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SYNTHESIS AND CERTAIN CONVERSIONS OF 3-(3,3-DICHLOROALLYL)-4-HYDROXYCOUMARIN

A. A. Avetisyan, I. L. Aleksanyan, and A. G. Alvandzhyan

A method has been developed for the synthesis of 3-(3,3-dichloroallyl)-4-hydroxycoumarin and 2-thioxo-3-(3,3-dichloroallyl)-4-hydroxy-2H-chromene, and certain conversions of these compounds have been studied. They undergo acid hydrolysis readily, forming (respectively) 3-(4-hydroxy-3-coumarin)- and 3-(2-thioxo-4-hydroxy-2H-chromene-3)propionic acids; these compounds are converted to the corresponding lactones by the action of acetic anhydride.

In a continuation of our studies of the synthesis and chemical conversions of new derivatives of the coumarin series [1-3], we have now investigated the condensation of phenol with 3,3-dichloroallylmalonic acid in the presence of phosphorus oxychloride and zinc chloride, resulting in the formation of 3-(3,3-dichloroallyl)-4-hydroxycoumarin (I).

By the interaction of this coumarin I with phosphorus pentasulfide, 2-thioxo-3-(3,3-dichloroallyl)-4-hydroxy-2H-chromene (II) is obtained in high yield. Hydrolysis of compounds I and II by 96% sulfuric acid affords the corresponding carboxylic acids III and IV. (See scheme on following display page.)

3-(4-Hydroxy-3-coumarin)propionic acid (III) and 3-(2-thioxo-4-hydroxy-2H-chromene-3)propionic acid (IV) are converted by acetic anhydride to the corresponding lactones V and VI, with high yields. The IR spectra exhibit absorption bands at 1150, 1610, and 1670 cm^{-1}, characteristic for stretching vibrations of the thiolactone bond C=S, the double bond C=C, and the lactone group, respectively. The PMR spectra of the lactones V and VI contain a signal of methylene groups at 2.78 ppm and signals of four aromatic protons in the interval 7.1-7.8 ppm. The structure of the lactone V was also confirmed by mass spectrometric data. It was shown that when compounds V and VI interact with phosphorus pentasulfide under the conditions indicated above, they both form exactly the same substance, the dithio derivative VII.

By the interaction of compounds I, III, and IV with phosphorus oxychloride, the corresponding 4-chloro derivatives of these compounds were synthesized: 3-(3,3-dichloroallyl)-4-chlorocoumarin (VIII), 3-(4-chloro-3-coumarin)propionic acid (IX), and 3-(2-thioxo-4-chloro-2H-chromene-3)propionic acid (XI) were synthesized.

Acid hydrolysis of 3-(3,3-dichloroallyl)-4-chlorocoumarin (VIII) and 2-thioxo-3-(3,3-dichloroallyl)-4-chloro-2H-chromene (X) by 96% sulfuric acid also leads to the corresponding propionic acids (IX and XI). The 2-thioxo-3-(3,3-dichloroallyl)-4-chloro-2H-chromene (X) had been obtained by the interaction of compound VIII with phosphorus pentasulfide.

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrometer in white mineral oil. PMR spectra were obtained in Tesla BS-497 instruments (100 MHz), internal standard HMDS. In the TLC, Silufol UV-254 plates were used, with development by iodine vapor.

3-(3,3-Dichloroallyl)-4-hydroxycoumarin (I). A mixture of 10.8 g (0.05 mole) of 3,3-dichloroallylmalonic acid (obtained by a procedure given in [4], 4.7 g (0.05 mole) of phenol, 20.54 g (0.15 mole) of $ZnCl_2$, and 13.77 g (0.09 mole) of phosphorus oxychloride was heated and stirred for 40 h at a temperature of 60-70°C. After cooling, ice water was added,

