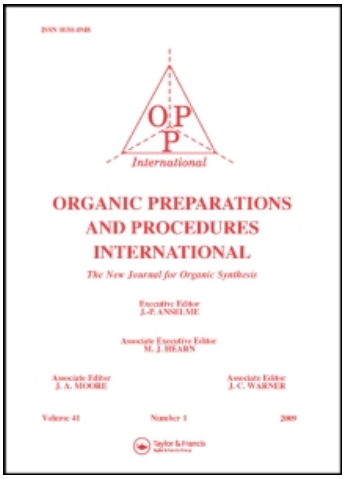

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STUDIES ON 4-HYDROXYCOUMARIN. 38. SYNTHESES OF 3-SUBSTITUTED DERIVATIVES. α-BROMOACYL AND 2-AMINOTHIAZOLO AND OF 4H-FURO-[3,2-c][1]-BENZOPYRAN-3-[2H],4-DIONE

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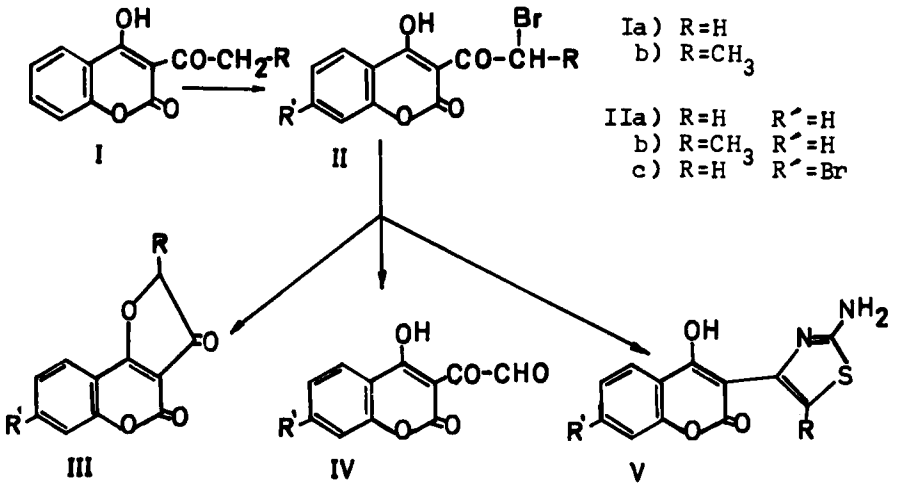
Halogenated,[1] amino,[2] and acyl[1,3] derivatives of 4-hydroxycoumarin are active as insecticides, bactericides and fungicides. The biological activity of 4-hydroxycoumarins increases when a halogen is introduced, especially in positions 6 or 7.[4] A patent protects the synthetic routes leading to 3-(α-bromoacyl)-4-hydroxycoumarins IIa, b and to 4H-furo-[3,2-c][1]-benzopyran-3-[2H], 4-dione (IIIb), compounds of strong bactericidal, insecticidal, and fungicidal activity.[1] We now describe syntheses of the above compounds by novel and easier routes and the introduction of bromine into the 7-position leading to products that might prove still stronger antiparasitic agents.

The potassium persulfate-catalyzed bromination of 3-acyl derivatives Ia, b with equimolar bromine in glacial acetic acid gave better than 90% yields of 3-(α-bromoacyl)-4-hydroxycoumarins IIa, b within ten minutes. With excess bromine and a reaction time of 5 hrs, 3-(α-bromoacyl)-4-hydroxy-7-bromocoumarin (IIc) was obtained from Ia. Dehydrohalogenation of IIa, b with triethylamine, 1% NaOH or pyridine or by long reflux in glacial acetic acid, gave the corresponding 4H-furo[3,2-c][1]-benzopyran-3-[2H],4-diones (IIIa, b). The coumarino glyoxals IVa, b were obtained in excellent yields by the procedure of Kornblum and coworkers.[5]



We also tried to obtain thiazolo-substituted derivatives of 4-hydroxycoumarin by condensation of 3-(α-bromoacyl)-4-hydroxycoumarins (II) or 3-acyl-4-hydroxycoumarins (I) with thiourea, in the presence of iodine. Either attempt yielded the expected 2-amino-4-(4-hydroxycoumarin-3-yl)-thiazoles (V), but yields were much better with II than with I as the starting compound.

