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Reaction of 4-Hydroxycoumarin with 2-Acetyloxiranes

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Abstract—The reaction of 4-hydroxycoumarin with 2-acetyloxiranes in dimethylformamide in the presence of triethylamine gave 2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-ones which were converted into 4*H*-furo[3,2-*c*]-chromen-4-one derivatives as a result of dehydration or fragmentation.

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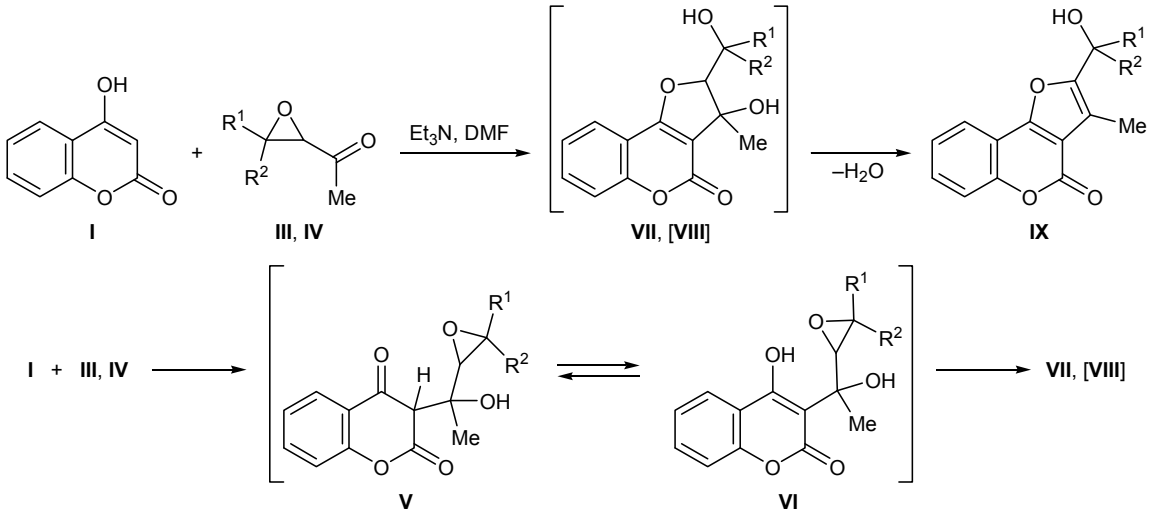
Furocoumarins occupy an important place among biologically active 4-hydroxycoumarin derivatives. They exhibit a broad spectrum of pharmacological properties, in particular antifungal, anticoagulant, spasmolytic, vasodilator, antitumor, etc. [1–6]. Furocoumarins can be isolated from natural sources [7] or prepared by synthetic methods [8–11]. Known methods of synthesis of furocoumarin derivatives are based on C-alkylation of 4-hydroxycoumarin with α-halo ketones or halo alkynes, followed by cyclization [9, 10], or on oxidative addition of olefins in the presence of silver(I) salts [11]. We recently showed [12] that 4-hydroxycoumarin (**I**) reacts with 2-acetyl-3-phenyloxirane in dimethylformamide in the presence of triethylamine at room temperature to give 3-hydroxy-2-[hydroxy(phenyl)methyl]-3-methyl-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (**II**). With a view to estimate the scope of this reaction, in the present work we examined the reaction of 4-hydroxycoumarin (**I**) with 2-acetyloxiranes **III** and **IV** containing aromatic (**III**, R^1 = 3-ClC_6H_4, R^2 = H) or aliphatic substituents (**IV**, R^1 = R^2 = Me) in position *3* of the three-membered ring (Scheme 1).

As with 2-acetyl-3-phenyloxirane, 4-hydroxycoumarin (**I**) reacted with 2-acetyl-3-(3-chlorophenyl)-oxirane (**III**) to produce 2-[(3-chlorophenyl)(hydroxy)-

Scheme 1.



III, **VII**, R^1 = 3-ClC_6H_4, R^2 = H; **IV**, **VIII**, **IX**, R^1 = R^2 = Me.

methyl]-3-hydroxy-3-methyl-2,3-dihydro-4*H*-furo-[3,2-*c*]chromen-4-one (**VII**) (Scheme 1, cf. [12]) as a mixture of two diastereoisomers **A** (Fig. 1) and **B** at a ratio of 3:1, which were characterized by different melting points and spectral parameters.

