SYNTHESIS AND PROPERTIES OF 2-AMINO-1-THIO-4-CHROMONE DERIVATIVES

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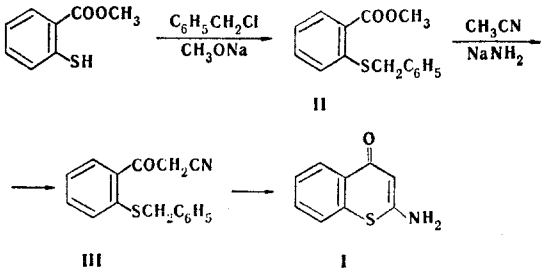
2-Amino-1-thio-4-chromone was synthesized and its substitution reactions at the N and C_3 atoms were studied. The mass spectrometric behavior of the synthesized 2-amino-1-thio-4-chromone derivatives was studied.

Up until now, 2-amino-1-thio-4-pyrone and its benzo derivatives were unknown. The molecules of these compounds should have several highly reactive centers and should be potential tautomeric systems. In addition, 2-aminothiopyrones may serve as the basis for the search for pharmacologically active substances, since some 1-thiochrome and 1-thioxanthone derivatives display biological activity [1-3].

In this connection, we synthesized 2-amino-1-thio-4-chromone (I) and obtained a number of its derivatives. Compound I was synthesized from methyl 2-benzylthiosalicyclate (II).



The condensation of ester II with acetonitrile leads to keto nitrile III in good yield. When III is treated with strong acids (CF_3COOH, $HClO_4$, and H_2SO_4), it undergoes debenzylation and cyclization to 2-aminothiochromone (I). Better results were obtained when CF_3COOH was used. The absorption maximum in the UV spectrum of I is shifted to the longer-wave region as compared with the UV spectrum of 2-aminochromone [4]. The IR spectrum (in d_6-DMSO) at 1600-3500 cm^{-1} is similar to the IR spectrum of 2-aminochromone [4]. Absorption bands of the stretching vibrations of an associated amino group are observed at 3100-3300 cm^{-1}; the intense band at 1670 cm^{-1} is related to the deformation vibrations of the NH_2 group. With deuteration of compound I this band disappears. The 3-H proton resonates at 6.46 ppm in the PMR spectrum of I; the signal of the two protons of the NH_2 group at 7-8 ppm can be identified by deuteration.

The basic properties of the amino group in I are strongly suppressed, on the one hand, whereas, on the other hand, its acidic properties are relatively strongly expressed: It is soluble in alkalis and does not form a hydrochloride.

Some reactions of 2-amino-1-thio-4-chromone with electrophilic reagents were studied. Thus the corresponding N-acyl derivatives (IV and V) were obtained when it was acylated with acetic or benzoic anhydride in pyridine.

The absorption bands at 1675-1720 and 1605-1610 cm^{-1} in the IR spectra of IV and V should be assigned to the stretching vibrations of the amide carbonyl group and the pyrone carbonyl group (markedly dependent vibrations), respectively.

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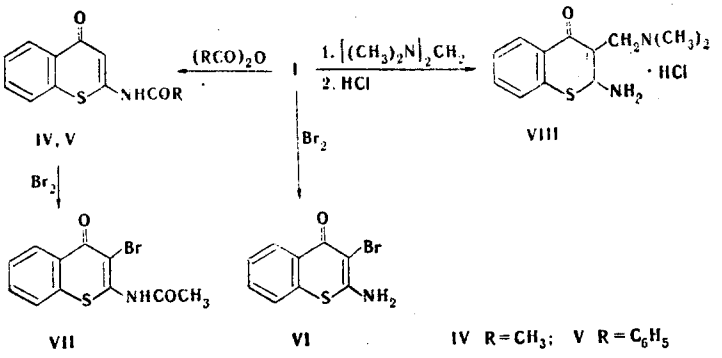
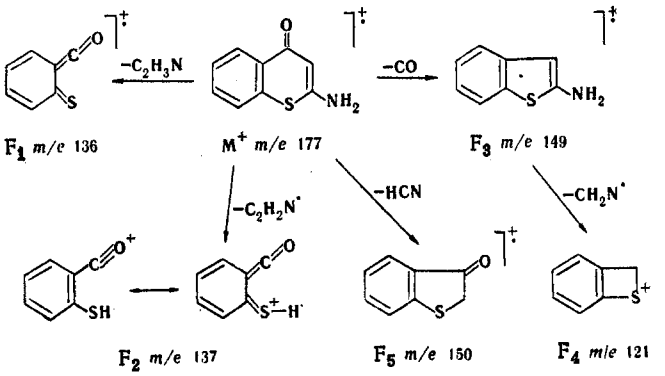


