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Syntheses on the Basis of 2*H*-Chromen-2-one and 2*H*-Chromene-2-thione

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Abstract—4-Hydroxy-2*H*-chromen-2-one and 4-hydroxy-2*H*-chromene-2-thione reacted with allyl bromide, 1,1,3-trichloroprop-1-ene, and 1,3-dichlorobut-2-ene to give the corresponding ethers, which were oxidized to (2-oxo-2*H*-chromen-4-yloxy)acetic acid with potassium permanganate, and various derivatives of that acid were obtained. 3-(3,3-Dichloroprop-2-enyl)-7-hydroxy-4-methyl-2*H*-chromen-2-one and 3-(3,3-dichloroprop-2-enyl)-7-hydroxy-4-methyl-2*H*-chromene-2-thione were synthesized, and some their transformations were studied.

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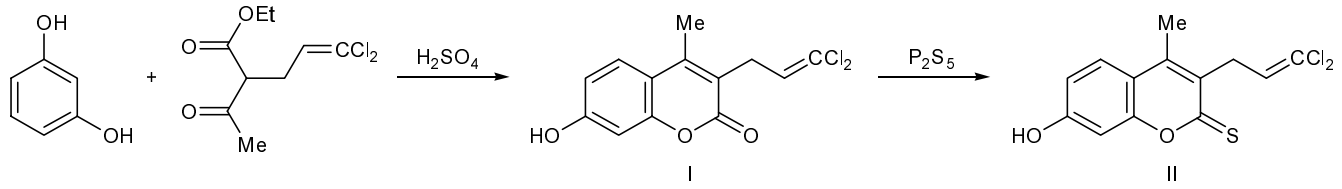
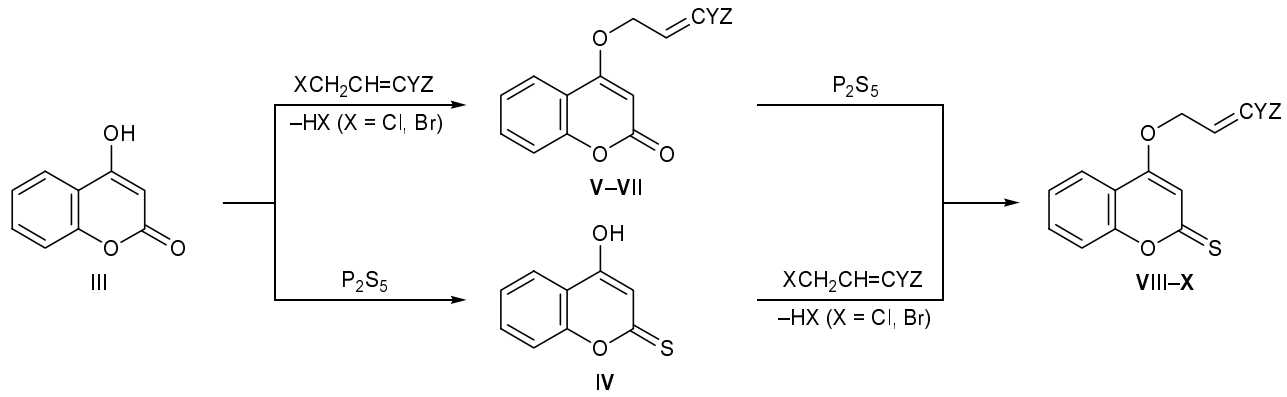
In continuation of our studies on the synthesis and chemical transformations of new coumarin derivatives [1–3], in particular of those derived from 7-hydroxycoumarin (umbeliferone), the present article reports on the condensation of resorcinol with ethyl 2-acetyl-5,5-dichloro-4-pentenoate. The reaction was found to occur at a temperature below 10°C in the presence of 75% sulfuric acid, and it resulted in the formation of 82% of 3-(3,3-dichloroprop-2-enyl)-7-hydroxy-4-methyl-2*H*-chromen-2-one (**I**). By treatment of the latter with phosphorus(V) sulfide in pyridine we obtained 3-(3,3-dichloropropen-2-yl)-7-hydroxy-4-methyl-2*H*-chromene-2-thione (**II**) (Scheme 1). We also performed O-alkylation of 4-hydroxy-2*H*-chromen-2-one (**III**) and 4-hydroxy-2*H*-chromene-2-thione (**IV**) [4, 5] with allyl bromide, 1,1,3-trichloroprop-1-ene, and 1,3-di-

Scheme 1.



