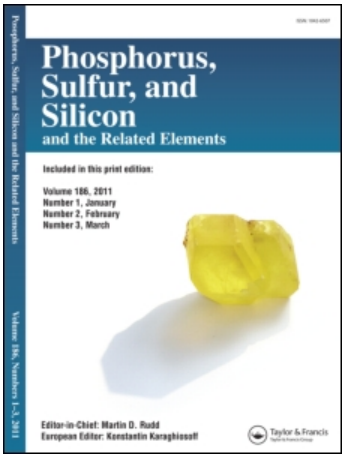

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SYNTHESIS OF N-(4-2H-1-BENZOPYRAN-2-ONE-2-THIAZOLYL)PHTHALIMIDES

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SYNTHESIS OF N-(4-2H-1-BENZOPYRAN-2-ONE-2-THIAZOLYL)PHTHALIMIDES

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3-(ω-Bromoacetyl)coumarins **I**, on reaction with potassium thiocyanate in absolute alcohol, gave 3-thiocyanato acetyl coumarins **II**. Treatment of **II** with dry HCl gas in chloroform afforded 3-(2-chlorothiazol-4-yl)-2H-1-benzopyran-2-ones **III**. Condensation of **III** with phthalimides resulted in the formation of N-(4-2H-1-benzopyran-2-one-2-thiazolyl)phthalimides **IV**, respectively.

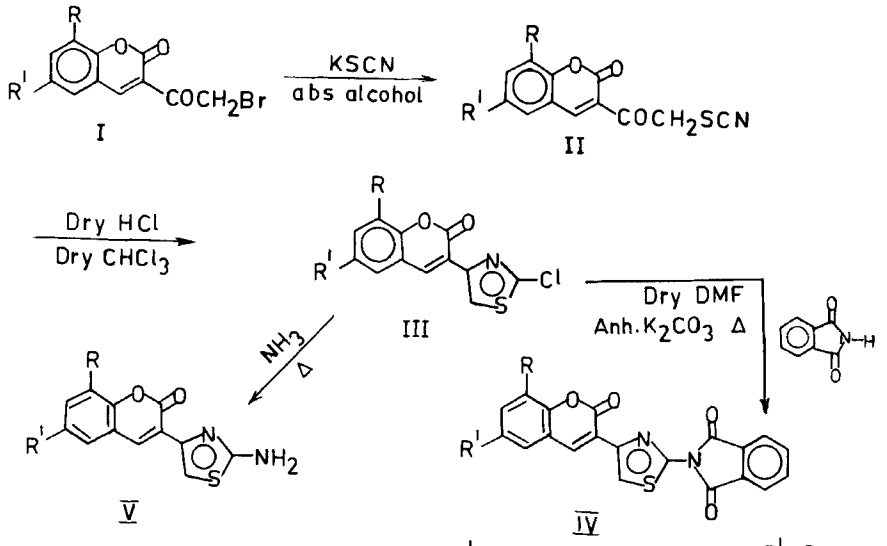
Key words: 3-(ω-Bromoacetyl)coumarin, thiazole and thiazolyl coumarins.

INTRODUCTION

Thiazole derivatives exhibit a wide spectrum of biological activities.[1–4] Coumarins are also found to have diverse biological activities.[5,6] We envisaged that incorporation of these heterosystems into a coumarin nucleus might impart enhanced biological activity to the resulting compounds.

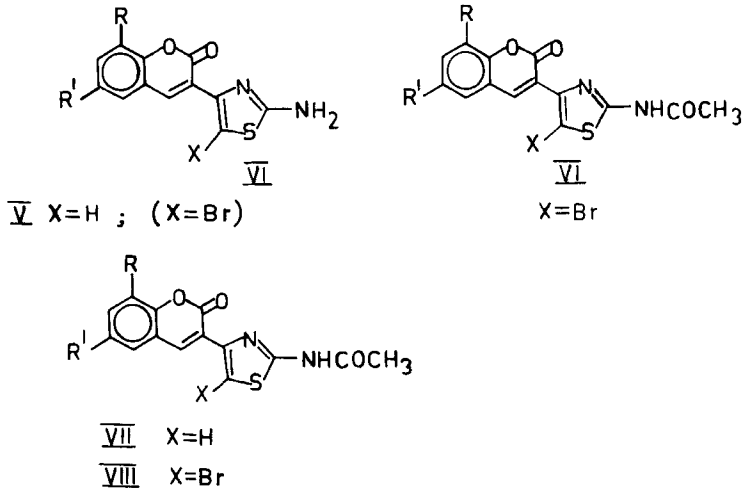
RESULTS AND DISCUSSION

In continuation of our earlier work on heterocyclic systems from coumarins,[7–11] we now report the preparation of N-(4-2H-1-benzopyran-2-one-2-thiazolyl)phthalimides in a three step process from 3-(ω-bromoacetyl)coumarin in good yields. Because of the considerable pharmaceutical interest in compounds containing a coumarin and thiazole ring system, we investigated the synthesis of the title compounds and their derivatives. Earlier, 2-chloro-4-(3-coumarinyl)thiazole was prepared by Koelsch.[12] Preparation of the compound by following this method seems cumbersome, due to low yields and long reaction times. Similarly, a modified procedure was adopted to prepare 2-aminothiazole reported by Koelsch. This communication describes an efficient method for the preparation of compounds **III** and **IV**. This modified synthesis of thiazoles made use of reaction between the 3-(ω-bromoacetyl)-coumarin **II** with potassium thiocyanate in absolute ethanol to yield 3-thiocyanatoacetyl coumarin **II** (70–80%) (Scheme I). Treatment of **II** with dry HCl gas in $HCCl_3$ afforded 3-(2-chlorothiazol-4-yl)-2H-1-benzopyran-2-ones **III**. Reaction of 3-(2-chlorothiazolyl)-2H-1-benzopyran-2-ones with ammonia gave corresponding 3-(2-aminothiazol-4-yl)-2H-1-benzopyran-2-ones **V**. Condensation of **III** or **V** with phthalimide and phthalic anhydride in the presence of dry DMF/K_2CO_3 or dry DMF afforded the corresponding N-(4-2H-1-benzopyran-2-one-2-thiazolyl)phthalimides **IV**, respectively.