The reaction of bromine with I and IV in acetic acid gives adducts, which are converted to 3-bromo derivatives (VI and VII) when they are treated with sodium sulfite. The signal of the 3-H proton of the thiopyrone ring is absent in the PMR spectra of VI and VII at 6-7 ppm.

A Mannich base (VIII), which gives a monohydrochloride, was obtained by aminomethylation of thiochromone I. The structure of VIII was confirmed by its IR and PMR spectra.

Thus electrophilic substitution in 2-aminothiochromone I proceeds in the same way as in 2-aminochromone [5], i.e., at the amino group or at the C_3 atom of the pyrone ring.



The mass spectrometric behavior of 2-aminothiochromone I and its derivatives IV, VI, and VII was studied. The principal fragmentation pathways of I coincide with the fragmentation of 2-aminochromone [6]: fragmentation of the molecular ion (M^+) of the retrograde diene type with the formation of ion F_1 (m/e 136), similar fragmentation of M^+ accompanied by migration of the hydrogen atom to the benzene portion of the molecule (F_2, m/e 137), and successive loss of a carbonyl group from M^+ (F_3, m/e 149), and a CH_2N fragment (F_4, m/e 121) are observed. One's attention is directed to the fact that the stability of the rearranged F_2 fragment (fraction in the total ion current $W_{137} = 1.57$) is substantially lower than the stability of the similar fragment formed in the fragmentation of 2-aminochromone ($W_{121} = 12.97$); this is in agreement with the known facts of the higher stability under electron impact of oxo derivatives as compared with their thio analogs. The dominant process in the fragmentation of I as compared with 2-aminochromone is elimination of HCN from M^+ to give intense (64.4% of the maximum) F_5 ion peaks; this is characteristic for aromatic and heterocyclic amines [7, 8]. As in the case of acetyl derivatives of 2-aminochromone [6], the fragmentation of the molecular ions of N-acetyl derivatives IV and VII consists in the loss of a $COCH_2$ group to give pseudomolecular ions of I and VI, respectively, which subsequently undergo fragmentation via the general scheme. The fragmentation of 3-bromo derivatives VI and VII also follows the general scheme; however, in addition to the examined fragmentation pathways, elimination of Br· or HBr in the first steps of the dissociative ionization is observed in this case.

EXPERIMENTAL

The UV spectra of alcohol solutions of the compounds were recorded with a Perkin–Elmer 402 spectrophotometer. The IR spectra of mineral oil suspensions, KBr pellets, or DMSO solutions

of the compounds were obtained with a Perkin–Elmer 457 spectrometer. The PMR spectra of DMSO, CF_3COOH, and D_2O solutions of the compounds were recorded with a Varian T-60 spectrometer with hexamethyldisiloxane as the external standard. The mass spectra were obtained with a Varian MAT-112 chromatographic mass spectrometer with a system for direct introduction of the samples into the ion source at 150°C, an ionizing voltage of 70 eV, and an ionization-chamber temperature of 200°C. Aluminum oxide (the alkaline form, activity II) was used for the thin-layer chromatography (TLC) (elution with benzene).