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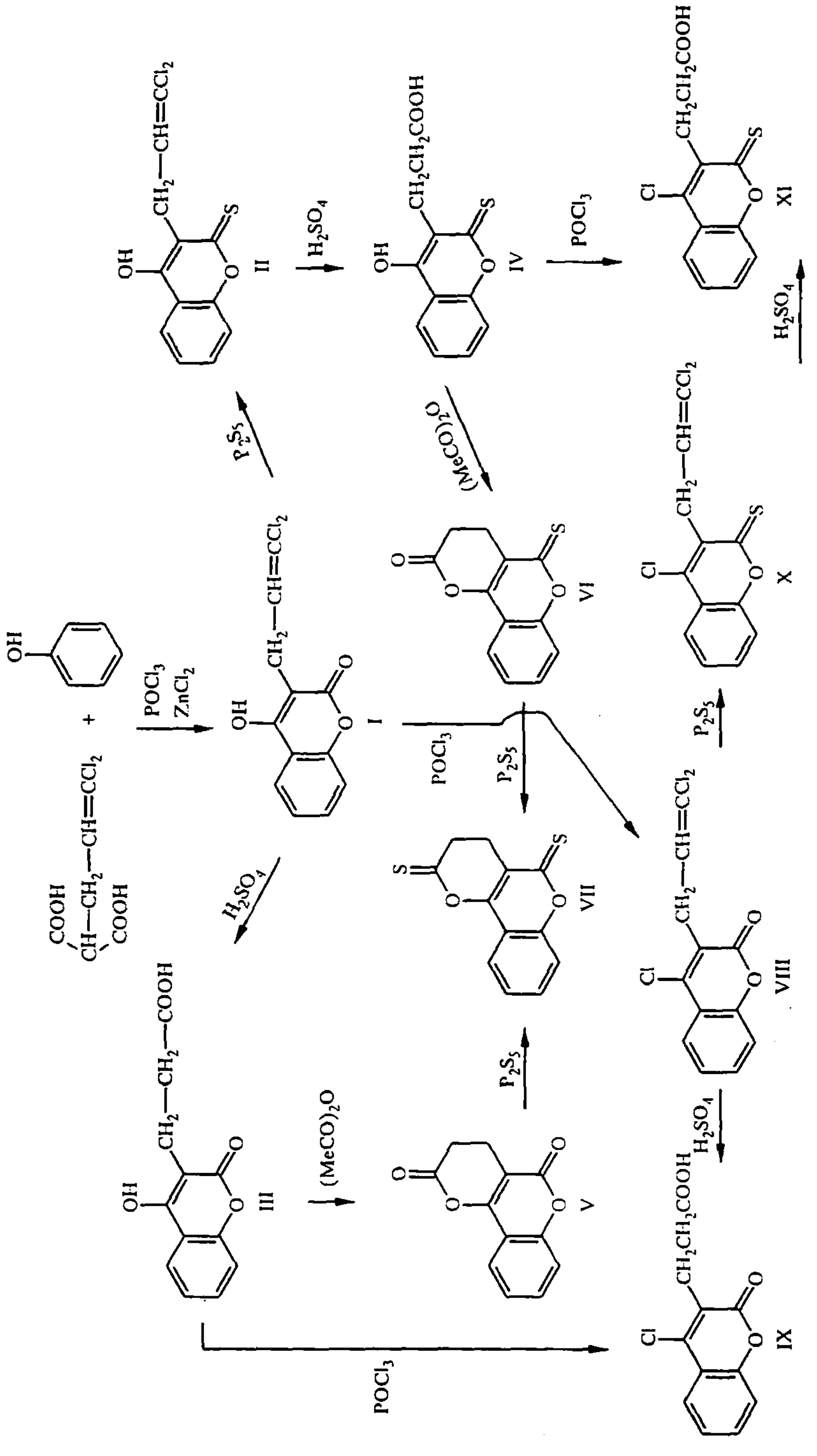

I
II
III
IV
V
VI
VII
VIII
IX
X
XI
POCl$_3$
ZnCl$_2$
P$_2$S$_5$
H$_2$SO$_4$
(MeCO)$_2$O

and the mixture was allowed to stand overnight. The precipitate was filtered off, washed with water, and recrystallized from heptane. Yield 8.54 g (63%), mp 175-176°C, R_f 0.78 (benzene–ethyl acetate, 1:1). IR spectrum: 1610 (C=C), 1660 ($CH=CCl_2$), 1690 cm^{-1} (C=O). PMR spectrum ($CDCl_3$:DMSO-d_6, 1:1): 3.5 (2H, d, CH_2–); 6.0 (1H, t, –$CH=CCl_2$); 7.1-8.0 ppm (4H, m, H_{arom}).

