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Synthesis of Dihydrocoumarin Carbamate Derivatives

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Abstract—The condensation at room temperature in the trifluoroacetic acid of *para*- and *meta*-hydroxy-substituted methylphenylcarbamate with cinnamic acids or their esters containing electron-donor substituents in the benzene ring yielded dihydrocoumarins with a carbamate function attached to C^6 or C^7. Under similar conditions the methyl(2-hydroxyphenyl)carbamate, cinnamic acids or their esters containing electron-acceptor substituents or electron-donor substituents in the *ortho*-position of the benzene ring are not involved into the condensation.

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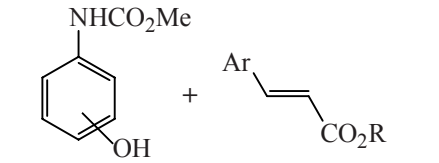
Recently a procedure was developed for the synthesis of dihydrocoumarin derivatives by a reaction of β-naphthol and phenols containing in the ring electron-donor (OMe, Me) or weak electron-acceptor (Br) substituents with cinnamic acids or their esters in trifluoroacetic acid at room temperature [1].

With a goal of preparation of potential biologically active dihydrocoumarins with a carbamate function the possibility of involving into this reaction methyl phenylcarbamate hydroxy derivatives appeared significant.

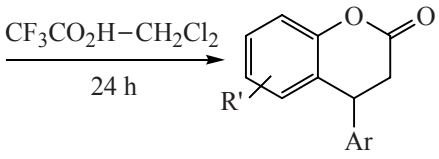
We studied the condensation of methyl (3-hydroxyphenyl)- (**I**), methyl (4-hydroxyphenyl)- (**II**), and methyl (2-hydroxyphenyl)carbamates (**III**) with 3-phenyl-, 3-(4-methoxyphenyl)-, 3-(3,4-dimethoxyphenyl)-, 3-(1,3-benzodioxol-5-yl)-, 3-(2-methoxyphenyl)-, 3-(4-bromophenyl)-2-propenic acid, and also with ethyl 3-(4-methoxyphenyl)- and ethyl 3-(4-bromohenyl)-2-propenoates.

The process was performed by keeping equimolar quantities of the reagents in a mixture CF_3CO_2H–CH_2Cl_2, 2:1 by volume, at room temperature for 24 h. It was established that only 3– and 4-hydroxyphenylcarbamates **I, II** were involved into the reaction yielding dihydrocoumarins **IV–VIII**.

The parameters of ^{1}H NMR spectra of compounds obtained are consistent with the assumed structures and are analogous to the spectra of similarly built compounds [1–6]. For instance, in the ^{1}H NMR spectra of compounds **IV–VIII** the H^3 protons appear as a double doublet of doublets in the region 2.94 and 3.04 ppm, and the H^4 proton gives rise to a triplet at 4.21–4.22 ppm (*J* 6.6–6.9 Hz). The structure of dihydrocoumarin **IV** was additionally proved by the ^{13}C NMR spectrum.



