Synthesis of thiohydantoin and rhodanine derivatives from 4-substituted cinnamoyl isothiocyanates

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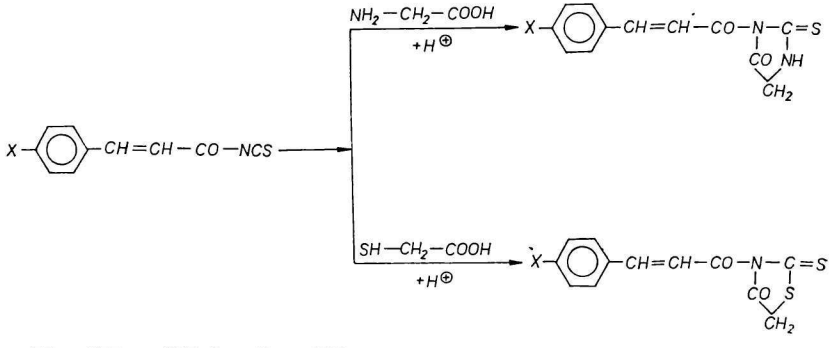
Synthesis of 3-(4-substituted cinnamoyl)-2-thiohydantoins and 3-(4-substituted cinnamoyl)rhodanines by cyclization of 4-substituted cinnamoyl isothiocyanates with glycine and thioglycolic acid, respectively in acid medium is described. The structures of the synthesized compounds are proved by infrared and ultraviolet spectra.

Thiohydantoins and rhodanines represent a small but, from the point of view of the biological activity, a very important group of organic compounds. There is a number of works of various authors in the literature dealing with the preparation and properties of thiohydantoins and rhodanines from different types of alkyl and aryl isothiocyanates [1—9]. From acyl isothiocyanates only benzoyl isothiocyanate was used for the preparation of 3-benzoyl-2-thiohydantoin till now [10]. Taking into account the high biological activity of cinnamoyl isothiocyanates [11], we focused our attention on the synthesis of 3-(4-substituted cinnamoyl)-2-thiohydantoins and rhodanines as their synthetic producers.

Thiohydantoins were synthesized by reaction of the appropriate isothiocyanate with glycine according to Scheme 1. Cyclization was achieved in hydrochloric acid.

Rhodanines were prepared by reaction of cinnamoyl isothiocyanate with an excess of thioglycolic acid which represented a medium acidic enough for cyclization. 3-Cinnamoylrhodanine and 3-(4-methylcinnamoyl)rhodanine were prepared by the mentioned synthesis in the melt. 3-(4-Bromocinnamoyl)rhodanine could be prepared by this reaction only in a solvent (methanol) and 3-(4-nitrocinnamoyl)rhodanine only in triethylamine



X = H, CH_3, CH_3O, Br, NO_2.

Scheme 1

buffer. We failed to synthesize 3-(4-methoxycinnamoyl)rhodanine by the mentioned methods.

All of the synthesized 3-(4-substituted cinnamoyl)-2-thiohydantoins and 3-(4-substituted cinnamoyl)rhodanines were crystalline compounds of high melting points and slightly soluble in organic solvents.

Experimental

Cinnamoyl isothiocyanate (m.p. 41—43°C), 4-methylcinnamoyl isothiocyanate (m.p. 46—47°C), 4-methoxycinnamoyl isothiocyanate (m.p. 47—48°C), 4-bromocinnamoyl isothiocyanate (m.p. 106—108°C), and 4-nitrocinnamoyl isothiocyanate (m.p. 145—147°C) were prepared from the appropriate acyl halides with lead(II) thiocyanate in benzene [12].

Infrared spectra of the synthesized compounds were recorded with a double-beam UR-20 (Zeiss, Jena) spectrophotometer in the range of 700—3600 cm^{-1} using KBr pellets (0.4—0.6 mg compound/500 mg KBr). Polystyrene foil was used for calibration.

Ultraviolet spectra of 3-(4-substituted cinnamoyl)-2-thiohydantoins and 3-(4-substituted cinnamoyl)rhodanines in methanol (concentration 4×10^{-5} mol l^{-1}) were taken with a Perkin—Elmer 402 recording spectrophotometer in the region of 210—400 nm at 20 ± 2°C using 10-mm cells.

Preparation of 3-(4-substituted cinnamoyl)-2-thiohydantoins

4-Substituted cinnamoyl isothiocyanate (0.13 mole) dissolved in ethanol (50 ml) was added to a mixture of glycine (0.14 mole) and sodium hydroxide (0.225 mole) in water (20 ml). This mixture was refluxed for 1 hr while a precipitate was formed. Then ethanol was distilled off and the precipitate dissolved in water. Addition of hydrochloric acid resulted in precipitation of the appropriate thiohydantoin, which was filtered off and crystallized from a suitable solvent.

The following thiohydantoins were prepared in this way:

3-Cinnamoyl-2-thiohydantoin, yield 76.9%, m.p. 208—210°C.

For $C_{12}H_{10}N_2O_2S$ (246.27) calculated: 58.53% C, 4.09% H, 11.38% N; found: 58.64% C, 4.13% H, 11.44% N.

ν_1(C=O) 1733 cm^{-1}, ν_2(C=O) 1761 cm^{-1}, ν(C=C) 1650 cm^{-1}; λ_{max} 280 nm, log ε 4.25.

3-(4-Methylcinnamoyl)-2-thiohydantoin, yield 53.8%, m.p. 155—158°C.

For $C_{13}H_{12}N_2O_2S$ (260.29) calculated: 59.99% C, 4.64% H, 10.75% N; found: 59.87% C, 4.73% H, 10.73% N.

