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Synthesis of Aromatic Carbamates Derivatives with a Chromen-2-one Fragment

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Abstract—Condensation of methyl *N*-(3-hydroxyphenyl)carbamate with ethyl trifluoromethylacetoacetate, 2-methoxyethyl acetoacetate in the presence of conc. sulfuric acid, and also with acetonedicarboxylic acid formed in situ from citric acid under the action of conc. sulfuric acid afforded chromene derivatives. The esterification of 2-{7-[(methoxycarbonyl)amino]-2-oxo-2*H*-chromen-4-yl}acetic acid with methanol in the presence of TsOH provided the corresponding ester. The oxidation of its α-methylene group with selenium dioxide led to the formation of methyl 2-{7-[(methoxycarbonyl)amino]-2-oxo-2*H*-chromen-4-yl}-2-oxo-acetate entering into a condensation with *o*-phenylenediamine resulting in a derivative with a dihydroquinoxaline fragment. The reaction of phenyl *N*-(4-formylphenyl)carbamate with 3-acetyl-2*H*-chromen-2-one in butanol in the presence of catalytic quantity of piperidine and acetic acid furnished 4-[(*E*)-3-oxo-2*H*-chromen-3-yl)-1-propenyl]phenyl *N*-phenylcarbamate.

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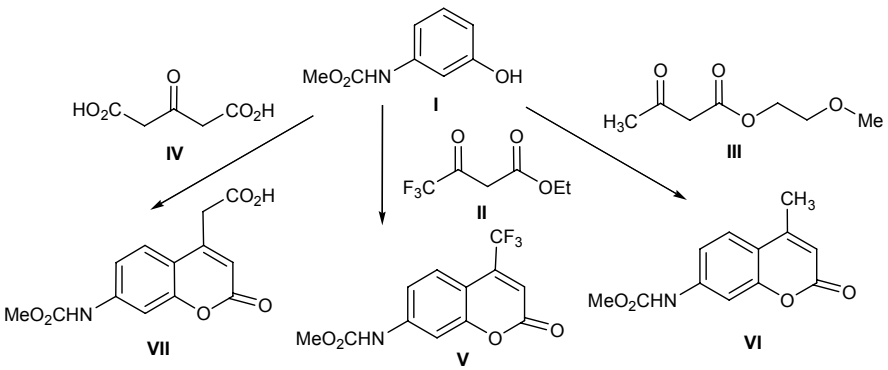
Coumarins and their derivatives exhibit a wide range of biological action. Compounds found among them possess antiphlogistic [1], anesthetic [2], fungicidal [3], antibacterial [4], antiviral, neuroleptic [5], tuberculocidal, anti-HIV, anticancer, and antioxidant activity [6–8]. Insignificant changes in the coumarin structure essentially alter its activity. Therefore the synthesis of new coumarin derivatives and their subsequent pharmaceutical screening are of obvious interest.

In extension of research on the synthesis of new chromen-2-one derivatives possessing a carbamate function [9, 10] we studied the condensation of methyl *N*-(3-hydroxyphenyl)carbamate (**I**) with ethyl trifluoromethylacetoacetate (**II**), 2-methoxyethyl acetoacetate (**III**) in the presence of conc. sulfuric acid, and also of acetonedicarboxylic acid (**IV**) formed in situ from citric acid under the action of conc. sulfuric acid [11]. Basing on the investigation of the structure of the reaction products by IR, ^{1}H, ^{13}C NMR spectroscopy, and of the product of the reaction with ethyl trifluoromethylacetoacetate also by mass spectrometry we established that the reaction products were chromene derivatives **V–VII** (Scheme 1).

