 2.95 d and 3.17 d (2H, $\underline{CH}_2COOCH_3$, *J* 15.50 Hz), 3.55 s (3H, OCH_3), 5.55 s (1H, CH), 6.90–7.18 m (4H, C_6H_4), 7.79 s (1H, OH), 12.23 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.90 (C^{5a}), 18.74 (C^{4a}), 39.86 (C^{1b}), 45.02 (C^{3a}), 52.57 (C^{3b}), 91.22 (C^{1a}), 94.11 (C^2), 115.84 (C^6), 117.51 (C^7), 123.15 (C^5), 123.49 (C^8), 125.97 ($C^{4'}$), 141.71 ($C^{8'}$), 149.65 (C^3), 171.40 (C^{2b}), 202.58 (C^{2a}). Found, %: C 62.94; H 6.27; N 4.59. $C_{16}H_{19}NO_5$. Calculated, %: C 62.78; H 6.44; N 4.35. *M* 305.33.

Methyl (2*Z*)-[2-hydroxy-2-(2-oxobutyl)-2*H*-1,4-benzoxazin-3(4*H*)-ylidene]acetate (IV). IR spectrum, ν, cm^{-1}: 3379 (NH), 3294 (OH), 1662 (MeOC=O), 1624 (EtC=O), 1600, 1500, 1458 (C=C, arom.), 1288, 1272 [δ_{planar}(C–OH)], 1179 (C–O–C, ester), 1080 [δ_{planar}(CH, arom.)], 747 [δ(CH, arom.)]. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.13 t (3H, CH_2CH_3, *J* 7.7 Hz), 2.56 q (2H, CH_2CH_3, *J* 7.7 Hz), 2.75 d and 3.22 d (2H, $\underline{CH_2}COOCH_3$, *J* 15.9 Hz), 3.75 s (3H, OCH_3), 5.00 s (1H, CH), 6.41 s (1H, OH), 6.80–7.10 m (4H, C_6H_4), 10.36 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 7.29 (C^{4b}), 38.83 (C^{3b}), 45.36 (C^{1b}), 51.08 (C^{3a}), 82.51 (C^{1a}), 95.55 (C^2), 115.36 (C^6), 117.60 (C^7), 122.88 (C^5), 123.22 (C^8), 126.15 ($C^{4'}$), 141.85 ($C^{8'}$), 150.58 (C^3), 171.13 (C^{2a}), 211.86 (C^{2b}).

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