ν_1(C=O) 1745 cm^{-1}, ν_2(C=O) 1758 cm^{-1}, ν(C=C) 1649 cm^{-1}; λ_{max} 286 nm, log ε 4.38.

3-(4-Methoxycinnamoyl)-2-thiohydantoin, yield 24.8%, m.p. 161—163°C.

For $C_{13}H_{12}N_2O_3S$ (276.16) calculated: 56.53% C, 4.34% H, 10.13% N; found: 56.72% C, 4.39% H, 10.07% N.

ν_1(C=O) 1717 cm^{-1}, ν_2(C=O) 1732 cm^{-1}, ν(C=C) 1643 cm^{-1}; λ_{max} 303 nm, log ε 4.33.

3-(4-Bromocinnamoyl)-2-thiohydantoin, yield 44.1%, m.p. 260°C, with decomposition,

For $C_{12}H_9BrN_2O_2S$ (325.15) calculated: 44.30% C, 2.78% H, 8.61% N; found: 44.45% C, 2.83% H, 8.54% N.

ν_1(C=O) 1745 cm^{-1}, ν_2(C=O) 1760 cm^{-1}, ν(C=C) 1640 cm^{-1}; λ_{max} 295 nm, log ε 4.38.

3-(4-Nitrocinnamoyl)-2-thiohydantoin, yield 37.2%, m.p. above 260°C, with decomposition.

For $C_{12}H_9N_3O_4S$ (291.25) calculated: 49.70% C, 3.11% H, 14.42% N; found: 49.83% C, 3.03% H, 14.45% N.

ν_1(C=O) 1758 cm^{-1}, ν_2(C=O) 1771 cm^{-1}, ν(C=C) 1651 cm^{-1}; λ_{max} 298 nm, log ε 4.36.

Preparation of 3-(4-substituted cinnamoyl)rhodanines

The appropriate isothiocyanate (0.01 mole) and thioglycolic acid (0.02 mole) were heated in a flask provided with a reflux condenser for 1—2 hrs at 120—130°C. Then the reaction mixture was poured into water and the formed rhodanine was filtered off, washed with water, and recrystallized from ethanol—water.

The following rhodanines were prepared in this way:

3-Cinnamoylrhodanine, yield 53.8%, m.p. 130—133°C.

For $C_{12}H_9NO_2S_2$ (263.31) calculated: 54.76% C, 3.44% H, 5.31% N; found: 54.90% C, 3.49% H, 5.39% N.

ν_1(C=O) 1693 cm^{-1}, ν_2(C=O) 1715 cm^{-1}, ν(C=C) 1634 cm^{-1}, $\nu(>N-C=S)$ 1285, 1310, and 1420 cm^{-1}; λ_{max} 273 nm, log ε 4.53.

3-(4-Methylcinnamoyl)rhodanine, yield 31.3%, m.p. 191—193°C.

For $C_{13}H_{11}NO_2S_2$ (277.33) calculated: 56.27% C, 3.99% H, 5.04% N; found: 56.43% C, 3.95% H, 5.12% N.

ν_1(C=O) 1691 cm^{-1}, ν_2(C=O) 1712 cm^{-1}, ν(C=C) 1633 cm^{-1}, $\nu(>N-C=S)$ 1284, 1311, and 1423 cm^{-1}; λ_{max} 283 nm, log ε 4.47.

Preparation of 3-(4-bromocinnamoyl)rhodanine

4-Bromocinnamoyl isothiocyanate (0.01 mole) was dissolved in methanol (90 ml) and thioglycolic acid (0.02 mole) was added. The reaction mixture was refluxed for 2 hrs and then the solvent was distilled off. The formed rhodanine was filtered off and crystallized from ethanol—water. Yield 63%, m.p. 155—156°C.

For $C_{12}H_8BrNO_2S_2$ (342.20) calculated: 42.11% C, 2.35% H, 4.09% N; found: 42.18% C, 2.39% H, 4.03% N.

ν_1(C=O) 1706 cm^{-1}, ν_2(C=O) 1717 cm^{-1}, ν(C=C) 1623 cm^{-1}, $\nu(>N-C=S)$ 1288, 1303, and 1455 cm^{-1}; λ_{max} 310 nm, log ε 4.5.

Preparation of 3-(4-nitrocinnamoyl)rhodanine

4-Nitrocinnamoyl isothiocyanate (0.001 mole) was dissolved in acetone (20 ml) and thioglycolic acid (0.0014 mole) in triethylamine buffer (1.6 ml of 2 N acetic acid and 0.96 ml of triethylamine filled up to 20 ml with water) was added. The reaction mixture was heated for 1 hr at 30°C. Then the solvent was evaporated and the residue was dissolved in glacial acetic acid (10 ml) saturated with hydrogen chloride. The solvent was distilled off *in vacuo* and the crude product was crystallized from ethanol—water. Yield 33.1%, m.p. 195—197°C.

For $C_{12}H_8N_2O_4S_2$ (308.31) calculated: 46.74% C, 2.61% H, 9.08% N; found: 46.64% C, 2.64% H, 9.04% N.

ν_1(C=O) 1708 cm^{-1}, ν_2(C=O) 1722 cm^{-1}, ν(C=C) 1620 cm^{-1}, $\nu(>N-C=S)$ 1280, 1304, and 1412 cm^{-1}; λ_{max} 315 nm, log ε 4.25.

ν_1(C=O) — stretching vibration of carbonyl group of the cinnamoyl residue,

ν_2(C=O) — stretching vibration of carbonyl group of the thiohydantoin and rhodanine ring, respectively.

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