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LETTERS TO THE EDITOR

On the 100th anniversary of V.V. Perekalin

Synthesis of Benzoyl- and Ethoxycarbonyl-Containing Dihydrofurocoumarins

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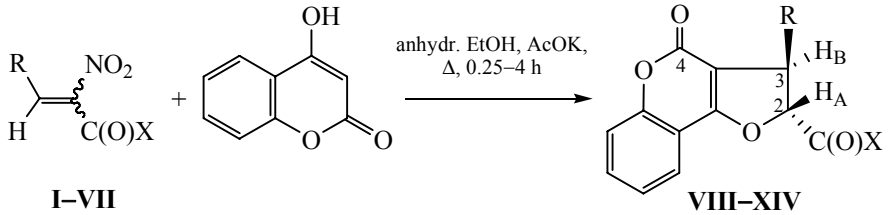
Coumarin ring is a key fragment of many natural substances and some drugs possessing anti-inflammatory, anticancer, antibacterial, and antiviral (including anti-HIV-1) activities. Other compounds containing coumarin cycle (such as warfarin, nitrofarin, and syncumar) are important of blood anticoagulants [1–3]. Moreover, coumarin-based compounds are used in technology [4] due to their unique optical properties.

In order to obtain the new representatives of functionalized coumarins, we investigated the reactions of 4-hydroxycoumarin with readily available nitroethenes **I–VII**, containing the benzoyl or ester group in the *gem*-position with respect to the nitro moiety. Reactions were performed by refluxing the equimolar mixtures of the reagents in ethanol in the presence of anhydrous potassium acetate (0.25–4 h). As result, substituted dihydrofurocoumarins **VIII–XIV** were obtained with yields up to 91%. Their formation was a result of a one-pot process involving nucleophilic addition of 4-hydroxycoumarin to the C=C bond of nitroalkene and subsequent intramolecular O-alkylation of the Ad_N product accompanied by elimination of nitrous acid. Our previous studies [5, 6] revealed that reactions of nitroalkenes with a linear β-diketone, acetylacetone, gave the linear Michael adducts or the dihydrofuran type structures.



I–VII **VIII–XIV**

X = Ph: R = Ph (**I**, **VIII**), 4-$MeOC_6H_4$ (**II**, **IX**); X = OEt: R = Ph (**III**, **X**), 4-$Me_2NC_6H_4$ (**IV**, **XI**), 4-ClC_6H_4 (**V**, **XII**), 4-$O_2NC_6H_4$ (**VI**, **XIII**), 2-thienyl (**VII**, **XIV**).

Melting points of compounds **VIII–X** corresponded to those of the reference samples obtained by other methods [7–11].

Structures of the so prepared dihydrofurocoumarins **VIII–XIV** were confirmed by IR, ^1H, and $^{13}C–\{^1H\}$ NMR spectroscopy. In particular, the IR spectra (in $CHCl_3$) contained the absorption bands of carbonyl groups stretching vibrations at 1720–1725 and 1650 cm^{-1}.

In the ^1H NMR spectra of dihydrofurocoumarins **VIII–XIV** (in $CDCl_3$), the proton signals of aryl (thienyl) substituents were observed at 6.68–8.23 ppm. Methine protons H_A and H_B signals were found at 5.22–5.32 and 4.68–5.09 ppm; the spin–spin coupling constants values ($^3J_{AB}$ 4.88–5.29 Hz) revealed that those cyclic compounds were *trans*-isomers [12]. In the ^1H NMR spectra of **X–XIV**, a triplet and two doublets of quartets (due to magnetic nonequivalence

of diastereotopic methylene protons) were observed at 1.33–1.36 and 4.28–4.33, 4.35–4.38 ppm (^3J 7.15, ^2J 10.75–10.85 Hz) assigned to the protons of methyl and methylene groups in the ester fragment, respecively.