Scheme 2.

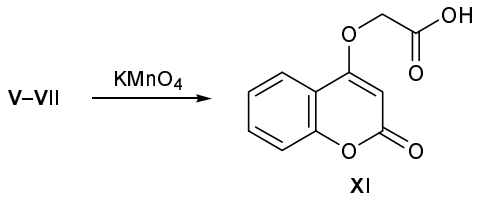


V, **VIII**, Y = Z = H; **VI**, **IX**, Y = Z = Cl; **VII**, **X**, Y = Cl, Z = Me.

chlorobut-2-ene and found optimal conditions for these reactions. The target 4-allyloxy- (**V**, **VIII**), 4-(3,3-dichloroprop-2-enyloxy)- (**VI**, **IX**), and 4-(3-chlorobut-2-enyloxy)-substituted (**VII**, **X**) 2*H*-chromen-2-ones and 2*H*-chromene-2-thiones were synthesized by heating equimolar amounts of the initial reactants in anhydrous acetone in the presence of potassium carbonate (Scheme 2). Compounds **VIII**–**X** were also synthesized in another way, by treatment of chromen-2-ones **V**–**VII** with phosphorus(V) sulfide. The IR spectra of compounds **VIII**–**X** contained absorption bands at 1150 and 1645, 1660 cm^{-1} due to stretching vibrations of the C=S and C=C bonds, respectively, as well as absorption bands belonging to the C–O–C fragments at 1260, 1275, and 1245 cm^{-1}.

Many derivatives of 2-oxo-2*H*-chromen-4-carboxylic acid are known to exhibit a soporific effect and other kinds of biological activity [6, 7]. Ethers **V**–**VII** were oxidized with potassium permanganate with a view to obtain (2-oxo-2*H*-chromen-4-yloxy)acetic acid (**XI**); in all cases, the oxidation smoothly afforded the desired acid (Scheme 3).

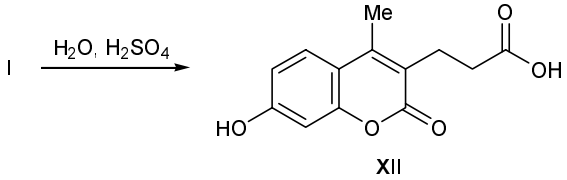
Scheme 3.



XI

3-(7-Hydroxy-4-methyl-2-oxo-2*H*-chromen-3-yl)-propionic acid (**XII**) was synthesized by hydrolysis of compound **I** in the presence of sulfuric acid (Scheme 4).

Scheme 4.

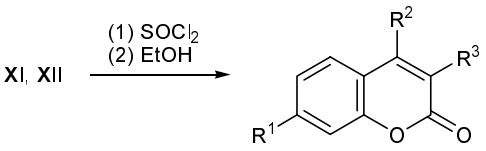


XII

Acids **XI** and **XII** were converted into the corresponding acid chlorides **XIII** and **XIV** by treatment with thionyl chloride in DMF, and the subsequent reaction with ethanol gave esters **XV** and **XVI**, respectively (Scheme 5).

Many 2*H*-chromen-2-one derivatives possessing a triazole ring exhibit antimicrobial activity [8], and some of these are used in agriculture as herbicides [8].

Scheme 5.

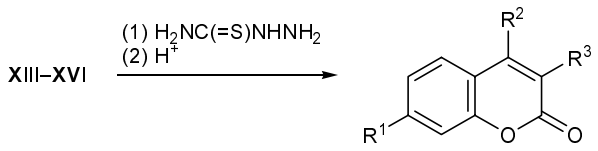


XIII–**XVI**

XIII, **XV**, R^1 = H; **XIV**, **XVI**, R^1 = OH; **XIII**, R^2 = $ClC(O)CH_2$; **XIV**, **XVI**, R^2 = Me; **XV**, R^2 = $EtOC(O)CH_2$; **XIII**, **XV**, R^3 = H; **XIV**, R^3 = $ClC(O)(CH_2)_2$; **XVI**, R^3 = $EtOC(O)(CH_2)_2$.

