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SYNTHESIS AND SOME TRANSFORMATIONS OF FUNCTIONALLY-SUBSTITUTED COUMARINS AND 2-THIOXO-2H-CHROMENES

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A synthesis has been developed for substituted coumarins and 2-thioxo-2H-chromenes and some of the chemical transformations of these compounds were studied.

In a continuation of a study of the synthesis and chemical transformations of new coumarin derivatives [1-3], we investigated the condensation of salicylaldehyde with cyanoacetamide under phase transfer catalysis conditions. Condensation of an equimolar mixture of these components in the presence of Katamine AB and 5% potassium hydroxide in benzene carried out at reflux for 6 h leads to the amide of coumarin-3-carboxylic acid (I) in 71% yield.

The reaction of amide I with phosphorus pentoxide in pyridine or xylene gave the amide of 2-thioxo-2H-chromene-3-thiocarboxylic acid (II) in 76% yield. The IR spectrum of this compound has bands at 1150 and 1630 cm^{-1} characteristic for the C═S and C═C groups, respectively, while the PMR spectrum shows a singlet at 5.1 ppm and multiplet at 7.4-7.9 ppm corresponding to the protons at the C═C bond and aromatic ring.

Hydrolysis of amides I, II, and 3-cyanocoumarin (III) using 75% sulfuric acid gave the corresponding carboxylic acids IV and V. The action of thionyl chloride in dimethylformamide on 3-thiocarboxy-2-thioxo-2H-chromene (V) gave acid chloride VI. The reaction of VI with ethanol and diethylamine or dibutylamine gave ethyl ester (VII) and dialkylamides of 2-thioxo-2H-chromene-3-thiocarboxylic acid (VIII and IX).

We also studied the reaction of 3-cyano- (III), 3-carboxy- (IV), 3-carboxamido-6-nitro- (X), 3-carboxy-6-nitro- (XI), and 3-ethoxycarbonyl-6-nitrocoumarins (XII) with phosphorus pentasulfide. The corresponding thio analogs XIII-XVI are formed under these conditions in high yield.

The IR spectra of these compounds show bands at 1150, 1210, and 1380 cm^{-1} characteristic for C═S stretching vibrations of the thiolactone, thioamide, and alkoxythiocarbonyl groups, respectively, as well as at 1345 and 1515 cm^{-1} for the nitro group and 2225 cm^{-1} for the nitrile group.

We also studied the nitration of coumarin and thioxochromenes containing various functional groups at $C_{(3)}$. Thus, the nitration of coumarin I and 2-thioxo-2H-chromenes II, V, and VII by a mixture of nitric (d = 1.38) and sulfuric acids (d = 1.83) at room temperature leads to the formation of the corresponding 6-nitro derivatives X, XIV, XV, and XVI in quantitative yield.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrophotometer for vaseline mulls. The PMR spectra were taken on a Tesla BS-497 spectrometer at 100 MHz in 1:1 $CDCl_3$—DMSO with HMDS as the internal standard. Silufol UV-254 plates were used for the thin-layer chromatography with development by iodine vapor.

