Novel pyrano[3,2-*b*]indole derivatives: synthesis and some properties

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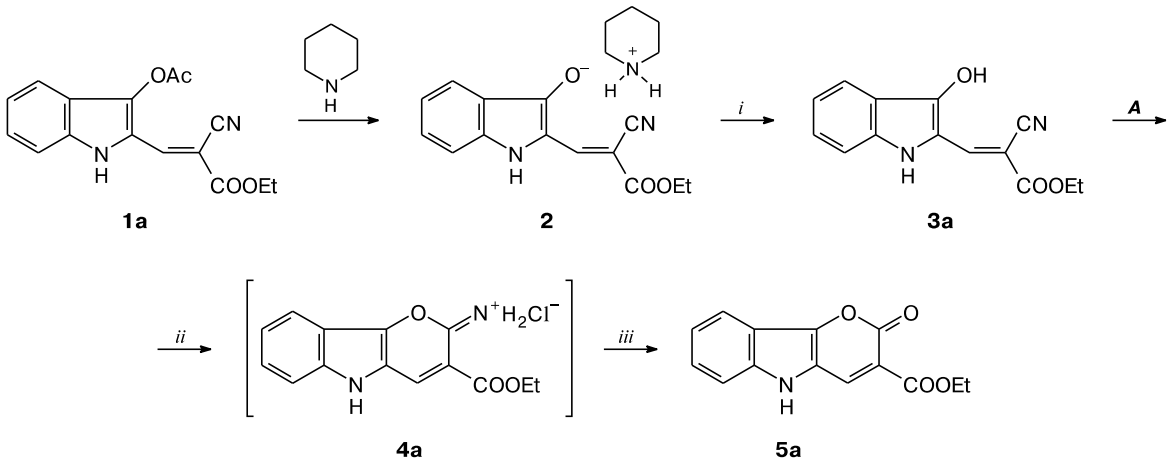
Acid treatment of β-(3-acetoxyindol-2-yl)-α-cyanoacrylic acid derivatives (ethyl ester and nitrile) with aqueous or gaseous HCl afforded novel 3-substituted 2-oxo-2,5-dihydropyrano[3,2-*b*]indoles. 2-Oxo-2,5-dihydropyrano[3,2-*b*]indole-3-carbonitrile was converted into ethyl 2-oxo-2,5-dihydropyrano[3,2-*b*]indole-3-carboximidate.

Key words: ethyl indolylacrylate, indolylacrylonitrile, cyclization, hydrolysis, pyrano[3,2-*b*]-indoles, imidate.

Earlier, we have studied the transformations of β-(3-acetoxyindol-2-yl)-α-cyanoacrylic acid derivatives (ethyl ester **1a** and nitrile **1b**) under the action of basic agents such as primary and secondary amines[1,2] and substituted hydrazines (for nitrile **1b** only).[3] The goal of the present work was to investigate acid-catalyzed transformations of these compounds. Interest in these reactions is due to the reported[4] transformations of 2-vinylindolin-3-ones in hydrochloric acid into pyrano[3,2-*b*]indol-2-ones, which can be regarded as heteroanalogs of benzopyran-2-ones. Some benzopyran-2-ones are used in medical practice, *e.g.*, as anticoagulants (neodicoumarin, phepromaron, and sintrom)[5] and antitonsillitis drugs (carbocromen).[5] Some benzopyran-2-ones annulated with the furan ring are photosensitizers and photoprotectors (beroxan and amimifurin).[5] It should be noted that ethyl 4-oxopyrano[3,2-*b*]-indole-2-carboxylates,[6,7] which are isomeric with pyrano[3,2-*b*]indol-2-one, exhibit antiallergic activity.

Ethyl 3-acetoxyindolylacrylate **1a** prepared according to a known procedure[1] was transformed, through the formation of piperidinium salt **2** followed by treatment with aqueous HCl, into earlier unknown ethyl α-cyano-β-(3-hydroxyindol-2-yl)acrylate (**3a**). When heated in ethanol in the presence of dilute hydrochloric acid (1 : 1), compound **3a** underwent the expected cyclization (pyran ring formation *via* the cyano and hydroxy groups) leading most likely to imine hydrochloride **4a**, which was *in situ* hydrolyzed to ethyl 2-oxo-2,5-dihydropyrano[3,2-*b*]indole-3-carboxylate (**5a**) isolated in 43% yield (Scheme 1).