^{1}H NMR spectrum of compound **VI** contained the singlet from proton H^3 in the region 6.22 ppm, in the

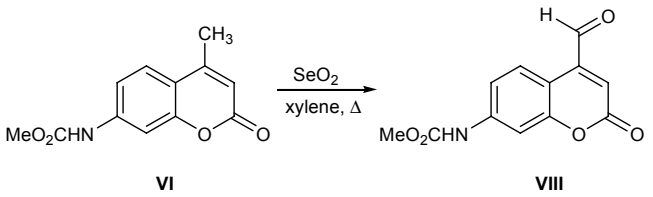
Scheme 1.



spectra of compounds **V** and **VII** this signal shifted downfield (δ 6.84–6.85 ppm) due to the deshielding effect of electron-acceptor groups.

The oxidation of the methyl group of compound **VI** with selenium dioxide led to the formation of the corresponding aldehyde **VIII** (Scheme 2).

Scheme 2.



VI **VIII**

In the ^{1}H NMR spectrum of compound **VIII** in the downfield region along with the singlet signal of the NH group at 10.59 ppm a singlet is observed belonging to a formyl group (δ 10.20 ppm), and the singlet of the proton H^3 appears at 7.00 ppm.

The heating of 2-{7-[(methoxycarbonyl)amino]-2-oxo-2*H*-chromen-4-yl}acetic acid (**VII**) with methanol in the presence of a catalytic quantity of *p*-toluenesulfonic acid provided the corresponding ester **IX** (Scheme 3).

In the ^{1}H NMR spectrum of ester **IX** unlike the spectrum of compound **VII** the singlet signal of one proton of the carboxy group at 10.07 ppm disappeared, but a singlet appeared at 3.65 ppm belonging to three protons of the methoxycarbonyl group.

The oxidation of the α-methylene group of the ester with selenium dioxide afforded methyl 2-{7-[(methoxycarbonyl)amino]-2-oxo-2*H*-chromen-4-yl}-2-oxoacetate (**X**) interesting for the syntheses of polyheterocyclic compounds.

The ^{1}H NMR spectrum of α-ketoester **X** in contrast to the spectrum of acid **IX** did not contain the singlet at 3.75 ppm belonging to two protons of the methylene group, and in its IR spectrum an additional absorption band appears from the carbonyl group at 1680 cm^{-1}.

In order to further functionalize compound **X** we examined its reaction with *o*-phenylenediamine. The reaction was carried out by boiling the reagents mixture in butanol for 6 h.

We established proceeding from the data of IR and ^{1}H NMR spectra that the reaction led to the formation of methyl *N*-[2-oxo-4-(3-oxo-3,4-dihydro-2-quinoxalinyl)-2*H*-chromen-7-yl]carbamate (**XI**) (Scheme 4).

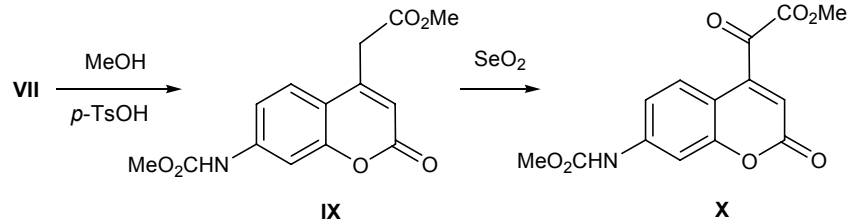
The condensation of phenyl *N*-(4-formylphenyl) carbamate (**XII**) [12] with 3-acetyl-2*H*-chromen-2-one (**XIII**) [13] in butanol in the presence of catalytic quantities of piperidine and acetic acid yielded 4-{[(*E*)-3-oxo-2*H*-chromen-3-yl]-1-propenyl}phenyl *N*-phenyl-carbamate (**XIV**) whose structure was confirmed by IR and ^{1}H NMR spectra (Scheme 5).

The ^{1}H NMR spectrum of chalcone **XIV** along with the signals of the aromatic protons and NH group contained a singlet at 8.50 ppm corresponding to the proton H^4 of coumarin, and also a doublet from one proton attached to the C=C group at 7.82 ppm (*J* 15.6 Hz), indicating the formation of the *E*-isomer of chalcone [14, 15].