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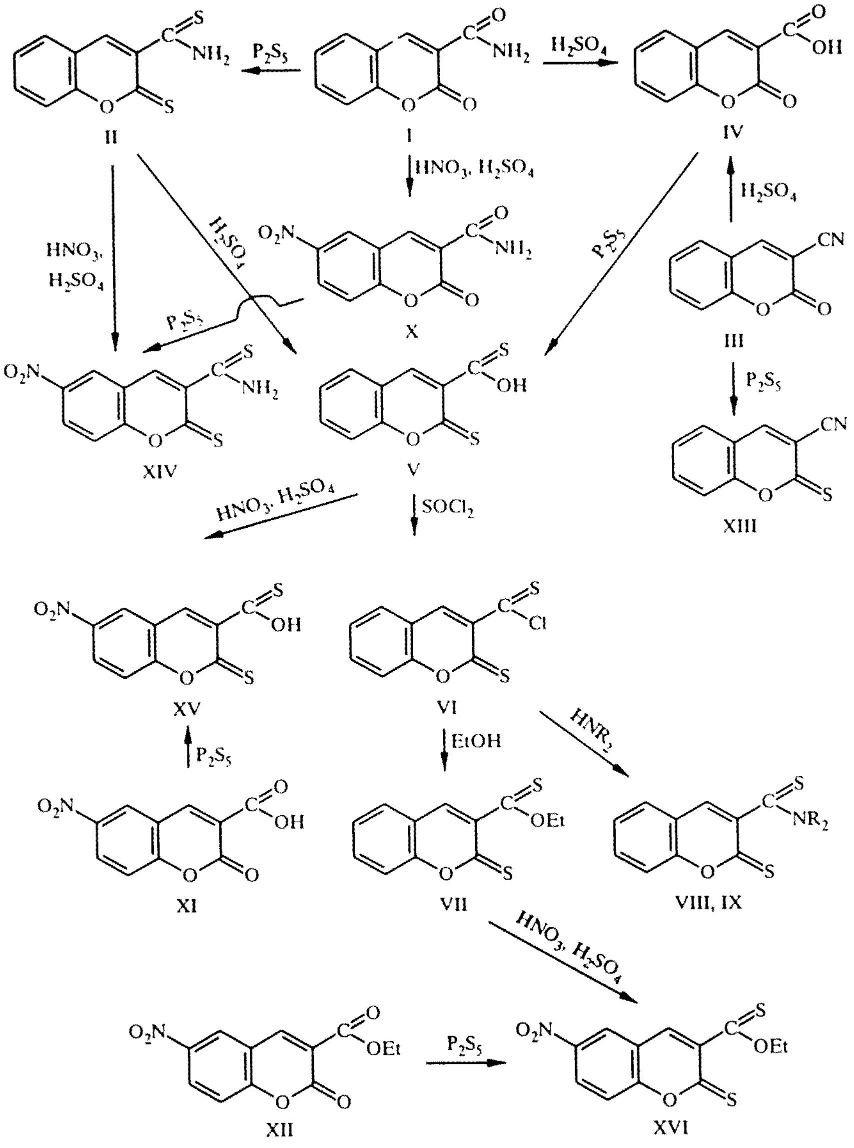

VIII R = Et, IX R = Bu

Amide of Coumarin-3-carboxylic Acid (I). A mixture of 12.21 g (0.1 mole) salicylaldehyde, 8.4 g (0.1 mole) cyanoacetamide, 20 ml benzene, 20 ml 5% aqueous potassium hydroxide, and 4 ml Katamine AB was heated with stirring on a water bath for 6 h. After cooling, the resultant crystals were filtered off, washed with benzene, and recrystallized from acetic acid to give 13 g (71%) I, mp 264°C [4].

Amide of 2-Thioxo-2H-chromene-3-thiocarboxylic Acid (II). A mixture of 3.78 g (0.02 mole) amide of 3-carboxycoumarin (I) and 6.66 g (0.03 mole) P_2S_5 in 40 ml abs. pyridine or xylene was heated at reflux for 2 h. The solvent was removed and 50 ml ice water was added to the residue and left overnight. The product obtained was filtered off and recrystallized from benzene to give 3.35 g (76%) II, mp 205°C, R_f 0.67 (4:1 benzene—ethyl acetate). Found: N, 6.50; S, 28.75%. Calculated for $C_{10}H_7NOS_2$: N, 6.33; S, 28.96%. IR spectrum: 1150 (C=S), 1385 (C—N=), 1480 (C—N), 1630 (C=C), 1718 (C=NH), 2900 cm^{-1} (CH). PMR spectrum: 3.1 (1H, s, C—NH), 5.1 (1H, s, HC=C), 7.4-7.9 ppm (4H, m, arom).