2-Benzylthiobenzoylacetonitrile (III). A solution of 3.28 g (80 mmole) of acetonitrile in 5 ml of absolute ether and a solution of 10.32 g (40 mmole) of thioether II [9] in 150 ml of absolute ether were added dropwise to a suspension of sodium amide, obtained from 2.3 g (0.1 g-atom) of sodium in 200 ml of liquid ammonia, and the mixture was stirred with cooling for 1 h and allowed to stand without cooling for 16 h. The ammonia was allowed to evaporate, 100 ml of water was added to the residue, and the aqueous solution was acidified with acetic acid. The precipitate was removed by filtration and washed successively with 10% sodium acetate solution and warm water to give 9.5 g (89%) of nitrile III with mp 135–136°C (from alcohol) and R_f 0.70 (activity IV Al_2O_3, elution with chloroform). UV spectrum, λ_{max} (log ε): 204 (4.42), 238 (4.34), 263 (3.93), 270 (3.90), and 352 (3.44). IR spectrum (in oil): 2260 (C≡N) and 1681 cm^{-1} (C=O). PMR spectrum (in d_6-DMSO), δ: 4.46 (2H, s, $CH_2C_6H_5$), 4.90 (2H, s, CH_2CN), and 7.40–8.33 ppm (9H, C_6H_4 + C_6H_5). Found: C 72.0; H 4.8; N 5.2; S 12.1%. $C_{16}H_{13}NOS$. Calculated: C 71.9; H 4.9; N 5.2; S 12.0%.

2-Amino-1-thio-4-chromone (I). A 6-g (22 mmole) sample of nitrile III in 15 ml of trifluoroacetic acid was allowed to stand for 16 h (during which III gradually dissolved). The solution was diluted with 5 ml of alcohol and poured into a mixture of 200 ml of water and 100 ml of benzene, and the mixture was made alkaline to pH 8 with 16 g of $NaHCO_3$. The resulting precipitate was removed by filtration and washed with water to give 3.20 g (80.5%) of I with mp 255–256°C (dec., from alcohol) and R_f 0.45. UV spectrum, λ_{max} (log ε): 233 (4.48), 310–330 (4.18), 252, and 258 nm (inflection). IR spectrum (d_6-DMSO): 3100–3200 (ν_{NH_2}), 1660 (δ_{NH_2}), and 1600 cm^{-1} (C=O and C=C). PMR spectrum (in d_6-DMSO), δ: 6.46 (1H, s, 3-H) and 7.8–8.4 ppm (6H, C_6H_4 and NH_2). Mass spectrum, m/e: (%)*: 177 (100), 175 (22), 150 (64), 149 (13), 137 (6), 136 (40), 122 (10), 121 (16), 120 (13), 110 (11), 109 (6), 108 (31). Found C 61.1; H 4.1; N 7.8; S 18.0%. C_9H_7NOS. Calculated: C 61.0; H 4.0; N 7.9; S 18.1%.

2-Acetamido-1-thio-4-chromone (IV). A mixture of 0.89 g of I, 15 ml of acetic anhydride, and 5 ml of anhydrous pyridine was heated on a boiling-water bath for 6 h, and the resulting precipitate was removed by filtration and washed with water to give 1.0 g (91%) of IV with mp 320°C (dec., from alcohol) and R_f 0.52. IR spectrum (in oil): 3195 (ν_{NH}), 1720 (amide I), 1609 and 1594 (C=O and C=C), 1550, 1535 cm^{-1}. PMR spectrum (in CF_3COOH), δ: 2.17 (3H, s, CH_3), 7.26 (1H, s, 3-H), and 7.46–8.43 ppm (C_6H_4). Mass spectrum, m/e (%): 219 (42), 177 (100), 175 (13), 152 (5), 151 (10), 150 (99), 149 (17), 137 (8), 136 (28), 135 (6), 134 (5), 133 (13), 122 (9), 121 (21), 120 (10), 110 (8), 109 (6), 108 (18), 106 (3), 105 (12), 104 (5), 96 (21). Found: N 6.5; S 14.5%. $C_{11}H_9NO_2S$. Calculated: N 6.4; S 14.6%.

2-Benzamido-1-thio-4-chromone (V). This compound was similarly obtained from 0.89 g (5 mmole) of 2-aminothiochromone I and 2.26 g (10 mmole) of benzoic anhydride. The yield of V, with mp 299–300°C (dec., from butanol) and R_f 0.53, was 1.2 g (85%). IR spectrum (in oil): 3185 (ν_{NH}), 1675 (amide I), and 1605 and 1570 cm^{-1} (C=O and C=C). Found: N 5.1; S 11.2%. $C_{16}H_{11}NO_2S$. Calculated: N 5.0; S 11.4%.