EXPERIMENTAL

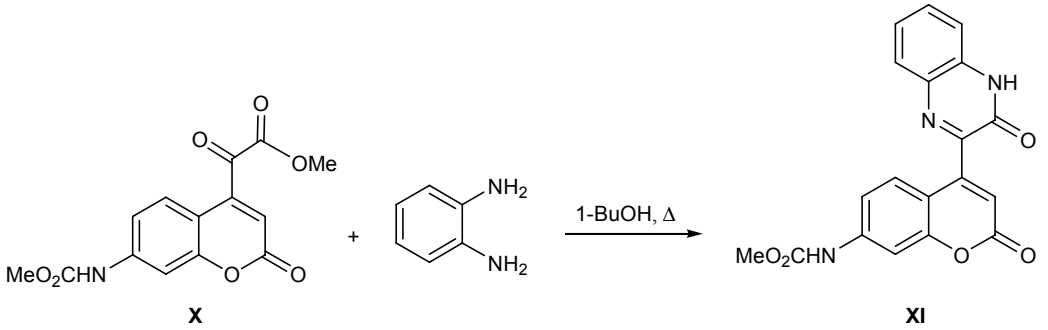
^{1}H NMR spectra were registered on a spectrometer Bruker DRX-500 (500.13 MHz). ^{13}C NMR spectra were recorded on a spectrometer Bruker WM-400 (100 MHz) with a wide-band decoupling from protons, solvent DMSO-d_6. IR spectra were obtained on an IR Fourier spectrophotometer Infra-LUM FT-02 in the range 4000–400 cm^{-1} from pellets with KBr. Mass spectra were measured on an instrument Finnigan MAT INCOS 50 at ionizing electrons energy 70 eV. The purity of compounds obtained was tested by TLC

Scheme 3.



IX **X**

Scheme 4.



X **XI**

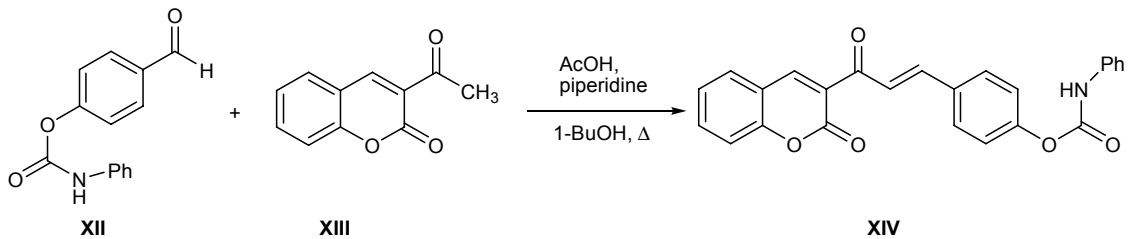
on Silufol UV-254 plates, development in iodine vapor.

Methyl *N*-[2-oxo-4-(trifluoromethyl)-2*H*-chromen-7-yl]carbamate (V). To 4 mL of conc. H_2SO_4 cooled to 0–5°C was added at vigorous stirring 0.7 g (4.2 mmol) of methyl N-(3-hydroxyphenyl)carbamate (**I**) and 0.61 mL (4.2 mmol) of ethyl trifluoromethylacetoacetate (**II**), maintaining the temperature below 10°C. The mixture was maintained at room temperature for 24 h, poured into 50 mL of ice water, the separated precipitate was filtered off, thoroughly washed with water on the filter, dried in desiccator, and recrystallized from chloroform. Yield 1.16 g (96%), colorless crystals, mp 155–157°C. IR spectrum, ν, cm^{-1}: 3310 (NH), 1710, 1665 (C=O), 1610, 1575, 1565 (C=C, C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 3.73 s (3H, $NHCO_2\underline{Me}$), 6.85 s (1H, H^3), 7.46 d.d (1H, H^6, *J* 2.0, 9.0 Hz), 7.65 d.d (1H, H^5, *J* 2.0, 9.0 Hz), 8.32 s (1H, H^8), 10.35 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 52.22 ($NHCO\underline{C}H_3$), 104.93, 107.55, 113.92, 115.09, 120.63 (C_{Ar}), 122.82 (CF_3), 125.53, 143.87, 153.77 (C_{Ar}), 154.92 ($NH\underline{C}O_2CH_3$), 158.67 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 289 (1.7) $[M + 2]^+$, 288 (12) $[M + 1]^+$, 287 (100) $[M]^+$, 268 (5), 255 (17), 227 (37), 214 (40), 200 (20), 173 (8), 152 (12), 145 (7), 125 (3), 83 (5), 75 (3), 59 (17). Found, %: C 50.15; H 2.80; N 4.75. $C_{12}H_8F_3NO_4$. Calculated, %: C 50.17; H 2.79; N 4.88. *M* 287.