3-Carboxycoumarin (IV) and 3-Thiocarboxy-2-thioxo-2H-chromene (V). A. A mixture of 0.01 mole I, II, or III [6] and 10 ml 75% sulfuric acid was heated at 150-160°C for 3 h and then for 1 h at 190°C. After cooling, the mixture was poured onto 50 g crushed ice. The aqueous solution was brought to pH 10 by adding sodium carbonate and evaporated on a water bath to one-third volume. The solution was then brought to pH 3 by adding hydrochloric acid. The precipitate was filtered off.

The yield of IV was 1.5 g (79%), mp 184°C (xylene) [5].

The yield of V was 1.7 g (76%), mp 178°C (xylene). Found: C, 54.18; H, 2.54; S, 28.98%. Calculated for $C_{10}H_6O_2S_2$: C, 54.05; H, 2.70; S, 28.83%. IR spectrum: 1210 (C═S), 1610 (C═C), 1690 (C═O), 2340 (C—SH), 2900 cm^{-1} (CH). PMR spectrum: 5.1 (1H, s, HC=C), 7.4-8.8 ppm (4H, m, arom).

B. Product V was obtained analogously to amide II from 1.9 g (0.01 mole) acid IV, 3.33 g (0.015 mole) P_2S_5, and 20 ml abs. pyridine or xylene.

The yield of thioacid V was 1.55 g (70%), mp 178°C (xylene). A mixture of samples of V obtained by methods A and B did not give a depressed melting point.

Acid Chloride of 2-Thioxo-2H-chromene-3-thiocarboxylic Acid (VI). A sample of 0.71 ml (0.01 mole) thionyl chloride and 0.77 ml (0.01 mole) dimethylformamide were added with stirring and cooling to a suspension of 2.22 g (0.01 mole) thioacid V in 25 ml dry benzene. The mixture was heated at reflux on a water bath for 1 h. After cooling, the resultant crystals were filtered off and washed with dry benzene to give a quantitative yield of VI, mp 99-100°C.

Ethyl Ester of 2-Thioxo-2H-chromene-3-thiocarboxylic Acid (VII). A mixture of 2.4 g (0.01 mole) acid chloride VI and 40 ml abs. ethanol was heated at reflux on a water bath for 2 h. At the end of the reaction, excess ethanol was distilled off and 30 ml ice water was added to the residue. The precipitate was filtered off to give 2.17 g (87%) VII, mp 92°C, R_f 0.73 (2:1 ethyl acetate—xylene). Found: C, 57.72; H, 3.86; S, 25.81%. Calculated for $C_{12}H_{10}O_2S_2$: C, 57.60; H, 4.00; S, 25.60%. IR spectrum: 1150 (C=S), 1610 (C=C), 1740 cm^{-1} (C—O—C). PMR spectrum: 1.4 (3H, t, CH_3), 4.4 (2H, q, CH_2), 5.1 (1H, s, CH), 7.2-8.0 ppm (4H, m, arom).

Diethylamide (VIII) and Dibutylamide of 2-Thioxo-2H-chromene-3-thiocarboxylic Acid (IX). A mixture of 2.4 g (0.01 mole) acid chloride VI and 0.02 mole diethylamine or dibutylamine in 15 ml abs. benzene was heated for 3 h at 50-60°C. After cooling, the crystals obtained were filtered off and the solvent was removed to give amide VIII or IX.

The yield of VIII was 2.6 g (92%), mp 117-118°C, R_f 0.75 (1:3 ethyl acetate—benzene). Found: N, 5.23; S, 23.36%. Calculated for $C_{14}H_{15}NOS_2$: N, 5.05; S, 23.10%.

The yield of IX was 3.0 g (90%), mp 121°C, R_f 0.67 (1:5 ethyl acetate—benzene). Found: N, 4.34; S, 19.07%. Calculated for $C_{18}H_{23}NOS_2$: N, 4.20; S, 19.21%.