2-Thioxo-3-(3,3-dichloroallyl)-4-hydroxy-2H-chromene (II). A mixture of 2.71 g (0.01 mole) of compound I and 1.66 g (0.0075 mole) of phosphorus pentasulfide in 20 ml of xylene was refluxed for 2 h. After removing the solvent, 50 ml of ice water was added to the residue, and the mixture was allowed to stand overnight. The precipitate was filtered off, washed with water, and recrystallized from a 1:1 mixture of ethanol and water. Yield 2.5 g (87%), mp 168°C, R_f 0.62 (xylene–ethyl acetate, 1:1). Found, %: S 11.20, Cl 24.69. $C_{12}H_8Cl_2O_2$. Calculated, %: S 11.15, Cl 24.74. IR spectrum: 1150 (C=S), 1610 (C=C), 1660 cm^{-1} ($CH=CCl_2$). PMR spectrum ($CDCl_3$:DMSO-d_6): 3.5 (2H, d, $=C-CH_2-$); 6.0 (1H, t, $CH=CCl_2$); 7.1-8.0 ppm (4H, m, H_{arom}).

3-(4-Hydroxy-3-coumarin)propionic acid (III) and 3-(2-Thioxo-4-hydroxy-2H-chromene-3)propionic Acid (IV). A mixture of 0.01 mole of compound I or II and 10 ml of 96% sulfuric acid was heated on a water bath at 60°C for 4 h. After cooling, the mixture was poured onto 50 g of crushed ice and left overnight. The resulting crystals were filtered off, washed with water, and recrystallized from acetic acid. Yield of the acid III 1.6 g (68%), mp 132-133°C, R_f 0.65 (benzene–ethyl acetate, 2:1). Found, %: C 61.70, H 4.3. $C_{12}H_{10}O_5$. Calculated, %: C 61.54, H 4.27. IR spectrum: 1670 (C=O), 1730 (C=O acid), 2700-3000 cm^{-1} (OH acid). PMR spectrum ($CDCl_3$: DMSO-d_6): 2.2-2.5 (4H, m, $-CH_2-$); 7.0-7.8 ppm (4H, m, H_{arom}). Yield of compound IV 1.8 g (72%), mp 128°C, R_f 0.70 (ethyl acetate–benzene, 5:1). Found, %: C 57.55, H 3.92, S 12.7. $C_{12}H_{10}O_4S$. Calculated, %: C 57.6, H 4.00, S 12.8. IR spectrum: 1150 (C=S), 1630 (C=C), 1730 cm^{-1} (C=O acid).

3,4-Dihydropyran-2-one[3,2-c]coumarin (V) and 3,4-Dihydropyran-2-one-5-thioxo-5H-[3,2-c]chromene (VI). A mixture of 0.01 mole of compound III or IV and 30 ml of acetic anhydride was refluxed for 2 h. Then the acetic anhydride was completely removed under vacuum; the residue, after cooling, was washed with dilute caustic and recrystallized from acetic acid. Obtained 1.73 g (80%) of compound V, mp 215°C, R_f 0.59 (ethyl acetate–benzene, 1:2). Found, %: C 66.64, H 3.69. $C_{12}H_8O_4$. Calculated, %: C 66.67, H 3.7. IR spectrum: 1670 (C=O), 1610 cm^{-1} (C=C). PMR spectrum (CF_3COOD): 2.78 (4H, s, $2CH_2$); 7.0-7.8 ppm (4H, m, H_{arom}). Yield of compound VI 1.4 g (61%), mp 175°C, R_f 0.62 (ethyl acetate–benzene, 1:2). Found, %: C 62.10; H 3.51; S 13.80. $C_{12}H_8O_3S$. Calculated, %: C 62.07; H 3.45; S 13.79. IR spectrum: 1150 (C=S); 1670 (C=O), 1610 cm^{-1} (C=C).