No expected 3-hydroxy-2-(1-hydroxy-1-methylethyl)-3-methyl-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (**VIII**) was detected in the reaction of **I** with 2-acetyl-3,3-dimethyloxirane (**IV**). Obviously, intermediate compound **VIII** undergoes fast dehydration to form 2-(1-hydroxy-1-methylethyl)-3-methyl-4*H*-furo-[3,2-*c*]chromen-4-one (**IX**) (Scheme 1). The yield of **IX** was lower than the yield of **VII**, and we failed to appreciably improve it by raising the reaction temperature or increasing the reaction time.

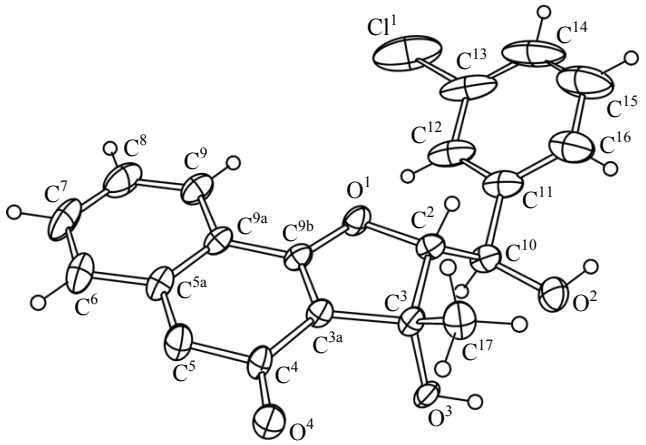


Fig. 1. Structure of the molecule of 2-[(3-chlorophenyl)-(hydroxy)methyl]-3-hydroxy-3-methyl-2,3-dihydro-4*H*-furo-[3,2-*c*]chromen-4-one (**VII**, diastereoisomer **A**) according to the X-ray diffraction data. Non-hydrogen atoms are shown as thermal vibration ellipsoids with a probability of 30%.

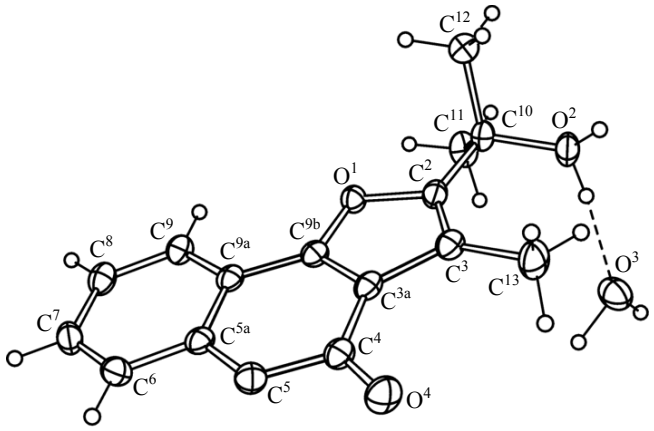


Fig. 2. Structure of the molecule of 2-(1-hydroxy-1-methylethyl)-3-methyl-4*H*-furo-[3,2-*c*]chromen-4-one (**IX**) according to the X-ray diffraction data. Solvate water molecule is shown. Non-hydrogen atoms are shown as thermal vibration ellipsoids with a probability of 50%.