2-Thioxo-3-cyano-2H-chromene (XIII) was obtained analogously to II from 1.71 g (0.01 mole) 3-cyanocoumarin (III) [6] and 1.66 g (0.0075 mole) P_2S_5 in 20 ml abs. pyridine or xylene. The yield of XIII was 1.35 g (72%), mp 147°C (ethyl acetate), R_f 0.66 (1:7 ethyl acetate—benzene). Found: N, 7.36; S, 17.28%. Calculated for $C_{10}H_5NOS$: N, 7.49; S, 17.11%. IR spectrum: 1380 (C═S), 1600 (C═C), 2225 cm^{-1} (C≡N). PMR spectrum: 3.6 (1H, s, HC═C—), 7.0-8.0 ppm (4H, m, arom).

Amide of 6-Nitro-2-thioxo-2H-chromene-3-thiocarboxylic Acid (XIV). A. This amide was obtained analogously to II from 2.34 g (0.01 mole) amide X [7] and 3.33 g (0.015 mole) P_2S_5 in 25 ml abs. pyridine or xylene. The yield of XIV was 1.86 g (70%), mp 165°C (from acetone—water), R_f 0.66 (6:1 chloroform—acetone). Found: C, 45.26; H, 2.12; N, 10.40; S, 24.21%. Calculated for $C_{10}H_6N_2O_3S_2$: C, 45.11; H, 2.26; N, 10.53; S, 24.06%.

B. A mixture of 2.21 g (0.01 mole) amide II and 6 ml nitrating mixture (1:1 nitric acid (d = 1.38) and sulfuric acid (d = 1.83)) was stirred at room temperature for 2 h. Then, 40 ml ice water was added. The precipitate was filtered off and recrystallized to give 2.1 g (85%) amide XIV. A mixture of sample of XIV obtained by methods A and B did not give a depressed melting point.

6-Nitro-2-thioxo-2H-chromene-3-thiocarboxylic Acid (XV). A. This compound was obtained analogously to II from 2.35 g (0.01 mole) 3-carboxy-6-nitrocoumarin (XI) [8] and 3.33 g (0.01 mole) P_2S_5 in 20 ml abs. pyridine or xylene. The yield of XV was 1.82 g (68%), mp 132°C (ethyl acetate).

B. Acid XV was obtained analogously to the synthesis of amide XIV (method B) from 2.22 g (0.01 mole) 2-thioxo-2H-chromene-3-thiocarboxylic acid (V) and 6 ml nitrating mixture. The yield of XV was 2.5 g (84%). A mixture of samples of XV obtained by methods A and B did not give a depressed melting point. Found: N, 5.02; S, 24.08%. Calculated for $C_{10}H_5NO_4S_2$: N, 5.24; S, 23.90%. IR spectrum: 1100, 1210 (C═S), 1615 (C═C), 1345 ($N({=}O)_2$ symm), 1515 ($N({=}O)_2$ asymm), 1610 cm^{-1} (C═C). PMR spectrum: 3.3 (1H, s, HC═C—), 6.5-8.4 ppm (3H, m, arom).

Ethyl Ester of 6-Nitro-2-thioxo-2H-chromene-3-thiocarboxylic Acid (XVI). A. Ester XVI was synthesized analogously to II from 2.63 g (0.01 mole) 3-ethoxycarbonyl-6-nitrocoumarin (XII) [9] and 3.33 g P_2S_5 in 20 ml abs. pyridine or xylene. The yield of XVI was 2.4 g (81%), mp 114-115°C (ethyl acetate), R_f 0.67 (2:1 ethyl acetate—benzene). Found: N, 4.46; S, 26.91%. Calculated for $C_{12}H_9NO_4S_2$: N, 4.75; S, 21.69%.

B. By analogy to the synthesis of amide XIV (method B), 2.5 g (0.01 mole) ester VII and 6 ml nitrating mixture gave 2.5 g (85%) XVI. A mixture of the samples of XVI obtained by methods A and B did not give a depressed melting point.

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