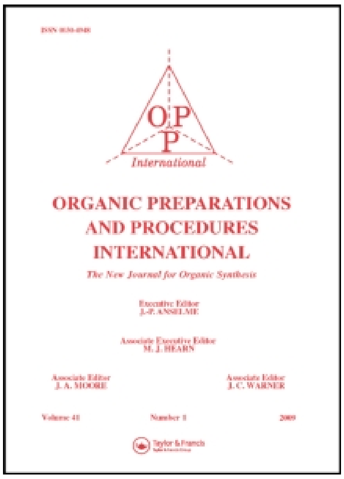

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SYNTHESIS OF SOME BICOUMARYL SULPHIDES AND SULPHONES

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SYNTHESIS OF SOME BICOUMARYL SULPHIDES AND SULPHONES

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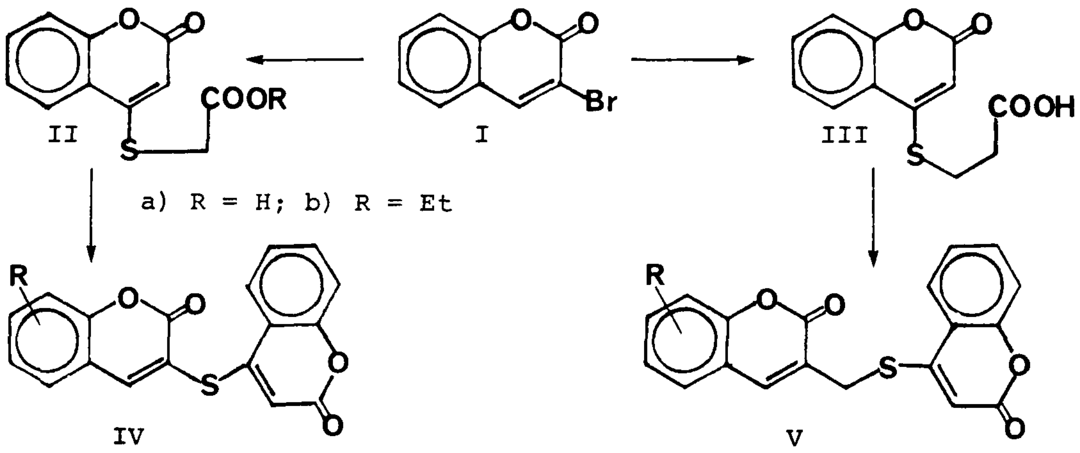
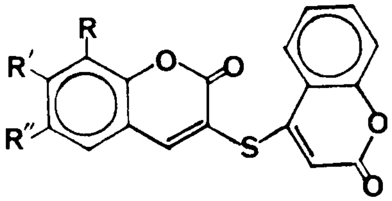
3-Bromocoumarin (I)[1] reacted with thioglycolic acid in the presence of pyridine to give 2H(1)benzopyran-2-one-4-S-mercaptoacetic acid (II). Its ^{1}H-NMR spectrum as well as that of its ethyl ester showed a singlet (1H) at δ 6.3 which was attributed to C_3 proton of coumarin ring. Similarly the Perkin-Oglialoro[2] reaction of the sodium salt of IIa with various *o*-hydroxybenzaldehydes afforded 3-(4'-coumarylthio)-2H(1)benzopyran-2-ones (IV). The latter could also be obtained by the Knoevenagel reaction of the ethyl ester of 2H(1)benzopyran-2-one-4-S-mercaptoacetic acid with *o*-hydroxybenzaldehydes (Table 1). The re-



action of I with 3-mercaptopropionic acid afforded 2H(1)benzopyran-2-one-4-S-mercaptopropionic acid (III) whose sodium salt reacted with o-hydroxybenzaldehydes to yield 3-(4'-coumarylthiomethylene)-2H(1)benzopyran-2-ones (V) which were further oxidized to corresponding sulphones (VI). (Tables 2 and 3). Oxidation of IVa with H_2O_2 gave a sulphoxide, mp. 235-236°. (M^+: 338; IR (KBr): 1700 (C=O), 1075 (-SO) cm^{-1}); however, compounds IVb-IVe failed to be oxidized under these conditions.