Recently, Chinese authors reported [13] the preparation of the substituted dihydrofurocoumarins via condensation of α-nitrocinnamic esters **III** and **VI** with 4-hydroxycoumarin (taken in two-fold excess). The reaction was performed in water in the presence of triethylamine and tetrabutylammonium bromide at 70°C (6 h). The final dihydrofurocoumarins were isolated by chromatography on silica gel. However, the melting point of **XII** (152–154°C) as presented in [13] differed significantly from that of the reference sample prepared by us (170–172°C).

To conclude, the studied reactions illustrated the possibility of using *gem*-acyl- and *gem*-alkoxycarbonylnitroethenes as synthons for preparation of substituted 2,3-dihydrofuro[3,2-*c*]coumarins, which are of interest from both practical and theoretical points of view.

The initial *gem*-benzoylnitroethenes **I** and **II** were prepared as described in [14]. Synthesis of α-nitroacrylate **VII** was performed according to [15]. Compounds **III**–**V** were obtained similarly, and **VI** was synthesized according to [16].

***trans*-2-Benzoyl-3-phenyl-2,3-dihydrofuro[3,2-*c*]-coumarin (VIII).** A mixture of 0.506 g (2 mmol) of 1,3-diphenyl-2-nitro-2-propen-1-one **I**, 0.32 g (2 mmol) of 4-hydroxycoumarin, and 0.196 g (2 mmol) of potassium acetate in 10 ml of anhydrous ethanol was refluxed for 1 h. After cooling, the formed precipitate was filtered off and washed with water to yield 0.33 g of compound **VIII** (colorless crystals). The mother liquor was poured into ice; the oily product was extracted with diethyl ether. The extract was dried over $MgSO_4$ and the solvent was evaporated to give additionally 0.03 g of **VIII**. The overall yield of **VIII** was 0.36 g (49%), mp 205°C (carbon tetrachloride) {mp 192–194°C (methanol) [7]}. IR spectrum, ν, cm^{-1}: 1720, 1650 (C=O). ^1H NMR spectrum ($CDCl_3$), δ_H, ppm: 4.79 d (1H, H_B, $^3J_{AB}$ 4.88 Hz), 6.18 d (1H, H_A, $^3J_{AB}$ 4.88 Hz), 7.05–7.95 m (14H, C_6H_4, $2C_6H_5$). $^{13}C–\{^1H\}$ NMR spectrum ($CDCl_3$), δ_C, ppm: 49.45 (C^3), 92.73 (C^2), 105.45, 112.26, 117.13, 123.31, 124.28, 127.65, 128.26, 129.14, 129.19, 129.40, 133.02, 133.25, 134.54, 139.64, 155.49, 159.38 (C_6H_4, $2C_6H_5$, C=C), 166.47 (C^4), 192.18 [C(O)Ph].

Compounds **IX**–**XIV** were obtained similarly, the reaction time being of 1, 1.67, 3, 4 0.25, and 1 h, respectively.

***trans*-2-Benzoyl-3-(4-methoxyphenyl)-2,3-dihydrofuro[3,2-*c*]coumarin (IX).** Yield 48%, beige crystals, mp 189–190°C (carbon tetrachloride) {mp 185–186°C (ethanol) [8]}. IR spectrum, ν, cm^{-1}: 1720, 1650 (C=O). ^1H NMR spectrum ($CDCl_3$), δ_H, ppm: 3.80 s (3H, OCH_3), 4.72 d (1H, H_B, $^3J_{AB}$ 4.88 Hz), 6.14 d (1H, H_A, $^3J_{AB}$ 4.88 Hz), 6.90 d, 7.21 d (4H, OC_6H_4, ^3J 8.70 Hz), 7.34 d.t, 7.38 d.d, 7.49 t, 7.60 d.t, 7.65 d.t, 7.84 d.d, 7.89 d.d (9H, C_6H_4, C_6H_5). $^{13}C–\{^1H\}$ NMR spectrum ($CDCl_3$), δ_C, ppm: 48.95 (C^3), 55.43 (OCH_3), 92.86 (C^2), 105.57, 112.32, 114.76, 117.12, 123.28, 124.21, 128.73, 129.11, 129.15, 131.67, 132.93, 133.26, 134.49, 155.47, 159.41, 159.51 (OC_6H_4, C_6H_4, C_6H_5, C=C), 166.27 (C^4), 192.29 [C(O)Ph].