EXPERIMENTAL

All mps are uncorrected. IR spectra (KBr pellets) were recorded on a Perkin Elmer M-377 spectrophotometer and NMR spectra (in d_6-DMSO) on a Varian A-60 spectrograph. The progress of reactions was monitored by thin layer chromatography on silica gel HF_{254} with benzene-methyl ethyl ketone-acetic acid (8:1:1) as the mobile phase; spots were detected under 360-nm radiation filtered from the output of a UV lamp.[6]

3-(α-Bromoacetyl)-4-hydroxycoumarin (IIa).- To a solution of 2 g (9.8 mmoles) of Ia in 20 ml of glacial acetic acid (heating), was added a solution of 0.05 g of $K_2S_2O_8$ and 1.9 g (0.61 ml, 24 mmoles) of bromine dissolved in 5 ml of acetic acid. The resulting mixture was heated to 100°.

After 10 minutes, the bromine color had disappeared and the mixture was allowed to cool. The precipitated product, 2.5 g (91%) of light yellow needles, was recrystallized from acetic acid (or from 96% ethanol) to give 2.1 g (76%) pure IIa, mp. 145-146°, lit.[1] 144-146°. IR cm^{-1}: 3400 (OH), 3040, 3000, 2950 (OH), 1705 (CO).

Anal. Calcd for $C_{11}H_7O_4Br$: C, 46.67, H, 2.49, Br, 28.23.

Found: C, 46.96, H, 2.57, Br, 28.08.

3-(α-Bromopropionyl)-4-hydroxycoumarin (IIb).- This compound was obtained from Ib using the same procedure as in the preparation of IIa; crude yield: 95%. Recrystallization from 96% ethanol gave 92% of pure IIb, mp. 128-129°, lit.[1] 129°.

3-(α-Bromoacetyl)-7-bromo-4-hydroxycoumarin (IIc).- Pure IIc, mp. 157-158°, lit.[7] 157-158°, was obtained in 45% yield, from Ia by the procedure described by A. Mustafa et al.[7]

4H-Furo[3,2-c][1]-8-bromo-benzopyran-3-[2H],4-dione (IIIa).- A solution of 3 g (8.28 mmoles) of IIc in 30 ml of acetone containing 1 ml of triethylamine was heated to reflux temperature and kept refluxing for 6 hrs. On cooling 2.2 g (94%) of crude product separated in the form of yellow crystals. With pyridine instead of triethylamine, or with 1% NaOH, the yields in crude product were 65 and 50% respectively. Recrystallization from acetone gave pure IIIa, mp. 203-205°. IR cm^{-1}: 1760, 1710 (CO). NMR δ: 7.35-7.50 (m, 2H), 7.65 (s, 6H), 7.72-8.05 (m, 8H, 9H).

Anal. Calcd for $C_{11}H_5O_4Br$: C, 47.01, H, 1.79, Br, 28.43.

Found: C, 46.99, H, 1.78, Br. 28.56.

4H-Furo[3,2-c][1]-benzpyran-3-[2H],4-dione (IIIb).- This compound was obtained by the same procedure as used for the preparation of IIIa; yield 98%. Recrystallized IIIb (acetone) had mp. 227-228, lit.[1] 227.5-228.5°.

4-Hydroxycoumarin-3-yl)-glyoxal (IVa).- A solution of 3.7 g. (13.1 mmoles) of IIa was prepared in DMSO at 80° (water bath, thermostated) and the solu-

tion was kept at this temperature for 24 hrs. The solvent was then completely removed under reduced pressure, and the residue was crystallized from toluene to yield 3 g. (95%), mp. 220-222° of yellow needles. IR cm^{-1}: 3450 (OH), 1765, 1646 (CO). NMR δ: 7.21-8.06 (m, 4H; arom.), 7.36 (s, OH), 10.88 (s, CHO).