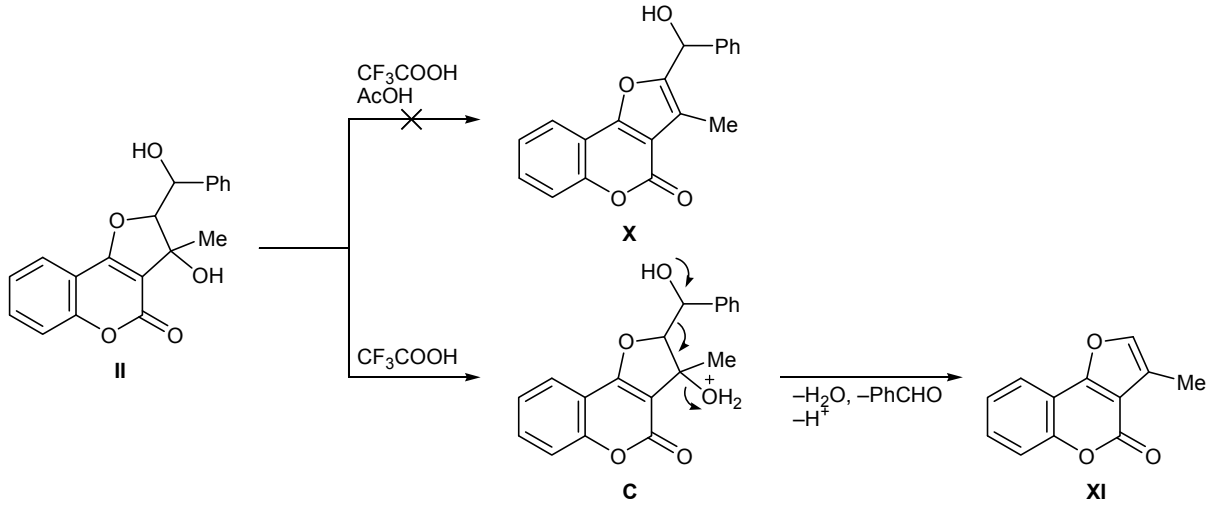
The observed difference in the behavior of oxiranes **III** and **IV** and 2-acetyl-3-phenyloxirane in the reaction with 4-hydroxycoumarin (**I**) may be related to the steric structure of compounds **II**, **VII**, and **VIII**. Presumably, the bulkier isopropyl group in poisition *2* of 2,3-dihydrofurocoumarin **VIII** favors elimination of water with formation of double C=C bond in the five-membered ring.

We made an attempt to effect dehydration of 3-hydroxy-2-[hydroxy(phenyl)methyl]-3-methyl-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (**II**) by treatment with trifluoroacetic acid at room temperature. However, instead of the expected dehydration product **X**, we isolated 3-methyl-4*H*-furo[3,2-*c*]chromen-4-one (**XI**) which was likely to be formed as a result of fragmentation of cation **C** (Scheme 2). No reaction occurred (even on heating to 50°C) when trifluoroacetic acid was replaced by acetic acid.

The structure of compounds **VII** (isomer **A**) and **IX** was determined by X-ray analysis (Figs. 1, 2). The furochromene skeleton of **VII** is almost planar, the mean-square deviation of atoms from the plane being 0.049 Å. The C^2 atom deviates by 0.214 (8) Å from the plane formed by the other atoms of the furan ring. Analogous deviation [0.178(5) Å] was observed for C^2 in 3-hydroxy-2-[hydroxy(phenyl)methyl]-3-methyl-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (**II**) [12]. On the whole, the bond lengths and bond angles in molecules **VIIA** and **II** coincide within 3σ with the corresponding standard values [13]. Like 3-hydroxy-2-[hydroxy(phenyl)methyl]-3-methyl-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (**II**), molecules **VIIA** in crystal are packed in such a way that through channels occupied by strongly disordered solvate hexane molecules with an overall volume of 371.8 $Å^3$ are formed.

The furochromene skeleton of molecule **IX** is planar within ±0.014(2) Å. The isopropyl group is oriented with respect to the furan ring so that the torsion angle $C^3C^2C^{10}O^2$ is equal to 8.7(3)°. The bond lengths in molecule **IX** are similar to the corresponding bond lengths in 3-[(4-bromophenyl)amino]-4*H*-furo-[3,2-*c*]chromen-4-one [14]. Molecules **IX** in crystal are packed to form stacks along the *c* axis due to intermolecular π-stacking between the aromatic rings with an interplane distance of 3.3 Å and intercentroid distance of 3.432(2)–3.888(2) Å. The stacks are linked to layers through several hydrogen bonds O–H···O (H···O 1.76–2.19 Å, ∠OHO 160–168°) with disordered water molecules.

Scheme 2.



Thus the reaction of 4-hydroxycoumarin with 2-acetyloxiranes leads to the formation of 2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-ones which may undergo dehydration or fragmentation to give 4*H*-furo[3,2-*c*]-chromen-4-one derivatives.