In order to synthesize new triazole-containing 2*H*-chromen-2-ones, we examined reactions of acid chlorides **XIII** and **XIV** and esters **XV** and **XVI** with thiosemicarbazide. Equimolar amounts of the reactants in anhydrous pyridine were heated on a water bath over a period 5–6 h to produce the expected thiosemicarbazide derivatives **XVII** and **XVIII**. The latter underwent intramolecular cyclization in acid medium with formation of 4-(5-sulfanyl-1*H*-1,2,4-triazol-3-yl-methoxy)- and 3-[2-(5-sulfanyl-1*H*-1,2,4-triazol-3-yl)-ethyl]-2*H*-chromen-2-ones **XIX** and **XX**, respectively (Scheme 6). The reaction of compound **XIX** with hydrazine hydrate involved nucleophilic replacement of the thiol group in the triazole ring to give substituted

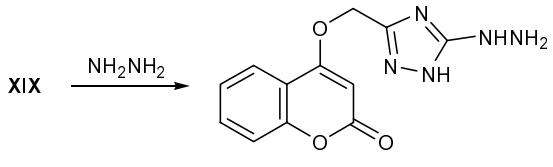
Scheme 6.



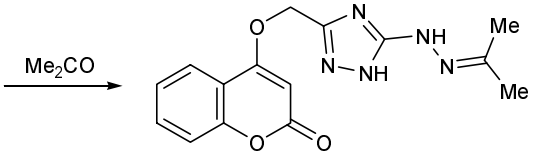
XVII–**XX**

XVII, R^1 = R^3 = H, R^2 = $H_2NC(S)NHNHC(O)CH_2O$; **XVIII**, R^1 = OH, R^2 = Me, R^3 = $H_2NC(S)NHNHC(O)(CH_2)_2$; **XIX**, R^1 = R^3 = H, R^2 = 5-sulfanyl-1*H*-1,2,4-triazol-3-yl-methyloxy; **XX**, R^1 = OH, R^2 = Me, R^3 = 2-(5-sulfanyl-1*H*-1,2,4-triazol-3-yl)ethyl.

Scheme 7.



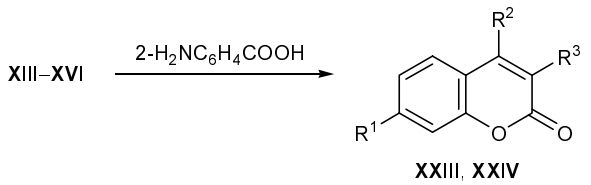
XXI



XXII

hydrazine **XXI** which reacted with acetone to form hydrazone **XXII** (Scheme 7). The IR spectrum of **XXI** lacked SH absorption bands but contained those typical of NH_2 and NH groups in the region 3180–3400 cm^{-1}. By reactions of acid chlorides **XIII** and **XIV** and esters **XV** and **XVI** with anthranilic acid in boiling pyridine we synthesized 3,1-benzoxazine derivatives **XXIII** and **XXIV** (Scheme 8).

Scheme 8.



XXIII, XXIV

XXIII, $R^1 = R^3 = H$, R^2 = 4-oxo-3,1-benzoxazin-2-yloxymethyl; **XXIV**, R^1 = OH, R^2 = Me, R^3 = 2-(4-oxo-3,1-benzoxazin-2-yl)ethyl.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from samples dispersed in mineral oil. The ^1H NMR spectra were obtained on a Tesla BS-497 instrument (100 MHz) from solutions in $CDCl_3$ using HMDS as internal reference. Thin-layer chromatography was performed on Silufol UV-254 plates (spots were visualized by treatment with iodine vapor).

3-(3,3-Dichloroprop-2-enyl)-7-hydroxy-4-methyl-2*H*-chromen-2-one (I). A mixture of 5.5 g (0.05 mol) of resorcinol and 8.4 g (0.05 mol) of freshly distilled ethyl 2-acetyl-5,5-dichloropent-4-enoic acid was added dropwise to 50 ml of 75% sulfuric acid, maintaining the temperature below 10°C. The mixture was kept for 12–14 h at room temperature and poured into ice water. After 12 h, the precipitate was filtered off, washed with water, and recrystallized from heptane. Yield 11.5 g (82%), mp 200°C, R_f 0.76 (benzene–ethyl acetate, 1:1). IR spectrum, ν, cm^{-1}: 1610 (C=C), 1660 (CH=CCl_2), 1690 (C=O). ^1H NMR spectrum, δ, ppm: 3.50 d (2H, CH_2, J = 6.8 Hz), 6.01 t (1H, CH=CCl_2, J = 6.2 Hz), 3.02 s (3H, CH_3), 7.10–8.02 m (3H, H_{arom}).