These syntheses constitute a useful method for obtaining dicoumaryl sulphones (some of which exhibited good anti-T.B. activity *in vitro* in preliminary screening tests) which are not easily accessible by other synthetic routes.

TABLE 1. Mps and Analyses of Compounds



	R	R'	R"	mp. (°C)	Analysis % Calculated C	Analysis % Calculated H	Found C	Found H
IVa	H	H	H	245	67.3	3.1	67.6	3.3
IVb	H	H	Br	282-283	53.8	2.8	53.7	3.1
IVc	H	H	Cl	271	60.5	2.5	60.4	2.9
IVd	H	OAc	H	262-263	63.1	3.1	63.4	3.3
IVe	OMe	H	H	260	64.7	3.4	64.6	3.4

EXPERIMENTAL SECTION

All melting points are uncorrected. ^1H-NMR spectra were recorded on a 60MHz Varian spectrometer with TMS as internal standard. IR spectra were measured using Beckman-20 and UV spectra were taken with a Carl-Zeiss USU-2P spectrophotometers. The mass spectra were run on a Varian instrument model CH-5 at 70 eV.

2H(1)Benzopyran-2-one-4-S-mercaptoacetic acid.- To a solution of 3-bromocoumarin (4.5 g, 0.02 mole) in pyridine (30 ml) was added thioglycolic acid (1.8 ml, 0.02 mole) with stirring. The reaction mixture was then refluxed at 140° for 4 hrs. After cooling, it was acidified with dilute hydrochloric acid. The precipitated solid was collected and washed thoroughly with water. It was dried and recrystallized from methanol to yield 4.0 g (88%) of colourless needles, mp. 229°.

Anal. Calcd. for $C_{11}H_8O_4S$: C, 55.94; H, 3.4.

Found: C, 55.7; H, 3.6.

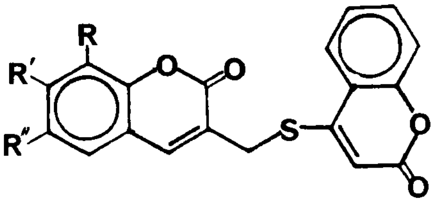
^{1}H-NMR (DMSO-d_6): δ 3.9 (s, 2H, methylene), 6.3 (s, 1H, C_3 proton of coumarin), 7.3-7.9 (m, 4H, aromatic).

IR (KBr): 1670 (C=O of COOH), 1730 (C=O of lactone), 2900 (OH of COOH), 1600, 1580, 1540 cm^{-1}. Its ethyl ester (colourless needles from hexane, mp. 122°) had the following spectral data. ^{1}H-NMR ($CDCl_3$): δ 1.3 (t, 3H, methyl), 3.9 (s, 2H, methylene next to sulphur), 4.3 (q, 2H, methylene-$OC\underline{H}_2CH_3$), 6.3 (s, 1H, C_3 proton of the coumarin), 7.2-7.8 (m, 4H, aromatic).

IR (KBr): 1710 (C=O of lactone), 1630 (C=O of ester) cm^{-1}.

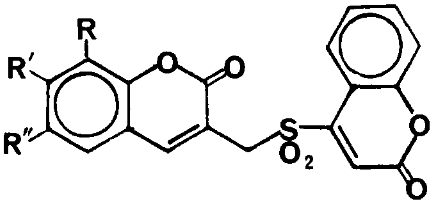
General Procedure for 3-(4'-coumarylthio)-2H(benzopyran-2-ones by Perkin-Oglialoro Reaction.- A mixture of an o-hydroxybenzaldehyde (0.01 mole) and dry sodium 2H(1)benzopyran-2-one-4-S-mercaptoacetate (0.02 mole) in acetic anhydride (50 ml) was refluxed at 170-180° for 4 hrs. It was cooled and poured over crushed ice. After standing overnight, the precipitated solid was collected, and washed with aqueous sodium bicarbonate. It was

TABLE 2. Mps and Analyses of Compounds



	R	R'	R"	mp. (°C)	Analysis % Calculated C	 H	 Found C	 H
Va	H	H	H	235	67.8	3.5	67.5	3.7
Vb	H	H	Br	250	54.9	2.7	54.6	3.0
Vc	H	H	Cl	266-267	61.4	2.9	61.1	3.2
Vd	H	OAc	H	244-245	63.9	3.5	63.6	3.8
Ve	OMe	H	H	162-164	65.5	3.8	65.4	3.7