Scheme 1



i. H_2O, HCl, 20 °C; *ii*. HCl, EtOH, H_2O, D; *iii*. H_2O, Δ.

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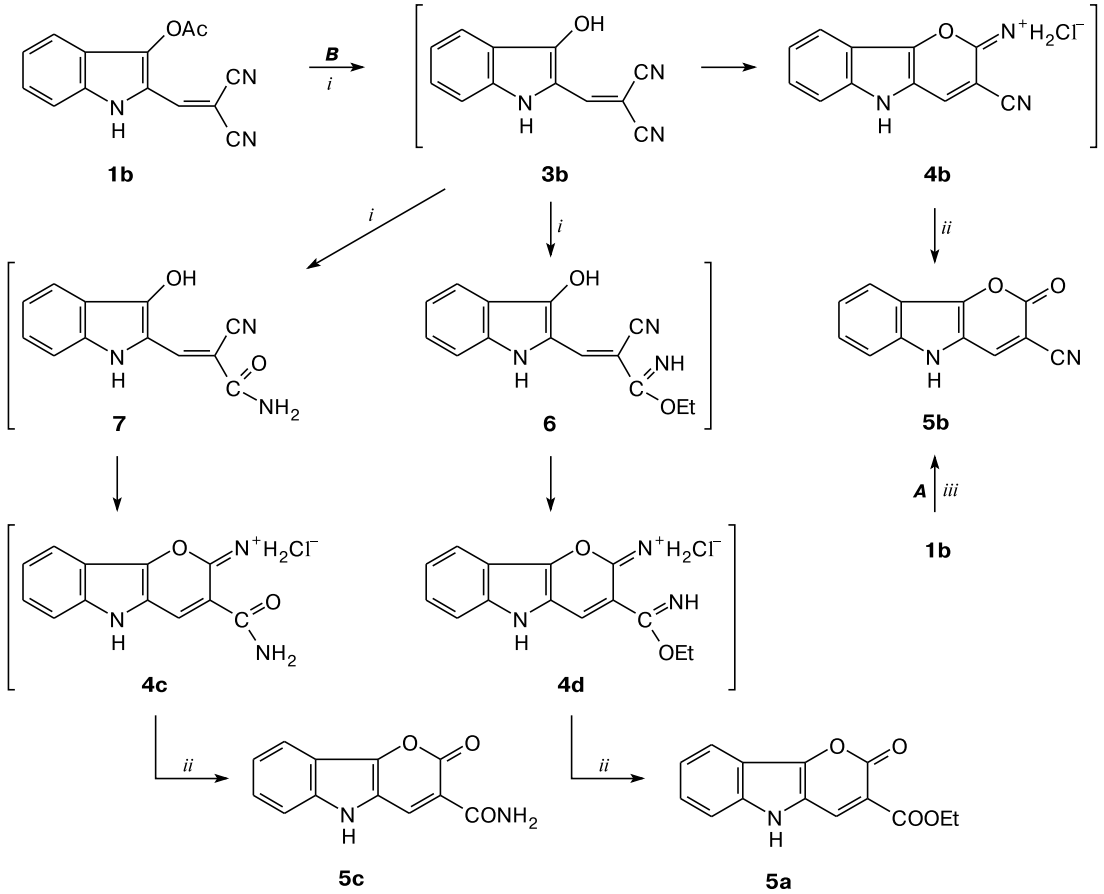
The structure of pyranoindole **5a** was confirmed by mass spectrometry. In the mass spectrum of compound **5a**, the molecular ion peak corresponds to its molecular mass. The ^{1}H NMR spectrum does not contain the singlet for the OH group observed in the spectrum of 3-hydroxyindole **3a** (δ 9.92) and the signals for the aromatic protons are shifted downfield by 0.06—0.4 ppm. The largest shift is experienced by the signal for the H(4) proton, probably because of its conjugation with the carbonyl group in position 2.

Under similar conditions, nitrile **1b** yields a mixture of three compounds: ethyl 2-oxo-2,5-dihydropyrano[3,2-*b*]-indole-3-carboxylate (**5a**), 2-oxo-2,5-dihydropyrano-[3,2-*b*]indole-3-carbonitrile (**5b**), and 2-oxo-2,5-dihydropyrano[3,2-*b*]indole-3-carboxamide (**5c**) (Scheme 2).