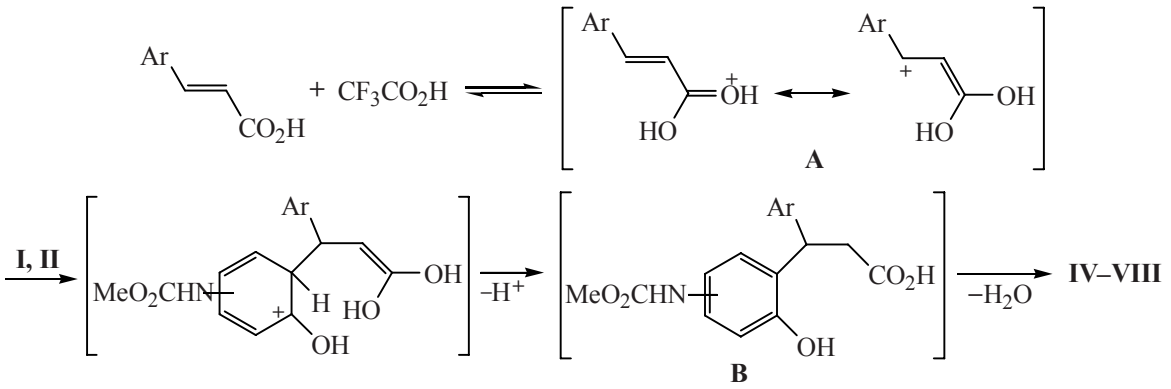
I, II



IV–VIII

3-OH (**I**), 4-OH (**II**); R = H, Et; R' = 7-$NHCO_2Me$, Ar = 4-$MeOC_6H_4$ (**IV**), 3,4-$(MeO)_2C_6H_3$ (**V**), 3,4-$(OCH_2O)C_6H_3$ (**VI**); R' = 6-$NHCO_2Me$, Ar = 4-$MeOC_6H_4$ (**VII**), 3,4-$(MeO)_2C_6H_3$ (**VIII**).

Yet the attempts to involve into the condensation methyl (2-hydroxyphenyl)carbamate (**III**) by varying the electronic character of the substituents in the benzene ring of cinnamic acid or its ester, and by prolonging the process to 72 h were unsuccessful. This result is evidently due to the steric hindrances for the carbamate moiety located in the *ortho*-position with respect to the phenol hydroxy group.



We also established that 3-phenyl-2-propenic, 3-(2-methoxyphenyl)-2-propenic acids, 3-(4-bromophenyl)-2-propenic acid and its ethyl ester did not react under similar conditions with hydroxy-substituted carbamates **I** and **II**. The results obtained are consistent with the probable mechanism given above.

The protonation of the carbonyl oxygen of the cinnamic acid or its ester effected by trifluoroacetic acid results in the formation of intermediate **A**; therewith the electron-donor substituents stabilize the latter and facilitate further transformations. Yet the unsubstituted phenyl and 4-bromophenyl groups cannot stabilize intermediate **A**, therefore the 3-phenyl-2-propenic and 3-(4-bromophenyl)-2-propenic acids do not condense with compounds **I** and **II**. Apparently owing to steric hindrances the 2-methoxyphenyl group of the 3-(2-methoxyphenyl)-2-propenic acid also cannot take part in the stabilization of the cationic intermediate.

The electrophilic substitution in hydroxy-substituted methyl phenylcarbamates **I** and **II** by the carbocation intermediate **A** leads to the formation of an intermediate 3-aryl-3-[2-hydroxy-4(5)-methoxycarboxyamidophenyl]propanic acid **B** that further undergoes an intramolecular heterocyclization with water elimination resulting in dihydrocoumarins **IV–VIII**.

EXPERIMENTAL

IR spectra were measured on an IR Fourier spectrophotometer Infralum FT-02 in the range 4000–400 cm^{-1} from pellets with KBr. ^{1}H NMR spectra were registered on a spectrometer Bruker AC-200 (200.13 MHz) in deuterochloroform, internal reference TMS. ^{13}C NMR spectrum was recorded on a spectrometer Bruker DRX 500 (126 MHz) in $CDCl_3$ with complete decoupling from protons. The purity of products obtained was checked by TLC on Silufol UV-254 plates, development in iodine vapor. Substituted cinnamic acids were prepared by Knoevenagel–Doebner procedure [6].