Methyl *N*-(4-methyl-2-oxo-2*H*-chromen-7-yl)carbamate (VI) was obtained similarly from 0.7 g (4.2 mmol) of methyl *N*-(3-hydroxyphenyl)carbamate (**I**) and 0.62 mL (4.2 mmol) of 2-methoxyethyl acetoacetate (**III**). Yield 0.91 g (93%), colorless crystals, mp 256–257°C (from ethanol) (mp 256–257°C [9]. IR spectrum, ν, cm^{-1}: 3280 (NH), 1730, 1692 (C=O), 1620, 1584, 1536, 1512 (C=C, C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 2.38 s (3H, Me), 3.73 s (3H, OMe), 6.22 s (1H, H^3), 7.38 d.d (1H, H^6, *J* 2.0, 8.4 Hz), 7.54 s (1H, H^8), 7.69 d (1H, H^5, *J* 8.4 Hz), 10.15 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 18.5 (CH_3), 52.42 ($NHCO_2\underline{Me}$), 105.60, 110.02, 113.14, 117.37, 127.56, 146.07, 152.14 (C_{Ar}), 154.86 ($NH\underline{C}O_2Me$), 155.78 (C_{Ar}), 159.58 (C=O). Found, %: C 61.72; H 4.57; N 5.81. $C_{12}H_{11}NO_4$. Calculated, %: C 61.80; H 4.72; N 6.01.

2-{7-[(Methoxycarbonyl)amino]-2-oxo-2*H*-chromen-4-yl}acetic acid (VII). To 16 mL of conc. sulfuric acid was added 0.96 g (5 mmol) of citric acid, and the mixture was heated at 60–65°C under continuous stirring for 30 min. The obtained solution of acetonedicarboxylic acid (**IV**) in conc. sulfuric acid was cooled to 0°C and was added thereto at vigorous stirring within 1 h 0.85 g (5 mmol) of methyl *N*-(3-hydroxyphenyl)carbamate (**I**) maintaining the temperature at 0–5°C. The reaction mixture was stirred for 2 h more at 5°C, then the reaction mixture was slowly warmed to 30°C, left for 24 h at room temperature, then poured in 50 g of crushed ice. The separated precipitate was filtered off, dissolved in 20 mL of saturated solution of sodium hydrogen carbonate, 2 g of activated carbon was added to remove colored

Scheme 5.



XII **XIII** **XIV**

impurities, and after removal of the adsorbent the filtrate was acidified with conc. hydrochloric acid. The separater precipitate was filtered off and dried in air. Yield 1.0 g (72%), colorless crystals, mp 249–250°C. IR spectrum, ν, cm^{-1}: 3330 (NH), 3250 (OH), 1710, 1695 (C=O), 1612, 1575, 1565 (C=C, $C=C_{arom}$). ^1H NMR spectrum, δ, ppm: 3.71 s (3H, $NHCO_2\underline{Me}$), 3.79 s (2H, $C\underline{H}_2CO_2H$), 6.84 s (1H, H^3), 7.22 d (1H, H^6, *J* 8.2 Hz), 7.59 s (1H, H^8), 7.84 d (1H, H^5, *J* 8.2 Hz), 10.07 br.s (1H, COOH), 10.58 br.s (1H, $NHCO_2Me$). ^{13}C NMR spectrum, δ, ppm: 44.17 (CH_2), 52.31 ($NHCO_2\underline{C}H_3$),105.25, 113.14, 113.81, 114.67, 128.18, 147.04, 152.81 (C_{Ar}), 154.94 ($NH\underline{C}O_2CH_3$), 155.25 (C_{Ar}), 162.35 (O–C=O), 175.20 (COOH). Found, %: C 56.27; H 4.01; N 4.87. $C_{13}H_{11}NO_6$. Calculated, %: C 56.32; H 3.97; N 5.05.