Anal. Calcd for $C_{11}H_6O_5$: C, 60.56, H, 2.77.
Found: C, 60.70, H, 2.45.

(7-Bromo-4-hydroxycoumarin-3-yl)-glyoxal (IVb).- A solution of 2.0 g. (5.52 mmoles) of IIc was prepared at 75°, in 40 ml of DMSO, and the solution was kept at this temperature for 16 hrs. The crude product that deposited during this period was collected and extracted with hot ethanol. The residue on crystallization from acetic acid, gave 1.3 g (79%) of pure IVb, mp. 246-247°. IR cm^{-1}: 3460 (OH), 3120 (CH), 1760, 1640 (CO). NMR δ: 7.35 (s, OH), 7.39 (s, 8H), 7.55-8.06 (m, 5H; 6H), 10.52 (s, CHO).

Anal. Calcd for $C_{11}H_5O_5Br$: C, 44.47, H, 1.70, Br, 26.89.
Found: C, 44.23, H, 1.89, Br, 26.72.

2-Amino-4-(4-hydroxycoumarin-3-yl)-thiazole (Va).

Route A; (from IIa).- A solution of 3.5 g (12.36 mmoles) of IIa in 55 ml of ethanol was mixed with a solution of 1.0 g (13.2 mmoles) of thiourea in 3 ml of water. The mixture was placed into a boiling water bath and kept at reflux for 45 minutes. Within 1-2 min. a dark brown coloration developed which did not appear to change further. After completion of the heating period, the reaction mixture was filtered and acidified with acetic acid whereupon brownish crystals separated. Recrystallization from ethanol gave 2.9 g (90%) of pure Va, mp. 290-291°. IR cm^{-1}: 3405 (OH), 3160 (NH), 1648 (CO). NMR δ: 7.21 (s, thiazole), 7.30-8.08 (m, 4H; arom.), 8.61 (s, NH_2).

Anal. Calcd for $C_{12}H_8O_3NS_2$: C, 55.83, H, 3.10, N, 10.76.
Found: C, 55.12, H, 3.32, N, 10.60.

Route B; from Ia.- A mixture of 2 g (9.8 mmoles) of Ia, 1.52 g (19.9 mmoles) of thiourea and 1.26 g (10 mmoles) of iodine were ground together and the mixture was kept at 115-120° on an oil bath for 12 hrs. The resulting gray solid was extracted with hot water to which a little ammonium hydroxide was added. The residue was crystallized from acetic acid to give 0.9 g (35%) of Va, mp. 290-291°. Spectral and analytical data of this product were identical to those of the product obtained in A.

2-Amino-4-(7-bromo-4-hydroxycoumarin-3-yl)-thiazole (Vb).- This compound was obtained by route A in 75% yield. Crystallization from acetic acid gave a product mp. 320°. IR cm^{-1}: 3340 (OH), 3285 (NH), 1605 (CO).

Anal. Calcd for $C_{12}H_7N_2SO_3Br$: C, 42.50, H, 2.08, N, 8.26, Br, 23.56.
Found: C, 42.26, H, 2.04, N, 8.53, Br, 23.42.

2-Amino-4-(4-hydroxycoumarin-3-yl)-5-methylthiazole (Vc).- Route A gave a 93% yield in crude product Vc. Crystallization from ethanol gave a product with mp. 283-284°. IR cm^{-1}: 3362 (OH), 3100 (NH), 1650 (CO). NMR δ: 2.08 (s, CH_3), 7.10-7.82 (m, 4H, arom.), 8.34 (s, NH_2).

Anal. Calcd for $C_{13}H_{10}O_3N_2S$: C, 56.92, H, 3.67, N, 10.21.
Found: C, 57.14, H, 3.47, N, 10.12.

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