Ethyl *trans*-3-phenyl-2,3-dihydrofuro[3,2-*c*]-coumarin-2-carboxylate (X). Yield 81%, colorless crystals, mp 114–116°C (ethanol) {mp 112–114°C (ethanol) [9]}. IR spectrum, ν, cm^{-1}: 1720, 1650 (C=O). ^1H NMR spectrum ($CDCl_3$), δ_H, ppm: 1.34 t (3H, CH_3, ^3J 7.15 Hz), 4.30 d.q and 4.36 d.q (2H, OCH_2, ^2J 10.80, ^3J 7.15 Hz), 4.77 d (1H, H_B, $^3J_{AB}$ 5.04 Hz), 5.28 d (1H, H_A, $^3J_{AB}$ 5.04 Hz), 7.26–7.86 m (9H, C_6H_4, C_6H_5). $^{13}C–\{^1H\}$ NMR spectrum ($CDCl_3$), δ_C, ppm: 14.27 (CH_3), 50.55 (C^3), 62.44 (OCH_2), 89.28 (C^2), 104.80, 112.19, 117.14, 123.29, 124.30, 127.25, 128.14, 129.26, 133.11, 139.63, 155.46, 159.43 (C_6H_4, C_6H_5, C=C), 166.71 (C^4), 168.85 (COOEt).

Ethyl *trans*-3-(4-*N*,*N*-dimethylaminophenyl)-2,3-dihydrofuro[3,2-*c*]coumarin-2-carboxylate (XI). Yield 65%, beige crystals, mp 168–170°C (ethanol). IR spectrum, ν, cm^{-1}: 1720, 1650 (C=O). ^1H NMR spectrum ($CDCl_3$), δ_H, ppm: 1.33 t (3H, CH_3, ^3J 7.15 Hz), 2.92s [6H, $N(CH_3)_2$], 4.28 d.q and 4.34 d.q (2H, OCH_2, ^2J 10.80, ^3J 7.15 Hz), 4.68 d (1H, H_B, $^3J_{AB}$ 5.04 Hz), 5.24 d (1H, H_A, $^3J_{AB}$ 5.04 Hz), 6.68 d and 7.14 d (4H, NC_6H_4, ^3J 8.77 Hz), 7.33–7.82 m (4H, C_6H_4). $^{13}C–\{^1H\}$ NMR spectrum ($CDCl_3$), δ_C, ppm: 14.27 (CH_3), 40.63 [$N(CH_3)_2$], 49.96 (C^3), 62.23 (OCH_2), 89.50 (C^2), 105.29, 112.34, 113.01, 117.07, 123.20, 124.17, 127.22, 127.90, 132.84, 150.34, 155.39, 159.54 (NC_6H_4, C_6H_4, C=C), 166.22 (C^4), 169.12 (COOEt). Found N, %: 3.87. $C_{22}H_{21}NO_5$. Calculated N, %: 3.69.

Ethyl *trans*-3-(4-chlorophenyl)-2,3-dihydrofuro-[3,2-*c*]coumarin-2-carboxylate (XII). Yield 54%, colorless crystals, mp 170–172°C (ethanol) {mp 152–

154°C [13]}. IR spectrum, ν, cm^{-1}: 1720, 1650 (C=O). ^1H NMR spectrum ($CDCl_3$), δ_H, ppm: 1.34 t (3H, CH_3, ^3J 7.15 Hz), 4.30 d.q and 4.35 d.q (2H, OCH_2, ^2J 10.75, ^3J 7.15 Hz), 4.75 d (1H, H_B, $^3J_{AB}$ 5.29 Hz), 5.22 d (1H, H_A, $^3J_{AB}$ 5.29 Hz), 7.22 d and 7.32 d (4H, ClC_6H_4, ^3J 8.55 Hz), 7.35–7.84 m (4H, C_6H_4). $^{13}C–\{^1H\}$ NMR spectrum ($CDCl_3$), δ_C, ppm: 14.27 (CH_3), 49.96 (C^3), 62.57 (OCH_2), 89.09 (C^2), 104.32, 112.04, 117.19, 123.32, 124.41, 128.71, 129.43, 133.30, 134.05, 138.07, 155.57, 159.31 (ClC_6H_4, C_6H_4, C=C), 166.89 (C^4), 168.59 (COOEt). Found, %: C 64.81; H 4.07. $C_{20}H_{15}ClO_5$. Calculated, %: C 64.78; H 4.05.