EXPERIMENTAL

Analytical and spectral measurements were carried out at the Joint Chemical Service Center (Siberian Branch, Russian Academy of Sciences). The IR spectra were recorded on a Bruker Vector 22 spectrometer. The UV spectra were measured on a Hewlett Packard 4853 spectrophotometer. The ^{1}H NMR spectra were obtained on a Bruker AV-400 instrument from solutions in $CDCl_3$ using the residual proton signal of the solvent as reference ($CHCl_3$, δ 7.26 ppm). The high-resolution mass spectra were recorded on a DFS mass spectrometer. The X-ray diffraction data for compounds **VIIA** and **IX** were acquired at 296 (**VIIA**) or 150 K (**IX**) on a Bruker Kappa ApexII CCD diffractometer [graphite monochromator, λ(MoK_α) = 0.71073 Å; ω,φ-scanning, 2θ < 50 (**VIIA**), 52° (**IX**)]. A correction for absorption was applied empirically using SADABS program [15]. The structures were solved by the direct method. The positions and temperature parameters of non-hydrogen atoms were refined by the full-matrix least-squares procedure in anisotropic approximation. The positions of hydrogen atoms were calculated geometrically and were refined according to the riding model. All calculations were performed using SHELX97 software package [16]. The CIF files for structures **VIIA** and **IX** were deposited to the Cambridge Crystallographic Data Centre (entry nos. CCDC 931267, 931268) and are available at *www.ccdc.cam.ac.uk/data_request/cif*. Slow evaporation of a solution of **VII** in hexane–acetone gave thin lamellar needle-shaped crystals of **VIIA**, and we failed to obtain single crystals of a higher quality. Single crystals of **IX** were obtained by slow evaporation of its solution in a mixture of petroleum ether (bp 40–70°C) with acetone.

Commercial dimethylformamide was distilled under reduced pressure first over calcium hydride and then over molecular sieves and was stored over molecular sieves under argon. Commercial 4-hydroxycoumarin (**I**) and 3-chlorobenzaldehyde were used without additional purification, 4-methylpent-3-en-2-one was distilled before use, and 1-(3,3-dimethyloxiran-2-yl)-ethanone (**IV**) was prepared according to the procedure described in [17] (its physical constants coincided with published data).

4-(3-Chlorophenyl)but-3-en-2-one. 3-Chlorobenzaldehyde, 3.6 ml (0.032 mol), was added dropwise over a period of 10 min to a mixture of 30 ml (0.4 mol) of acetone and 0.5 ml of 10% aqueous sodium hydroxide. The mixture was stirred for 2 h at 23–25°C, poured into 60 ml of water, neutralized with 10% aqueous HCl, and extracted with chloroform (2×30 ml), The combined extracts were dried over $MgSO_4$ and evaporated, and the residue, 5.5 g, was distilled under reduced pressure. Yield 2.2 g (38%), bp 108°C (20 mm). ^{1}H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 6.55 d (1H, CH, J = 16.4 Hz), 7.19 m (2H, H_{arom}), 7.25 m (1H, H_{arom}), 7.28 d (1H, CH, J = 16.4 Hz), 7.35 m (1H, H_{arom}). Found: m/z 180.0337 $[M]^+$. $C_{10}H_9ClO$. Calculated: M 180.0336.

1-[3-(3-Chlorophenyl)oxiran-2-yl]ethanone (III). Hydrogen peroxide, 6 ml, was added to a solution of 1.81 g (0.01 mol) of 4-(3-chlorophenyl)but-3-en-2-one in 50 ml of methanol, and a solution of 2 g (0.05 mol) of sodium hydroxide in 10 ml of water was then added in portions over a period of 30 min at room temperature. The mixture was stirred for 2.5 h at 23–25°C and extracted with chloroform (2×30 ml), and the combined extracts were dried over $MgSO_4$ and evaporated. Yield 1.8 g (92%), colorless oily substance. ^{1}H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 3.46 d (1H, CH, J = 1.7 Hz), 3.98 d (1H, CH, J = 1.7 Hz), 7.17 m (1H, H_{arom}), 7.25 m (1H, H_{arom}), 7.32–7.29 m (2H, H_{arom}). Found: m/z 196.0287 $[M]^+$. $C_{10}H_9ClO_2$. Calculated: M 196.0286.