TABLE 3. Mps and Analyses of Compounds



	R	R'	R"	mp. (°C)	Analysis % Calculated C	 H	 Found C	 H
VIa	H	H	H	194-195	61.9	3.1	61.6	3.2
VIb	H	H	Br	220	51.0	2.4	51.3	2.7
VIc	H	H	Cl	215-216	56.5	2.7	56.2	3.0
VId	H	OAc	H	202-203	59.1	3.3	59.0	3.4
VIe	OMe	H	H	192-193	60.3	3.5	60.2	3.7

crystallized from acetic acid to yield 1.0 g (25-30%) colourless needles.

The spectral data of a typical compound (IVa, Table I) is as follows:

m/e (70 eV): M^+ 322, 294, 266, 149, 117.

UV (dioxane) nm log ε: 235 (4.04), 270 (4.022), 310 (3.932).

IR (KBr): 1710 (C=O), 1600, 1540 cm^{-1}.

General Procedure for 3-(4'-coumarylthio)-2H(1)benzopyran-2-ones by Knoevenagel Reactions.- A mixture of an _o_-hydroxybenzaldehyde (0.02 mole), 2H(1)benzopyran-2-one-4-S-mercaptoethyl acetate (0.03 mole), ethanol (100 ml) and 5-6 drops of piperidine was refluxed on water bath for 8 hours. The crystalline solid which separated was filtered, washed with ethanol and crystallized from acetic acid to yield 3.2 g (40-45%) colourless needles.

This reaction failed with β-resorcylaldehyde.

Preparation of 2H(1)benzopyran-2-one-4-S-mercaptopropionic Acid.- This compound was prepared by reacting 3-bromocoumarin (4.5 g, 0.02 mole) and 3-mercaptopropionic acid (1.9 ml, 0.02 mole) according to the procedure described earlier. The product obtained was crystallized from ethyl acetate to yield 3.8 g (84%) of colourless needles, mp. 187-188°.

Anal. Calcd. for $C_{12}H_{10}O_4S$: C, 57.6; H, 4.0.

Found: C, 57.7; H, 4.3.

^{1}H-NMR (DMSO-d_6): δ 2.7 (t, 2H, CH_2 next to sulphur), 3.3 (t, 2H, CH_2 adjacent to carboxy), 6.3 (s, 1H, C_3 proton of coumarin ring), 7.3-7.9 (m, 4H, aromatic).

IR (KBr): 3100 (OH of COOH), 1730 (C=O of lactone), 1650 (C=O of COOH), 1600, 1550, 1480 cm^{-1}.

General Procedure for 3-(4-coumarylthiomethylene)-2H(1)-benzopyran-2-ones by Perkin-Oglialoro Reaction.- These compounds were prepared by reacting an o-hydroxybenzaldehyde (0.01 mole) with sodium 2H(1)benzopyrano-2-one-4-S-mercaptopropionate (0.02 mole) according to the procedure described earlier. The product obtained was crystallized from acetic acid to yield 2.0 g (40%) of colourless prisms.

A typical compound (Va, Table II) has the following spectral data:

m/e (70 eV): M^+ 336, 191, 171, 131, 117.

UV (dioxane) nm log ε: 235 (3.970), 295 (4.296).

IR (KBr): 1730 (C=O of lactones), 1600, 1540 cm^{-1}.

General Procedure for 3-(4'-coumarylsulphonylmethylene)-2H(1)-benzopyran-2-ones.- 3-(4'-Coumarylthiomethylene-2H(1)benzopyran-2-one (500 mg) was taken in glacial acetic acid (10 ml) and hydrogen peroxide (6 ml, 30%) was added. The reaction mixture was kept at room temperature for five days. The crystalline solid which separated was filtered and crystallized from alcohol to yield 250 mg (50%) of colourless needles. A typical sulphone (VIa, Table III) has the following spectral data: m/e (70 eV): M^+ 368, 353, 336, 320, 308, 209, 159.

IR (KBr): 1740 (broad, C=O of lactone), 1560, 1140, 1340 (SO_2) cm^{-1}.

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