According to HPLC data, the ratio of compounds **5a**, **5b**, and **5c** in the reaction mixture is 38 : 52 : 10. Their molecular masses are 257, 210, and 228, respectively (GC-MS). We isolated in the individual state only ethyl carboxylate **5a** identical with the product obtained from ethyl ester **3a**. Carbonitrile **5b** or carboxamide **5c** were not separated from ethyl carboxylate **5a** by either fractional recrystallization or column chromatography. Nevertheless, these compounds were obtained in the individual state by following the procedures described below.

Possible transformations of dicyanovinylindole **1b** under the action of hydrochloric acid are shown in Scheme 2. In the first step, compound **1b** seems to undergo hydrolysis to the corresponding 3-hydroxyindole **3b**, which is sequentially transformed into imine hydrochloride **4b** and carbonitrile **5b** by analogy with Scheme 1. According to HPLC data, carbonitrile **5b** is the major product of this reaction. The formation of by-products is probably due to acid-promoted activation of the CN group of compound **3b** followed by cyclization of ethyl imidate **6** into imine hydrochloride **4d**, which undergoes hydrolysis to ethyl carboxylate **5a**. On the other hand, hydrolysis of the CN group of compound **3b** can give indolylacrylamide **7**, which undergoes cyclization into imine hydrochloride **4c** followed by hydrolysis to carboxamide **5c**. Alternative pathways for the transformation of dicyanovinylindole **1b** into pyranoindoles **5a—c** are also possible.

Scheme 2

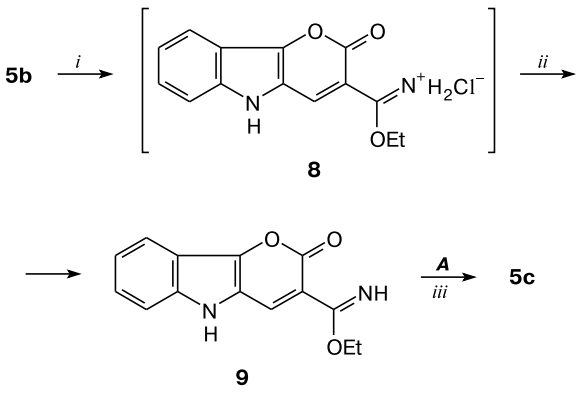


i. HCl, EtOH, H_2O, D; *ii*. H_2O, D; *iii*. HCl, EtOH.

When gaseous HCl was bubbled through a suspension of compound **1b** in anhydrous ethanol and the reaction mixture was treated with water, carbonitrile **5b** was isolated in the individual state in 52% yield (see Scheme 2). The IR spectrum of compound **5b** contains an absorption band at 2220 cm^{-1} characteristic of the CN group. According to ^1H NMR data, the chemical shifts of analogous protons in compounds **5b** obtained in the individual state and in a mixture with ester **5a** are identical.

Interest in the chemical properties of carbonitrile **5b** was due to possible modification of the nitrile function for the synthesis of imidates. For this purpose, as well as for separation of nitrile **5b** from compounds **5a,c**, we passed hydrogen chloride through a suspended mixture of compounds **5a**—**c** in ethanol until carbonitrile **5b** was consumed completely (TLC). By treating the reaction mixture with water, we isolated imidate hydrochloride **8** from compounds **5a,c**, which were recovered unchanged. Alkalization of an aqueous solution of salt **8** gave free imidate **9** (Scheme 3).

Scheme 3

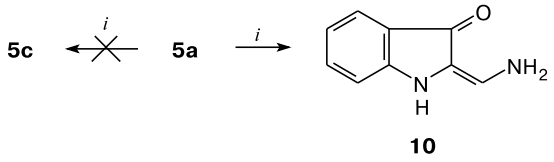


i. HCl, EtOH; *ii*. H_2O, NaOH; *iii*. HCl/EtOAc, Me_2CO.