2-[(3-Chlorophenyl)(hydroxy)methyl]-3-hydroxy-3-methyl-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (VII). A mixture of 0.324 g (2 mmol) of 4-hydroxycoumarin (**I**), 0.498 g (2.53 mmol) of oxirane **III**, and 0.202 g (2 mmol) of triethylamine in 2 ml of DMF was stirred for 15 h at 23–25°C. The mixture was poured into water and extracted with chloroform (3×10 ml), the extract was washed with water and dried over $MgSO_4$, and the aqueous phase was acidified with 10% aqueous HCl to isolate 80 mg of 4-hydroxycoumarin (**I**). The extract was evaporated, and the residue (0.34 g) was subjected to chromatography on a 20×20-mm glass plate coated with silica gel (5–40 μm) using chloroform as eluent. We thus isolated 0.18 g (25%) of diastereoisomer **A** with mp 130–132°C (from hexane–$CHCl_3$) and 0.06 g (8%) of diastereoisomer **B** with mp 155–156°C (from hexane–$CHCl_3$).

Diastereoisomer **VIIA**. IR spectrum (KBr), ν, cm^{-1}: 3433, 1709, 1645, 1420, 758. UV spectrum (EtOH), λ_{max}, nm (logε): 206 (4.55), 273 (3.98), 285 (4.06), 309 (3.97). ^{1}H NMR spectrum, δ, ppm: 1.92 s (3H, CH_3), 3.30 s (1H, OH), 3.80 d (1H, OH, J = 4.2 Hz), 4.58 d (1H, 2-H, J = 8.5 Hz), 5.17 d.d (1H, CH, J = 4.2, 8.5 Hz), 7.27–7.64 m (8H, H_{arom}), 7.63 m (1H, H_{arom}). Found: m/z 358.0605 $[M]^+$. $C_{19}H_{15}ClO_5$. Calculated: M 358.0603. X-Ray diffraction data: monoclinic crystal system, space group $P2_1/n$; unit cell parameters: a = 12.713(4), b = 7.824(2), c = 19.393(6) Å; β = 96.828(9)°; V = 1915.3(9) A^3; Z = 4; $C_{19}H_{15}O_5Cl\cdot C_6H_{14}$; d_{calc} = 1.543 g/cm^3; μ = 0.239 mm^{-1}; T_{min}/T_{max} = 0.75/0.98. Total of 10166 reflection intensities were measured, including 3284 independent reflections (R_{int} = 0.101). Solvate hexane molecules were located inside through channels and were strongly disordered; therefore, we failed to unambiguously identify atoms therein, and their positions were refined in isotropic approximation. The final divergence factors were wR_2 = 0.3007 (for all reflections) and R_1 = 0.0980 [for 1596 reflections with $I > 2\sigma(I)$]; goodness of fit S = 1.015. We did not succeed in improving the R factor because of disordering of solvent molecules and large thermal vibrations of the carbon and chlorine atoms in the phenyl substituent.

Diastereoisomer **VIIB**. IR spectrum (KBr), ν, cm^{-1}: 3420, 2924, 2853, 1705, 1647, 1420, 758. UV spectrum (EtOH), λ_{max}, nm (logε): 203 (4.42), 273 (3.76), 285 (3.81), 308 (3.73). ^{1}H NMR spectrum, δ, ppm: 1.74 s (3H, CH_3), 2.60 s (1H, OH), 4.23 d (1H, 2-H, J = 10.5 Hz), 4.96 s (1H, OH), 5.07 d (1H, CH, J = 10.5 Hz), 7.27–7.61 m (7H, H_{arom}), 7.78 m (1H, H_{arom}). Found: m/z 358.0605 $[M]^+$. $C_{19}H_{15}ClO_5$. Calculated: M 358.0603.