Methyl *N*-(4-formyl-2-oxo-2*H*-chromen-7-yl)-carbamate (VIII). A mixture of 1.17 g (5 mmol) of methyl *N*-(4-methyl-2-oxo-2*H*-chromen-7-yl)carbamate (**VI**), 0.72 g (6.5 mmol) of selenium dioxide was boiled for 7 h, filtered from selenium formed in the course of the reaction, the filtrate was cooled to 0°C, and the precipitated crystals were filtered off and recrystallized from a mixture hexane–dichloromethane, 4 : 1 (v/v). Yield 1.0 g (81%), yellow crystals, mp 224−226° C. IR spectrum, ν, cm^{-1}: 3327 (NH), 1710, 1705 (C=O), 1610, 1575, 1565 (C=C, $C=C_{arom}$). ^1H NMR spectrum, δ, ppm: 3.71 s (3H, $NHCO_2\underline{Me}$),7.00 s (1H, H^3),7.28 d (1H, H^6, *J* 8.1 Hz), 7.68 s (1H, H^8), 8.02 d (1H, H^5, *J* 8.1 Hz), 10.2 s (1H, CHO), 10.59 br.s (1H, $N\underline{H}CO_2Me$). Found, %: C 58.34; H 3.58; N 5.70 .$C_{12}H_9NO_5$. Calculated, %: C 58.30; H 3.64; N5.67.

Methyl 2-{7-[(methoxycarbonyl)amino]-2-oxo-2*H*-chromen-4-yl}acetate (IX). A mixture of 1.39 g (5 mmol) of 2-{7-[(methoxycarbonyl)amino]-2-oxo-2*H*-chromen-4-yl}acetic acid (**VII**), 3.8 mL (0.09 mol) of methanol, and 0.1 g of *p*-toluenesulfonic acid was boiled for 6 h, cooled to 5-10 °C, the product was filtered off, washed on the filter with 10 mL of 3% solution of sodium hydrogen carbonate, with water, dried in air, and recrystallized from methanol. Yield 1.3 g (90%), colorless crystals, mp 228–230°C. IR spectrum, ν, cm^{-1}: 3330 (NH), 1710, 1690 (C=O), 1610, 156515, 75 (C=C, $C=C_{arom}$). ^1H NMR spectrum, δ, ppm:3.6 s (3H, $CO_2\underline{Me}$),3.71 s (3H, $NHCO_2\underline{Me}$), 3.75 s (2H, $C\underline{H}_2CO_2Me$), 6.74 s (1H, H^3), 7.21 d (1H, H^6, *J* 8.2 Hz), 7.63–7.67 m (2H, $H_{arom.}$), 10.58 br.s (1H, NH). Found, %: C 57.59; H 4.46; N 4.79. $C_{14}H_{13}NO_6$. Calculated, %: C 57.73; H 4.47; N 4.81.