3-(3,3-Dichloroprop-2-enyl)-7-hydroxy-4-methyl-2*H*-chromene-2-thione (II). A mixture of 2.85 g (0.01 mol) of compound **I** and 3.33 g (0.015 mol) of phosphorus(V) sulfide in 20 ml of anhydrous pyridine was heated for 2 h under reflux. The solvent was removed, 50 ml of ice water was added to the residue, the mixture was kept for 12 h, and the precipitate was filtered off and recrystallized from benzene. Yield 2.2 g (73%), mp 142°C, R_f 0.65 (benzene–ethyl acetate, 3:1). IR spectrum, ν, cm^{-1}: 1150 (C=S), 1630 (C=C), 1660 (CH=CCl_2).

4-R-oxy-2*H*-chromen-2-ones V–VII and 4-R-oxy-2*H*-chromene-2-thiones VIII–X (*general procedure*). *a*. Allyl bromide, 1,3-dichlorobut-2-ene, or 1,1,3-trichloroprop-1-ene, 0.1 mol, was slowly added under stirring to a mixture of 100 ml of anhydrous acetone, 0.1 mol of compound **III** or **IV**, and 0.11 mol of anhydrous potassium carbonate. The mixture was heated for 18–20 h on a water bath, the solvent was distilled off, and the residue was treated with ice water. After 12 h, the precipitate was filtered off and recrystallized from heptane.

4-Allyloxy-2*H*-chromen-2-one (V). Yield 15.8 g (78%), mp 115°C. IR spectrum, ν, cm^{-1}: 1645 (CH=CH_2), 1725 (C=O), 1260 (C–O–C). ^1H NMR spectrum, δ, ppm: 4.72 d (2H, OCH_2, J = 6.2 Hz), 5.92 s (1H, CH), 6.03 m (1H, CH=CH_2), 7.20–7.91 m (4H, H_{arom}).

4-(3,3-Dichloroprop-2-enyloxy)-2*H*-chromen-2-one (VI). Yield 19.78 g (73%), mp 123°C. IR spectrum, ν, cm^{-1}: 1655 (CH=CCl_2), 1725 (C=O), 1275 (C–O–C). ^1H NMR spectrum, δ, ppm: 5.05 d (2H, OCH_2, J = 6.5 Hz), 6.13 s (1H, CH), 6.70 t (1H, CH=CCl_2, J = 6.2 Hz), 7.50–8.82 m (4H, H_{arom}).

4-(3-Chlorobut-2-en-1-yloxy)-2*H*-chromen-2-one (VII). Yield 17.82 g (71%), mp 118°C. IR spectrum, ν, cm^{-1}: 1660 (CH=CCl), 1725 (C=O), 1245 (C–O–C). ^1H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 4.71 d (2H, OCH_2, J = 6 Hz), 5.95 s (1H, CH), 5.35 t (1H, CH=CCl, J = 5.8 Hz), 7.23–7.80 m (4H, H_{arom}).

b. Ethers **VIII**–**X** were synthesized as described above for compound **II** from 0.01 mol of ether **V**–**VII** and 0.0075 mol of phosphorus(V) sulfide in 20 ml of pyridine. Compound **VIII**: yield 67%, mp 107°C; **IX**: yield 65%, mp 113°C; **X**: yield 63%, mp 109°C. Samples of **VIII**–**X** prepared according to methods *a* and *b* showed no depression of the melting point on mixing.

(2-Oxo-2*H*-chromen-4-yloxy)acetic acid (XI). Potassium permanganate, 0.02 mol, was slowly added over a period of 1 h to a mixture of 0.01 mol of 4-alkenyloxy-2*H*-chromen-2-one **V**–**VII**, 50 ml of acetone, and 0.01 mol of potassium carbonate under stirring and cooling with ice. The mixture was then stirred for 2 h and was left to stand for 12 h. The precipitate was filtered off, the filtrate was treated with

water, the aqueous phase was evaporated to 1/3 of the initial volume, cooled, and acidified with hydrochloric acid, and the precipitate was filtered off and recrystallized from water. Yield ~65%, mp 198°C, R_f 0.67 (chloroform–heptane, 1:1). IR spectrum, ν, cm^{-1}: 1630 (C=C), 1690 (C=O, lactone), 1730 (C=O, acid) 2700–3000 (OH), 1245 (C–O–C). ^1H NMR spectrum, δ, ppm: 5.01 s (2H, CH_2), 5.92 s (1H, CH), 7.30–8.05 m (4H, H_{arom}), 11.52 s (1H, OH). Found, %: C 60.50; H 4.00. $C_{11}H_8O_5$. Calculated, %: C 60.00; H 3.64.