The chemistry of imidates is quite extensive;[8] imidates can be synthesized from amidines, imidazoles, oxazoles, thiazoles, and various azines. Reactions of imidates with hydrazines, hydroxylamines, acids, and acid anhydrides have been described. Since such amidines as, for example, dienediamines of the indolin-3-one series[2] exhibit high antihypertensive activity, it was interesting to obtain an amidine from imidate **9** and, *e.g.*, benzylamine. Published methods of amidine synthesis involve imidate hydrochlorides. To obtain pure hydrochloride **8**, we treated a solution of imidate **9** in dry acetone with a saturated solution of HCl in ethyl acetate. However, instead of the expected hydrochloride **8**, the reaction under these conditions gave carboxamide **5c** in 86% yield. Apparently, reflux of imidate **9** in acetone to complete dissolution resulted in its transformation[8] into the corresponding carboxamide precipitated upon the addition of a solution of HCl in ethyl acetate.

It should be noted that attempted synthesis of carboxamide **5c** by heating ethyl carboxylate **5a** in a methanolic solution of ammonia in an autoclave failed because of sufficiently deep and unclear degradation of pyran derivative **5a**: instead of the expected carboxamide **5c**, 2-(aminomethylidene)indolin-3-one **10** was isolated in low yield (Scheme 4). The physicochemical characteristics of compound **10** obtained from pyranoindole **5a** agree with the literature data.[9]

Scheme 4



i. NH_3/MeOH

To sum up, reactions of indolylacrylic acid derivatives (ester and nitrile) **1a,b** with acid reagents afforded novel substituted pyrano[3,2-*b*]indoles **5a**—**c**. We determined the ratio of these products and developed the methods for their synthesis. Structures **5a**—**c** were confirmed by spectroscopic techniques. A reaction of carbonitrile **5b** with gaseous HCl gave imidate **9**.

Experimental

IR spectra were recorded on an FSM-1201 instrument (Nujol). The mass spectrum (EI) of compound **5b** was measured on a Finnigan SSQ-710 mass spectrometer (direct inlet probe). The mass spectra (ESI) of compounds **3a**, **5a**, **5c**, and **9** were recorded on a Waters ZQ-2000 mass spectrometer (direct inlet probe). ^1H NMR spectra were recorded on Bruker DRX-500 and Bruker AC-300 spectrometers. HPLC analysis of the reaction mixtures was performed on a Waters Breeze system including the Waters 1525 binary pump, the Waters 2487 dual absorbance detector, and the Rheodyne manual injector (the Empower software, Phenomenex Luna C18(2) HPLC column (150×4.6 mm), UV detector (365 nm), flow rate 1 mL min^{-1}, column temperature 20 °C, separation time 30 min). Methanol—aqueous buffer (45 : 55) was used as a mobile phase. The buffer was prepared by adding propylamine to 0.01% aqueous HCOOH to pH 5.2; samples of the compounds under study and the reaction mixtures were dissolved in methanol and diluted with the mobile phase to a concentration of 10 mg L^{-1}. The course of the reactions was monitored and the purity of the products was checked by TLC on Merck 60 F_{254} plates in chloroform—methanol (10 : 1). Spots were visualized under UV light.

Ethyl 2-cyano-3-(3-hydroxy-1*H*-indol-2-yl)acrylate (3a). A piperidinium salt of ethyl 2-cyano-3-(3-hydroxyindol-2-yl)acrylate (**2**)[1,10] (1.74 g, 0.005 mol) was dissolved in hot water (100 mL) and cooled. The resulting solution was filtered and acidified with 2 *M* HCl (10 mL) to pH 1—2. The precipitate that formed was filtered off, washed with water, MeOH, and ether,

and dried. The yield of compound **3a** was 1 g (45%), m.p. 210—214 °C (from MeOH). IR, ν/cm^{-1}: 1782, 1670 (CO), 2220 (CN), 3362, 3252 (NH). ^{1}H NMR (DMSO-d_6), δ: 1.32 (t, 3 H, $CH_2\underline{CH_3}$, J = 7.2 Hz); 4.25 (q, 2 H, $\underline{CH_2}CH_3$, J = 7.2 Hz); 6.96 (t), 7.28 (t), 7.48 (d), 7.76 (d) (1 H each, H(4)—H(7), J = 8.2 Hz); 8.24 (s, 1 H, H vinyl.); 9.92, 11.19 (both br.s, 1 H each, OH, NH). MS, m/z: 257 $[M + H]^+$, 279 $[M + Na]^+$, 295 $[M + K]^+$, 535 $[2 M + Na]^+$. Found (%): C, 65.46; H, 4.42; N, 10.95. $C_{14}H_{12}N_2O_3$. Calculated (%): C, 65.62; H, 4.72; N, 10.93.