2-5-Dithioxo-3,4-dihydro-5H-pyran[3,2-c]chromene (VII). In the same manner as described above, from 0.01 mole of compound V or VI and 1.67 g (0.0075 mole) of phosphorus pentasulfide in 20 ml of xylene, obtained 1.53 g (62%) of compound VII, mp 160°C, R_f 0.66 (ethyl acetate–benzene, 1:2). Found, %: C 58.10, H 3.3, S 25.83. Calculated, %: C 58.06, H 3.22, S 25.806.

A mixture of samples of compound VII obtained from compounds V and VI did not exhibit any depression of melting point.

3-(3,3-Dichloroallyl)-4-chlorocoumarin (VIII). A mixture of 2.71 g (0.01 mole) of compound I and 25 ml of phosphorus oxychloride was heated on a boiling water bath for about 4 h. The excess phosphorus oxychloride was taken off under vacuum, 50 g of crushed ice was added to the residue, and the mixture was left overnight. The precipitate was filtered off, washed with water, and recrystallized from a 1:1 mixture of alcohol and water. Yield quantitative, mp 88-90°C, R_f 0.65 (benzene–ethyl acetate, 1:5). Found, %: C 49.9, H 2.45, Cl 36.5. $C_{12}H_7Cl_3O_2$. Calculated, %: C 49.74, H 2.42, Cl 36.79.

3-(4-Chloro-3-coumarin)propionic Acid (IX). *A*. In the same manner as above, from 2.34 g (0.01 mole) of compound III and 25 ml of phosphorus oxychloride, obtained 2.25 g (88%) of the chloro derivative IX, mp 150-152°C.

B. In the same manner as in the preparation of the acids III and IV, from 2.9 g (0.01 mole) of compound VIII and 20 ml of 96% sulfuric acid, obtained 1.8 g (70%) of the white crystalline substance IX, mp 150-152°C. A mixed sample of compound IX obtained by methods A and B did not exhibit any melting point depression. R_f 0.63 (ethyl acetate–heptane, 1:3). Found, %: C 57.1, H 3.5, Cl 14.1. $C_{12}H_9ClO_4$. Calculated, %: C 57.03, H 3.56, Cl 14.06.

2-Thioxo-3-(3,3-dichloroallyl)-4-chloro-2H-chromene (X). In the same manner as in the preparation of compound II, from 2.9 g (0.01 mole) of compound VIII and 1.665 g (0.0075 mole) of phosphorus pentasulfide in 20 ml of dry xylene, obtained 2.6 g (85%) of compound X, mp 80°C, R_f 0.72 (ethyl acetate–heptane, 1:4). Found, %: S 10.45, Cl 34.9. $C_{12}H_7Cl_3OS$. Calculated, %: S 10.47, Cl 34.86. IR spectrum: 1150 (C=S), 1610 (C=C), 1660 cm^{-1} ($CH=CCl_2$).

3-(2-Thioxo-4-chloro-2H-chromene-3)propionic Acid (XI). *A*. By analogy with the preparation of compound VIII, from 2.5 g (0.01 mole) of compound IV and 25 ml of phosphorus oxychloride, obtained 1.88 g (70%) of the chromene XI, mp 140°C.

B. By analogy with the preparation of compound III, from 3.06 g (0.01 mole) of compound X and 10 ml of 96% sulfuric acid, obtained 1.96 g (73%) of compound XI, mp 140°C.

A mixed sample of XI obtained by methods A and B did not exhibit any melting point depression. R_f 0.61 (ethyl acetate–heptane, 1:2). Found, %: S 11.89, Cl 13.5. $C_{12}H_9ClO_3S$. Calculated, %: S 11.92; Cl 13.22. IR spectrum: 1150 (C=S), 1610 (C=C), 1730 (C=O acid), 2700-3000 cm^{-1} (OH acid).

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