3-(7-Hydroxy-4-methyl-2-oxo-2*H*-chromen-3-yl)-propionic acid (XII). A mixture of 2.85 g (0.01 mol) of compound **I** and 10 ml of 96% sulfuric acid was heated for 4 h at 60°C (on a water bath). The mixture was cooled and poured onto 50 g of crushed ice. After 12 h, the precipitate was filtered off and recrystallized from acetic acid. Yield 1.8 g (72%), mp 160°C, R_f 0.73 (benzene–ethyl acetate, 3:1). IR spectrum, ν, cm^{-1}: 1610 (C=C), 1690 (C=O), 1720 (C=O, acid), 2700–3000 (OH). ^1H NMR spectrum, δ, ppm: 2.20–2.40 m (4H, CH_2CH_2), 3.21 s (3H, CH_3), 7.10–8.05 m (3H, H_{arom}).

(2-Oxo-2*H*-chromen-4-yloxy)acetyl chloride (XIII) and 3-(7-hydroxy-4-methyl-2-oxo-2*H*-chromen-3-yl)propanoyl chloride (XIV) (*general procedure***).** Thionyl chloride, 0.01 mol, and DMF, 0.01 mol, were added under stirring and cooling to a suspension of 0.01 mol of compound **XI** or **XII** in 25 ml of anhydrous benzene. The mixture was heated for 1 h under reflux (on a water bath) and cooled, and the precipitate was filtered off and washed with anhydrous benzene. Yield of **XIII** 98%, mp 110°C; yield of **XIV** 97%, mp 102°C.

Ethyl (2-oxo-2*H*-chromen-4-yloxy)acetate (XV) and ethyl 3-(7-hydroxy-4-methyl-2-oxo-2*H*-chromen-3-yl)propionate (XVI) (*general procedure***).** A mixture of 0.01 mol of compound **XIII** or **XIV** and 40 ml of anhydrous ethanol was heated for 2 h under reflux (on a water bath). Excess alcohol was distilled off, the residue was treated with water, and the precipitate was filtered off and recrystallized. Yield of **XV** 82%, mp 167°C (from aqueous acetone), R_f 0.62 (chloroform–heptane, 1:2). Found, %: C 63.00; H 4.84. $C_{13}H_{12}O_5$. Calculated, %: C 62.90; H 4.83. Yield of **XVI** 84%, mp 114°C (from ethanol), R_f 0.67 (benzene–ethyl acetate, 2:1). IR spectrum, ν, cm^{-1}: 1610 (C=C), 1690 (C=O, ester), 1740 (C–O–C).

2-(2-Oxo-2*H*-chromen-4-yloxymethylcarbonyl)-hydrazine-1-carbothioamide (XVII) and 2-[3-(7-hydroxy-4-methyl-2-oxo-2*H*-chromen-3-yl)propanoyl]-hydrazine-1-carbothioamide (XVIII) (*general procedure***).** A mixture of 0.005 mol of compound **XIII**–**XVI** and 0.005 mol of thiosemicarbazide in 20 ml of anhydrous pyridine was heated for 5–6 h on a boiling water bath. After cooling, the precipitate was filtered off and recrystallized from aqueous ethanol. Samples of **XVII** and **XVIII** obtained from acid chlorides **XIII** and **XIV** and esters **XV** and **XVI**, respectively, showed no depression of the melting point on mixing.

Compound **XVII**. Yield 1.1 g (~76%, from **XIII**), 1 g (~70%, from **XV**); mp 223°C, R_f 0.68 (chloroform–heptane, 1:1). Found, %: C 49.23; H 3.70; N 14.40; S 11.10. $C_{12}H_{11}N_3O_4S$. Calculated, %: C 49.15; H 3.75; N 14.33; S 10.92.

Compound **XVIII**. Yield 1.48 g (~ 93%, from **XIV**), 1.32 g (~82%, from **XVI**); mp 203°C. Found, %: C 42.00; H 2.42; N 21.00; S 11.00. $C_{11}H_8N_4O_5S$. Calculated, %: C 41.78; H 2.53; N 20.25; S 10.13.