Ethyl 2-oxo-2,5-dihydropyrano[3,2-*b*]indole-3-carboxylate (5a). Method *A*. Concentrated HCl (0.4 mL) was added to a suspension of ester **3a** (0.23 g, 0.9 mmol) in ethanol (5 mL). The mixture was refluxed for 4 h. The precipitate that formed was filtered off hot, washed with ethanol, water, again ethanol, and ether, and dried. The yield of compound **5a** was 0.1 g (43%), m.p. 277—280 °C (from MeOH—DMF, 2 : 1). IR, ν/cm^{-1}: 1624, 1724, 1737 (CO), 3261 (NH). ^{1}H NMR (DMSO-d_6), δ: 1.32 (t, 3 H, $CH_2\underline{CH_3}$, J = 7.2 Hz); 4.29 (q, 2 H, $\underline{CH_2}CH_3$, J = 7.2 Hz); 7.20 (t), 7.45 (t), 7.57 (d), 7.82 (d) (1 H each, H(6)—H(9), J = 8.2 Hz); 8.64 (s, 1 H, H(4)); 11.53 (br.s, 1 H, N(5)H). MS, m/z: 258 $[M + H]^+$, 280 $[M + Na]^+$, 296 $[M + K]^+$, 515 $[2 M + H]^+$, 537 $[2 M + Na]^+$, 553 $[2 M + K]^+$. Found (%): C, 65.79; H, 4.24; N, 5.97. $C_{14}H_{11}NO_4$. Calculated (%): C, 65.35; H, 4.31; N, 5.47.

2-Oxo-2,5-dihydropyrano[3,2-*b*]indole-3-carbonitrile (5b). Method *A*. Hydrogen chloride was bubbled through a suspension of dicyanovinylindole **1b** (1 g, 4 mmol) in anhydrous ethanol (70 mL) for 20 h. The solution was concentrated and the residue was triturated with hexane, filtered off, and washed with ethyl acetate. The resulting precipitate was stirred in water (30 mL), filtered off, washed with water and isopropyl alcohol, and dried. The yield of compound **5b** was 0.44 g (52%), m.p. 285—287 °C (from MeOH). IR, ν/cm^{-1}: 1693, 1736 (CO), 2224 (CN), 3265 (NH). ^{1}H NMR (DMSO-d_6), δ: 7.24 (t), 7.49 (t), 7.57 (d), 7.84 (d) (1 H each, H(6)—H(9), J = 8.2 Hz); 8.82 (s, 1 H, H(4)); 11.93 (br.s, 1 H, N(5)H). MS (EI), m/z (I_{rel} (%)): 210 $[M]^+$ (100), 182 $[M - CO]^+$ (83). Found (%): C, 67.90; H, 2.09; N, 13.20. $C_{12}H_6N_2O_2$. Calculated (%): C, 68.57; H, 2.88; N, 13.33.

Synthesis of ethyl carboxylate 5a, carbonitrile 5b, and 2-oxo-2,5-dihydropyrano[3,2-*b*]indole-3-carboxamide (5c). Method *B*. Water (0.4 mL) and conc. HCl (0.4 mL) were added to a suspension of dicyanovinylindole **1b** (0.25 g, 1 mmol) in ethanol (5 mL). The mixture was refluxed for 4 h* and cooled. The precipitate that formed was filtered off and washed with ethanol, water, and acetone to give a mixture (0.12 g) of pyranoindoles **5a** and **5b**. Compound **5a** (0.03 g, 12%) was isolated from the mixture by recrystallization from MeOH—DMF (2 : 1). The melting point of a mixed sample of compounds **5a** obtained by methods ***A*** and ***B*** showed no depression.

After the recrystallization of compound **5a**, the mother liquor (MeOH—DMF) was evaporated to dryness and the residue was refluxed with stirring in methanol (10 mL). The suspension was cooled and the precipitate was filtered off, washed with methanol, and recrystallized from MeOH—DMF (2 : 1). The yield of a mixture of compounds **5a** and **5b** was 0.03 g. Their ratio (1 : 4) was determined from the intensities of the signals for the N(5)H protons in the ^{1}H NMR spectrum.