7-[(Methoxycarbonyl)amino]-4-(4-methoxyphenyl)-3,4-dihydrocoumarin (IV). *a*. A mixture of 0.36 g (2 mmol) of 3-(4-methoxyphenyl)-2-propenic acid, 0.34 g (2 mmol) of methyl (3-hydroxyphenyl)carbamate (**I**), 2 ml of trifluoroacetic acid, and 1 ml of methylene chloride was maintained in a stoppered flask at room temperature for 24 h. The reaction mixture was neutralized by a saturated water solution of sodium hydrogen carbonate and extracted with methylene chloride (2×15 ml), the organic solution was dried with sodium sulfate and was subjected to column chromatography on activated silica gel 100/400 μ. The solvent was removed, and the product was purified by recrystallization from a mixture methylene chloride–hexane, 1:2. Yield 0.30 g (46%), colorless crystals, mp 122–123°C. IR spectrum, ν, cm^{-1}: 3346 (NH), 1728 (C=O), 1620, 1600, 1528, 1510 (C=C, C–C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 2.94 d.d (1H, H^3, *J* 15.8, 8.0 Hz), 3.04 d.d (1H, H^3, *J* 15.8, 5.9 Hz), 3.52 s (3H, OMe), 3.71 s (3H, $NHCO_2CH_3$), 4.22 t (1H, H^4, *J* 6.6 Hz), 6.65 d.d (1H, H$_{arom}$, *J* 8.4, 2.5 Hz), 6.68 d (1H, H$_{arom}$, *J* 2.0 Hz), 6.82–6.87 m (3H, H$_{arom}$), 7.17 d (2H, H$_{arom}$, *J* 8.1 Hz), 8.54 br.s (1H, NH). Found, %: C 65.85; H 5.17; N 4.08. $C_{18}H_{17}NO_5$. Calculated, %: C 66.06; H 5.20; N 4.28.

b. Likewise from 0.34 g (2 mmol) of carbamate **I** and 0.41 g (2 mmol) of ethyl 3-(4-methoxyphenyl)-2-propenoate was obtained compound **IV**. Yield 0.31 g (48%), colorless crystals, mp 122–123°C. ^{13}C NMR spectrum, δ, ppm: 36.36 (C^3), 40.24 (C^4), 52.48 ($NHCO_2CH_3$), 54.32 (OMe), 106,27 (C^8), 113.44 (C$^{3',5'}$), 116.25 (C^{10}), 116.75 (C^6), 129.22 (C$^{6'}$), 130.54 (C^5), 132.07 (C$^{2'}$), 134.85 (C^1), 143.54 (C^7), 154.84 ($NHCO_2Me$), 156.04 (C^9), 158.58 (C$^{4'}$), 166.24 (C=O). Found, %: C 66.15; H 5.07; N 4.28. $C_{18}H_{17}NO_5$. Calculated, %: C 66.06; H 5.20; N 4.28.

Compounds **V–VIII** were similarly prepared.

7-[(Methoxycarbonyl)amino]-4-(3,4-dimethoxyphenyl)-3,4-dihydrocoumarin (V) was obtained from 0.34 g (2 mmol) of carbamate **I** and 0.42 g (2 mmol) of 3-(3,4-dimethoxyphenyl)-2-propenic acid. Yield 0.61 g (85%), colorless crystals, mp 133–134°C. IR spectrum, ν, cm^{-1}: 3328 (NH), 1728 (C=O), 1620, 1605, 1528, 1510 (C=C, C–:C_{arom}). ^1H NMR spectrum, δ, ppm: 2.94 d.d (1H, H^3, *J* 15.8, 8.0 Hz), 3.04 d.d (1H, H^3, *J* 15.8, 5.9 Hz), 3.56 s (6H, OMe), 3.71 s (3H, $NHCO_2CH_3$), 4.23 t (1H, H^4, *J* 6.6 Hz), 6.67 d (1H, H_{arom}, *J* 2.4 Hz), 6.83–6.87 m (3H, H_{arom}), 7.18 d (2H, H_{arom}, *J* 8.2 Hz), 8.54 br.s (1H, NH). Found, %: C 63.94; H 5.27; N 4.03. $C_{19}H_{19}NO_6$. Calculated, %: C 63.87; H 5.32; N 3.92.