Ethyl 3-(4-nitrophenyl)-2,3-dihydrofuro[3,2-*c*]-coumarin-2-carboxylate (XIII). Yield 88%, colorless crystals, mp 196–197°C (ethanol). IR spectrum, ν, cm^{-1}: 1350, 1525 (NO_2), 1725, 1650 (C=O). ^1H NMR spectrum ($CDCl_3$), δ_H, ppm: 1.36 t (3H, CH_3, ^3J 7.15 Hz), 4.33 d.q and 4.38 d.q (2H, OCH_2, ^2J 10.80, ^3J 7.15 Hz), 4.90 d (1H, H_B, $^3J_{AB}$ 5.19 Hz), 5.26 d (1H, H_A, $^3J_{AB}$ 5.19 Hz), 7.48 d and 8.23 d (4H, $O_2NC_6H_4$, ^3J 8.68 Hz), 7.30–7.90 m (4H, C_6H_4). $^{13}C–\{^1H\}$ NMR spectrum ($CDCl_3$), δ_C, ppm: 14.27 (CH_3), 50.15 (C^3), 62.85 (OCH_2), 88.60 (C^2), 103.69, 111.85, 117.31, 123.42, 124.55, 124.58, 128.47, 133.65, 146.54, 147.79, 155.57, 159.16 ($O_2NC_6H_4$, C_6H_4, C=C), 167.27 (C^4), 168.20 (COOEt). Found %: C 62.77; H 3.59; N 3.97. $C_{20}H_{15}NO_7$. Calculated %: C 62.99; H 3.95; N 3.68.

Ethyl 3-(2-thienyl)-2,3-dihydrofuro[3,2-*c*]-coumarin-2-carboxylate (XIV). Yield 91%, pale yellow crystals, mp 120–122°C (carbon tetrachloride). IR spectrum, ν, cm^{-1}: 1725, 1650 (C=O). ^1H NMR spectrum ($CDCl_3$), δ_H, ppm: 1.35 t (3H, CH_3, *J* 7.15 Hz), 4.31 d.q and 4.36 d.q (2H, OCH_2, ^2J 10.85, ^3J 7.15 Hz), 5.09 d (1H, H_B, $^3J_{AB}$ 4.88 Hz), 5.32 d (1H, H_A, $^3J_{AB}$ 4.88 Hz), 6.97 d.d, 7.24 d.d and 7.82 d.d (3H, 2-thienyl), 7.03 d, 7.34 t, 7.40 d, 7.62 m (4H, C_6H_4). $^{13}C–\{^1H\}$ NMR spectrum ($CDCl_3$), δ, ppm: 14.26 (CH_3), 45.77 (C^3), 62.58 (OCH_2), 89.18 (C^2), 123.40, 125.41, 127.50, 142.70 (2-thienyl), 104.34, 112.08, 117.18, 124.35, 125.62, 133.31, 155.48, 159.22 (C_6H_4, C=C), 166.64 (C^4), 168.38 (COOEt). Found, %: C 62.76; H 4.14. $C_{18}H_{14}O_5S$. Calculated, %: C 63.16; H 4.09.

The NMR spectra were recorded with Jeol ECX400A spectrometer [399.78 (^1H), 100.53 (^{13}C) MHz] in chloroform-*d*. The signal of residual $CHCl_3$ was used as internal standard.the IR spectra were registered with Shimadzu IRPrestige-21 Fourier spectrometer (CH_3Cl, c = 40 g ml^{-1}). Elemental analysis was performed with Eurovector EA 3000 (CHN Dual mode) analyzer.

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