2-(1-Hydroxy-1-methylethyl)-3-methyl-4*H*-furo[3,2-*c*]chromen-4-one (IX). *a*. A mixture of 1.62 g (10 mmol) of 4-hydroxycoumarin (**I**), 1.14 g (10 mmol) of 1-(3,3-dimethyloxiran-2-yl)ethan-1-one (**IV**), and 1.01 g (10 mmol) of triethylamine in 5 ml of DMF was stirred for 15 h at 23–25°C. The mixture was then poured into water and extracted with chloroform (2×50 ml), the extract was washed with water and dried over $MgSO_4$, and the aqueous phase was acidified with 10% aqueous HCl to isolate 1.5 g of unreacted 4-hydroxycoumarin (**I**). The extract was evaporated, and the residue, 0.14 g, was subjected to chromatography on a 20×20-mm glass plate coated with silica gel (5–40 μm) using chloroform as eluent. Yield 0.05 g (2%; 26%, calculated on the reacted 4-hydroxycoumarin), mp 134–135°C (from petroleum ether–$CHCl_3$, 1:1). IR spectrum (KBr), ν, cm^{-1}: 3471, 2978, 1749, 1715, 1184, 754. UV spectrum (EtOH), λ_{max}, nm (logε): 211 (4.27), 292 (3.81), 319 (4.03). ^{1}H NMR spectrum, δ, ppm: 1.72 s (6H, CH_3), 2.51 s (3H, CH_3), 7.29 m (1H, H_{arom}), 7.39 m (1H, H_{arom}), 7.45 m (1H, H_{arom}), 7.79 m (1H, H_{arom}). Found: m/z 258.0885 $[M]^+$. $C_{15}H_{14}O_4$. Calculated: M 258.0887.

b. A mixture of 0.43 g (2.65 mmol) of 4-hydroxycoumarin (**I**), 0.30 g (2.63 mmol) of oxirane **IV**, and 0.26 g (2.57 mmol) of triethylamine in 5 ml of DMF was stirred for 30 h at 76°C. The mixture was poured into water and extracted with chloroform (3×5 ml), the extract was washed with water and dried over $MgSO_4$, and the aqueous phase was acidified with 10% aqueous HCl to isolate 0.40 g of unreacted 4-hydroxycoumarin (**I**). The extract was evaporated, and the residue,

0.07 g, was subjected to chromatography on a 20×20-mm glass plate coated with silica gel (5–40 μm) using chloroform as eluent. Yield 0.045 g (7%; 94%, calculated on the reacted 4-hydroxycoumarin). X-Ray diffraction data: monoclinic crystal system, space group $P2_1/c$; unit cell parameters: a = 9.6912(6), b = 20.1556(11), c = 6.7125(4) Å; β = 97.500(2)°; V = 1299.95(13) Å^3; $C_{15}H_{14}O_4 \cdot 0.5\,H_2O$; Z = 4, d_{calc} = 1.366 g/cm^3; μ = 0.101 cm^{-1}. Total of 8219 reflection intensities were measured, 2550 of which were independent (R_{int} = 0.0448) and 2008 were characterized by $I \geq 2\sigma(I)$. The final divergence factors were wR_2 = 0.1921 (for all reflections) and R_1 = 0.0498 [for reflections with $I \geq 2\sigma(I)$]; goodness of fit S = 1.235. The OH hydrogen atom on C^{10} was disordered by two positions at a ratio of 0.5:0.5. The solvate water molecule was also disordered by two positions at the same ratio. The hydrogen atoms in the water molecule were localized by difference synthesis of electron density, and their positions were not refined.

3-Methyl-4*H*-furo[3,2-*c*]chromen-4-one (XI). 3-Hydroxy-2-[hydroxy(phenyl)methyl]-3-methyl-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (**II**), 0.10 g (0.31 mmol), was added to 5 ml of trifluoroacetic acid, and the mixture was stirred for 24 h at 25°C. The mixture was poured into water, and the precipitate was filtered off, washed with water, and dried. Yield 53 mg (86%), mp 135–136°C [9]. ^{1}H NMR spectrum, δ, ppm: 2.35 s (3H, CH_3), 7.24–7.82 m (5H, H_{arom}). Found: m/z 200.0467 $[M]^+$. $C_{18}H_8O_3$. Calculated: M 200.0468.

Compound **II** was added to acetic acid, the mixture was poured into water, and the precipitate was filtered off, washed with water, and dried. The product was initial compound **II** (recovery ~100%). Analogous result was obtained when the mixture was kept for 24 h at 25°C or heated for 5 h at 50°C.

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