4-(1,3-Benzodioxol-5-yl)-7-[(methoxycarbonyl)amino]-3,4-dihydrocoumarin (VI) was obtained from 0.34 g (2 mmol) of carbamate **I** and 0.38 g (2 mmol) of 3-(1,3-benzodioxol-5-yl)-2-propenic acid. Yield 0.56 g (83%), colorless crystals, mp 165–167°C. IR spectrum, ν, cm^{-1}: 3337 (NH), 1728 (C=O), 1620, 1600, 1530, 1510 (C=C, C–:C_{arom}). ^1H NMR spectrum, δ, ppm: 2.94 d.d (1H, H^3, *J* 15.8, 8.0 Hz), 3.04 d.d (1H, H^3, *J* 15.8, 5.9 Hz), 3.71 s (3H, $NHCO_2CH_3$), 4.23 t (1H, H^4, *J* 6.6 Hz), 5.93 s (2H, OCH_2O), 6.78 s (1H, H_{arom}), 6.86 d (2H, H_{arom}, *J* 8.6 Hz), 7.05 d (2H, H_{arom}, *J* 8.6 Hz), 7.12 s (1H, H_{arom}), 8.54 br.s (1H, NH). Found, %: C 63.57; H 4.24; N 3.93. $C_{18}H_{15}NO_6$. Calculated, %: C 63.34; H 4.40; N 4.11.

6-[(Methoxycarbonyl)amino]-4-(4-methoxyphenyl)-3,4-dihydrocoumarin (VII) was obtained from 0.34 g (2 mmol) of carbamate **II** and 0.36 g (2 mmol) of 3-(4-methoxyphenyl)-2-propenic acid. Yield 0.23 g (35%), colorless crystals, mp 89–91°C. IR spectrum, ν, cm^{-1}: 3347 (NH), 1730 (C=O), 1620, 1600, 1535, 1509 (C=C, C–:C_{arom}). ^1H NMR spectrum, δ, ppm: 2.94 d.d (1H, H^3, *J* 15.8, 7.7 Hz), 3.04 d.d (1H, H^3, *J* 15.8, 6.0 Hz), 3.57 s (3H, OMe), 3.73 s (3H, $NHCO_2CH_3$), 4.22 t (1H, H^4, *J* 6.9 Hz), 6.52 d (1H, H_{arom}, *J* 6.5 Hz), 6.78 d.d (1H, H_{arom}, *J* 8.5, 3.4 Hz), 6.85 d (2H, $H_{arom.}$, *J* 8.2 Hz), 7.12–7.17 m (3H, H_{arom}), 8.55 br.s (1H, NH). Found, %: C 65.76; H 5.21; N 4.16. $C_{18}H_{17}NO_5$. Calculated, %: C 66.06; H 5.20; N 4.28.

6-[(Methoxycarbonyl)amino]-4-(3,4-dimethoxyphenyl)-3,4-dihydrocoumarin (VIII) was obtained from 0.34 g (2 mmol) of carbamate **II** and 0.42 g (2 mmol) 3-(3,4-dimethoxyphenyl)-2-propenic acid. Yield 0.54 g (75%), colorless crystals, mp 165–166°C. IR spectrum, ν, cm^{-1}: 3339 (NH), 1730 (C=O), 1620, 1600, 1535, 1510 (C=C, C–:C_{arom}). ^1H NMR spectrum, δ, ppm: 2.93 d.d (1H, H^3, *J* 15.7, 8.0 Hz), 3.04 d.d (1H, H^3, *J* 15.7, 5.9 Hz), 3.56 s (6H, OMe), 3.73 s (3H, $NHCO_2CH_3$), 4.22 t (1H, H^4, *J* 6.7 Hz), 6.69 s (1H, H_{arom}), 6.84 d (2H, H_{arom}, *J* 8.9 Hz), 6.87 s (1H, H_{arom}), 7.15 d (2H, H_{arom}, *J* 8.3 Hz), 8.57 br.s (1H, NH). Found, %: C 63.71; H 5.19; N 3.84. $C_{19}H_{19}NO_6$. Calculated, %: C 63.87; H 5.32; N 3.92.

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