After the separation of the mixture of compounds **5a** and **5b**, the aqueous acid mother liquor was evaporated to dryness and the residue was triturated with water. The resulting precipitate was filtered off, washed with isopropyl alcohol, and recrystallized from DMF. The yield of a mixture of compounds **5a** and **5c** was 0.01 g. Their ratio (1 : 8) was determined from the intensities of the signals for the H(4) protons in the ^{1}H NMR spectrum.

Ethyl 2-oxo-2,5-dihydropyrano[3,2-*b*]indole-3-carboximidate (9). Gaseous HCl was bubbled for 28 h through a suspension of a mixture of compounds **5a**—**c** (3.13 g) in anhydrous ethanol until carbonitrile **5b** was consumed completely (TLC). The unreacted mixture (1.37 g) of ethyl carboxylate **5a** and carboxamide **5c** was filtered off and the mother liquor was concentrated. The dry residue (1.9 g) was dissolved in water (60 mL) and alkalized with aqueous ammonia (10 mL) to pH 12. The precipitate that formed was filtered off, washed with water, isopropyl alcohol, and ether, and dried. The yield of compound **9** was 0.6 g (30%), m.p. 238—240 °C. ^{1}H NMR (DMSO-d_6), δ: 1.35 (t, 3 H, $CH_2\underline{CH_3}$, J = 7.2 Hz); 4.25 (q, 2 H, $\underline{CH_2}CH_3$, J = 7.2 Hz); 7.20 (t), 7.44 (t), 7.58 (d), 7.83 (d) (1 H each, H(6)—H(9), J = 8.2 Hz); 8.52 (s, 1 H, H(4)); 9.51 (s, 1 H, C=NH); 11.61 (br.s, 1 H, N(5)H). MS, m/z: 257 $[M + H]^+$, 279 $[M + Na]^+$, 513 $[2 M + H]^+$, 535 $[2 M + Na]^+$, 770 $[3 M + H]^+$, 791 $[3 M + Na]^+$. Found (%): C, 65.50; H, 4.54; N, 10.73. $C_{12}H_8N_2O_3$. Calculated (%): C, 65.62; H, 4.72; N, 10.93.

2-Oxo-2,5-dihydropyrano[3,2-*b*]indole-3-carboxamide (5c). Method *A*. Imidate **9** (0.6 g, 2.3 mmol) was dissolved in boiling anhydrous acetone (60 mL). The solution was filtered to separate mechanical impurities and cooled to 30 °C. A saturated solution of HCl in ethyl acetate (1.2 mL) was added. The precipitate that formed was filtered off, washed with acetone, water, and again acetone, and dried. The yield of compound **5c** was 0.45 g (86%), m.p. 312—314 °C (from DMF). IR, ν/cm^{-1}: 1699, 1722 (CO), 3259, 3319, 3450 (NH, NH_2). ^{1}H NMR (DMSO-d_6), δ: 7.21 (t), 7.44 (t), 7.57 (d), 7.83 (d) (1 H each, H(6)—H(9), J = 8.2 Hz); 8.83 (s, 1 H, H(4)); 7.67, 8.22 (both br.s, 1 H each, NH_2); 11.70 (ws, 1 H, N(5)H). Found (%): N, 11.8. $C_{12}H_8N_2O_3$. Calculated (%): N, 12.28.

2-(Aminomethylidene)indolin-3-one (10). An autoclave was charged with pyranoindole **5a** (0.4 g, 0.0016 mol) and methanol (25 mL) saturated with ammonia (~11% w/w). The mixture was kept first at 55 °C for 7 h and then at 85 °C for 7 h. The solution was concentrated and the viscous residue was triturated with ethyl acetate containing a small amount of isopropyl alcohol. The resulting precipitate was filtered off, washed with ethyl acetate and ether, and dried. The yield of compound **10** was 0.05 g (3%), m.p. > 300 °C (from methanol, decomp.). The product is identical with that described earlier.[9] IR, ν/cm^{-1}: 3400, 3200 (NH, NH_2), 1680 (CO), 1630, 1580 (C=C). MS (EI), m/z (I_{rel} (%)): 160 $[M]^+$ (100).

* For determination of the ratio of the components by HPLC (as well as for the synthesis of compound **9**), the reaction mixture was evaporated to dryness. The ratio **5a** : **5b** : **5c** is 38 : 52 : 10.

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