Methyl 2-{7-[(methoxycarbonyl)amino]-2-oxo-2*H*-chromen-4-yl}-2-oxoacetate (X). To a mixture of 1.46 g (5 mmol) of ester **IX** in 5 mL of *o*-xylene heated to 60-70 °C was added 0.72 g (6.5 mmol) of selenium dioxide within 10 min, then the reaction mixture was boiled for 6 h, filtered from selenium formed in the course of the reaction, the filtrate was cooled to 0°C, the precipitated crystals were filtered off and recrystallized from a mixture dichloromethane–hexane, 1 : 2 (v/v). Yield 1.3g (85%), light yellow crystals, mp 190−191°C. IR spectrum, ν, cm^{-1}: 3330 (NH), 1710, 1680, 1695 (C=O), 1610, 1570, 1565 (C=C, $C=C_{arom}$). ^1H NMR spectrum, δ, ppm: 3.67 s (3H, $CO_2\underline{Me}$), 3.71 s (3H, $NHCO_2\underline{Me}$), 7.07 s (1H, H^3), 7.22 d (1H, H^6, *J* 8.2 Hz), 7.68 s (1H, H^8), 7.74 d (1H, H^5, *J* 8.2 Hz), 10.58 br.s (1H, $N\underline{H}CO_2Me$). Found, %: C 54.96; H 3.65; N 4.38. $C_{14}H_{11}NO_7$. Calculated, %: C 55.08; H 3.61; N 4.59.

Methyl *N*-[2-oxo-4-(3-oxo-3,4-dihydro-2-quinoxalinyl)-2*H*-chromen-7-yl]carbamate (XI) A mixture of 0.31 g (1.02 mmol) of α-ketoester **X**, 0.1 g (1.1 mmol) of *o*-phenylenediamine in 10 mL of *n*-butanol was boiled for 6 h, cooled, the separated precipitate was filtered off, washed on the filter with *n*-butanol (2 mL), acetone (2 mL), and recrystallized from dioxane. Yield 0.32 g (87%), light yellow crystals, mp 352–353°C. IR spectrum, ν, cm^{-1}: 3330–3390 (NH), 1710, 1695, 1685 (C=O), 1610, 1575, 1565 (C=C, $C=C_{arom}$). ^1H NMR spectrum, δ, ppm: 3.71 s (3H, $NHCO_2\underline{Me}$), 7.05 s (1H, H^3), 7.36–7.52 m ($4H_{arom}$),7.6 d ($1H_{arom}$, *J* 7.8 Hz), 7.82 s (1H, H^8), 7.87 d ($1H_{arom}$, *J* 8.0 Hz), 10.58 br.s (1H, $N\underline{H}CO_2Me$), 11.40 s (1H, NHCO). Found, %: C 62.79; H 3.55; N 11.54. $C_{19}H_{13}N_3O_5$. Calculated, %: C 6;2.81 H 3.58; N 11.57.

4-[(*E*)-3-Oxo-2*H*-chromen-3-yl)-1-propenyl]phenyl *N*-phenylcarbamate (XIV) A mixture of 2.89 g (0.012 mol) of phenyl *N*-(4-formylphenyl)carbamate (**XII**) and 1.74 g (0.01 mol) of 3-acetyl-2*H*-chromen-2-one (**XIII**) was dissolved in 10 mL of butanol-1 at heating, cooled to room temperature, 0.3 mL of freshly distilled piperidine and 0.3 mL of glacial acetic acid was added, and the mixture was boiled for 4 h. The reaction mixture was cooled to room temperature, 10 mL of ethanol was added, the separated precipitate was filtered off and recrystallized from 60% ethanol. Yield 3.66 g (89%), yellow crystals, mp 235–236°C. IR spectrum, ν, cm^{-1}: 3310 (NH), 1710, 1679, 1695, (C=O), 1610, 1585, 1565 (C=C, $C=C_{arom}$). ^1H NMR spectrum, δ, ppm: 6.94–7.15 m (2H, $1H_{arom.}$, $1H_{HC=CH}$), 7.21–7.64 m ($12H_{arom}$), 7.82 d ($1H_{HC=CH}$, *J* 15.6 Hz),

8.50 s (1H, H^4 of coumarin), 10.59 br.s (1H, NH). Found, %: C 73.01; H 4.1;2 N3.2 .3 $C_{25}H_{17}NO_5$. Calculated, %: C 72.99; H 4.14; N 3.41.

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