2-Amino-3-bromo-1-thio-4-chromone (VI). A 0.80-g (5 mmole) sample of bromine was added to a solution of 0.89 g (5 mmole) of I in 15 ml of acetic acid, and the mixture was allowed to stand for 16 h. The precipitate was removed by filtration and treated with 3.5 g of sodium sulfite in 75 ml of water. The precipitate was removed by filtration and washed with water to give 0.70 g (54.5%) of VI with mp 224–225°C (dec., from alcohol) and R_f 0.40. UV spectrum, λ_{max} (log ε): 231 (4.41), 258 (inflection), 270 (inflection), and 327 nm (4.10). IR spectrum (in KBr): 3405 and 3260 (ν_{NH_2}), 1630 (δ_{NH_2}), 1605 and 1590 cm^{-1} (C=O and C=C). Mass spectrum, m/e (%): 257 (50), 256 (5.5), 255 (50), 230 (5), 229 (6), 228 (5), 227 (5.5), 177 (75), 176 (100), 175 (98), 150 (31), 149 (23), 148 (14), 147 (5), 146 (13), 137 (6), 136 (35), 122 (13), 121 (75), 120 (75), 108 (34), 105 (21), 104 (11.5), 96 (9), 88 (21). Found: Br 31.1; N 5.2; S 12.8%. C_9H_6BrNOS. Calculated: Br 31.2; N 5.5; S 12.5%.

*Here and subsequently, with respect to the maximum peak; the ion peaks with intensities >3% are presented.

2-Acetamido-3-bromo-1-thio-4-chromone (VII). This compound was similarly obtained from 0.55 g (2.5 mmole) of 2-acetamidothiochromone IV. The yield of product with mp 237-238°C (dec., from alcohol) was 0.75 g (100%). UV spectrum, λ_{max} (log ε): 230 (4.18), 263 (4.37), 271 (4.44), 306 (3.64), and 347 nm (4.12). IR spectrum (in oil): 3300 (ν_{NH}), 1689 (amide I), and 1608 cm^{-1} (C=O and C=C). PMR spectrum (in CF_3COOH), δ: 2.26 (3H, s, CH_3), 7.4-7.66 (3H, 6-H, 7-H, 8-H), and 8.3 ppm (1H, 5-H). Mass spectrum, m/e (%): 299 (12), 297 (12), 258 (6), 257 (24), 256 (6), 255 (24), 230 (6), 229 (6), 228 (6), 227 (6), 219 (24), 218 (100), 217 (27), 207 (6), 201 (5), 199 (4), 178 (7), 177 (32), 176 (94), 175 (15), 150 (15), 149 (15), 148 (11), 137 (9), 136 (18), 121 (32), 120 (42). Found: Br 27.3; N 4.9; S 11.2%. $C_{11}H_8BrNO_2S$. Calculated: Br 26.8; N 4.7; S 10.7%.

2-Amino-3-dimethylaminomethyl-1-thio-4-chromone Hydrochloride (VIII). A mixture of 1.77 g (10 mmole) of I, 1.02 g (10 mmole of $[(CH_3)_2N]_2CH_2$, and 40 ml of absolute alcohol was heated to the boiling point and allowed to stand for 16 h, after which the alcohol was evaporated and the residual oil was treated with ether. The mixture was worked up to give 1.4 g of the base. The base was dissolved in a small amount of absolute alcohol, an ether solution of hydrogen chloride was added, and the mixture was treated with ethyl acetate and worked up to give 1.4 g (52%) of hydrochloride VIII with mp 253-254°C (dec., from alcohol) and R_f 0.51. PMR spectrum (in D_2O), δ: 3.3 [6H, s, $(CH_3)_2$], 4.37 (2H, s, CH_2), and 7.5-8.5 ppm (C_6H_4). Found: Cl 12.7; N 9.9; S 11.5%. $C_{12}H_{15}ClN_2OS$. Calculated: Cl 13.1; N 10.3; S 11.8%.

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