4-(5-Sulfanyl-1*H*-1,2,4-triazol-3-ylmethoxy)-2*H*-chromen-2-one (XIX) and 3-[2-(5-sulfanyl-1*H*-1,2,4-triazol-3-yl)ethyl]-4-methyl-2*H*-chromen-2-one (XX) (*general procedure***).** Concentrated sulfuric acid, 3 ml, was added to 0.002 mol of compound **XVII** or **XVIII**, the mixture was kept for 24 h at room temperature and poured into ice water, and the precipitate was filtered off and recrystallized from ethanol.

Compound **XIX**. Yield 0.45 g (81%), mp 192°C, R_f 0.62 (chloroform–heptane, 1:1). ^1H NMR spectrum, δ, ppm: 3.50 s (2H, CH_2), 5.81 s (1H, SH), 6.81–6.93 m (4H, H_{arom}), 7.51 s (1H, NH). Found, %: C 52.50; H 9.41; N 15.41; S 11.5. $C_{12}H_9N_3O_3S$. Calculated, %: C 52.36; H 3.27; N 15.27; S 11.69.

Compound **XX**. Yield 0.36 g (68%). IR spectrum, ν, cm^{-1}: 1180 (C=S), 1610 (C=C), 1630 (C=N), 1690 (C=O), 3180–3280 (NH, OH). ^1H NMR spectrum, δ, ppm: 2.01–25.2 m (4H, CH_2CH_2), 3.31 s (3H, CH_3), 7.03–8.02 m (3H, H_{arom}), 9.50 s (1H, SH), 10.51–11.50 s (2H, NH, NHC=S).

4-(5-Hydrazino-1*H*-1,2,4-triazol-3-ylmethoxy)-2*H*-chromen-2-one (XXI). A solution of 0.002 mol of compound **XIX** in 10 ml of anhydrous ethanol was heated to ~50°C, 0.5 ml of DMF and 2 ml of hydrazine hydrate were added, and the mixture was heated for 0.5 h under reflux. After cooling, the precipitate was filtered off and recrystallized from ethanol–water (4:1). Yield 0.35 g (63%), mp 203–204°C, R_f 0.65 (chloroform–heptane, 1:1). IR spectrum, ν, cm^{-1}: 1620 (C=C), 1630 (C=N), 1690 (C=O), 3180–3170 (NH). Found, %: C 52.50; H 4.21; N 25.52. $C_{12}H_{11}N_5O_3$. Calculated, %: C 52.74; H 4.03; N 25.64.

4-[5-(1-Methylethylidenehydrazino)-1*H*-1,2,4-triazol-3-ylmethoxy]-2*H*-chromen-2-one (XXII). A mixture of 1.37 g (0.005 mol) of compound **XXI** and 10 ml of anhydrous acetone was heated for 5 h under reflux. Excess acetone was distilled off, and the precipitate was filtered off and recrystallized from aqueous ethanol (1:1). Yield 1.3 g (~81%), mp 175°C, R_f 0.68 (chloroform–heptane).

4-(2-Oxo-2*H*-chromen-4-yloxymethyl)-4*H*-3,1-benzoxazin-4-one (XXIII) and 3-[2-(4-methyl-2-oxo-2*H*-chromen-3-yl)ethyl]-4*H*-3,1-benzoxazin-4-one (XXIV) (*general procedure*). A mixture of 0.002 mol of compound **XIII**–**XVI** and 0.002 mol of anthranilic acid in 15 ml of anhydrous pyridine was heated for 8–10 h under reflux. The solvent was distilled off under reduced pressure, the residue was treated with cold water and acidified to pH ~4, and the precipitate was filtered off and washed with water. Samples of **XXIII** and **XXIV** obtained from acid chlorides **XIII** and **XIV** and esters **XV** and **XVI**, respectively, showed no depression of the melting point on mixing.

Compound **XXIII**. Yield 75%, mp 247°C, R_f 0.68 (chloroform–heptane, 1:2). ^{1}H NMR spectrum, δ, ppm: 3.81 s (2H, CH_2), 6.92–7.51 m (4H, H_{arom}). Found, %: C 72.10; H 3.51; N 4.70. $C_{18}H_{11}NO_5$. Calculated, %: C 71.76; H 3.65; N 4.65.

Compound **XXIV**. Yield 67%, mp 268°C. ^{1}H NMR spectrum, δ, ppm: 2.01–2.50 m (4H, CH_2CH_2), 3.02 s (3H, CH_3), 7.02–8.21 m (3H, H_{arom}), 12.2 s (1H, OH).

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