I II III IV V

SCHEME I



VI VI

VII X=H

VIII X=Br

SCHEME II

TABLE I

Yields, m.p.s. and elementary analyses

Compd	R	R'	X	Yield (%)	m.p. (°C)	Elemental Analyses Calcd (Found)			
						C	H	N	S
IIa	H	H	-	70	243	58.78 (58.74)	2.86 (2.84)	5.70 (5.68)	13.06 (13.02)
IIb	OCH_3	H	-	68	110	56.73 (56.70)	3.27 (3.26)	5.09 (5.00)	11.64 (11.62)
IIc	Br	H	-	70	141	44.44 (44.41)	1.85 (1.83)	4.32 (4.31)	4.88 (4.82)
IId	Br	Br	-	64	210	35.73 (35.72)	1.24 (1.23)	3.47 (3.43)	7.94 (7.92)
IIe	H	Cl	-	62	135	51.52 (51.48)	2.15 (2.12)	5.01 (5.00)	11.45 (11.40)
IIf	Cl	Cl	-	60	90	45.86 (45.84)	1.59 (1.58)	4.46 (4.45)	10.19 (10.16)
IIIa	H	H	-	68	160	54.65 (54.61)	2.28 (2.25)	5.31 (5.29)	12.14 (12.12)
IIIb	OCH_3	H	-	64	175	53.15 (53.11)	2.73 (2.71)	4.17 (4.16)	10.90 (10.89)
IIIc	Br	H	-	72	135	42.04 (42.00)	1.46 (1.43)	4.09 (4.00)	9.34 (9.31)
IIId	Br	Br	-	70	230	34.16 (34.12)	0.95 (0.91)	3.32 (3.30)	7.59 (7.56)
IIIe	H	Cl	-	62	140	48.32 (48.30)	1.68 (1.67)	4.70 (4.70)	10.74 (10.71)
IIIf	Cl	Cl	-	68	110	43.31 (43.30)	1.20 (1.20)	4.21 (4.20)	9.62 (9.61)

TABLE I (*Continued*)

Compd	R	R'	X	Yield (%)	m.p. (°C)	Elemental Analyses (Calcd) (Found) C	H	N	S
IVa	H	H	-	80	201	64.17 (64.00)	2.67 (2.66)	7.49 (7.46)	8.56 (8.55)
IVb	OCH_3	H	-	78	215	62.38 (62.34)	2.97 (2.96)	6.93 (6.91)	7.92 (7.91)
IVc	Br	H	-	79	120	52.98 (52.96)	1.99 (1.98)	6.18 (6.15)	7.06 (7.02)
IVd	Br	Br	-	80	143	45.11 (45.10)	1.50 (1.50)	5.26 (5.23)	6.02 (6.00)
IVe	H	Cl	-	75	181	58.75 (58.71)	2.20 (2.20)	6.85 (6.81)	7.83 (7.82)
IVf	Cl	Cl	-	80	240	54.18 (54.10)	1.81 (1.80)	6.32 (6.30)	7.22 (7.21)
Va	H	H	-	80	210	59.02 (59.00)	3.28 (3.23)	11.48 (11.44)	13.11 (13.10)
Vb	OCH_3	H	-	76	235	56.93 (56.90)	3.65 (3.62)	10.22 (10.00)	11.68 (11.63)
Vc	Br	H	-	74	204	44.59 (44.56)	2.17 (2.16)	8.67 (8.66)	9.91 (9.89)
Vd	Br	Br	-	70	220	35.82 (35.81)	1.49 (1.46)	6.97 (6.96)	7.96 (7.93)
Ve	H	Cl	-	77	179	51.70 (51.60)	2.51 (2.50)	10.05 (10.00)	11.49 (11.45)
Vf	Cl	Cl	-	78	192	46.00 (46.00)	1.92 (1.91)	8.95 (8.85)	10.22 (10.20)
VIa	H	H	Br	68	170	44.58 (44.55)	2.17 (2.16)	8.67 (8.66)	9.91 (9.91)
VIb	OCH_3	H	Br	67	197	44.19 (44.00)	2.55 (2.52)	7.93 (7.91)	9.07 (9.00)
VIc	Br	H	Br	65	260	35.82 (35.80)	1.49 (1.46)	6.97 (6.96)	7.96 (7.92)

VId	Br	Br	Br	66	251	29.94 (29.92)	1.04 (1.00)	5.82 (5.80)	6.65 (6.64)
VIe	H	Cl	Br	70	265	40.28 (40.23)	1.68 (1.64)	7.83 (7.82)	8.95 (8.94)
VIf	Cl	Cl	Br	60	193	36.73 (36.70)	1.28 (1.26)	7.14 (7.13)	8.16 (8.13)
VIIa	H	H	H	70	205	58.74 (58.72)	3.50 (3.47)	9.79 (9.76)	11.19 (11.16)
VIIb	OCH_3	H	H	68	185	56.96 (56.95)	3.79 (3.76)	8.86 (8.83)	10.12 (10.11)
VIIc	Br	H	H	62	196	46.03 (46.00)	2.47 (2.46)	7.67 (7.66)	8.77 (8.76)
VIId	Br	Br	H	64	160	37.84 (37.82)	18.00 (18.00)	6.31 (6.30)	7.21 (7.21)
VIIe	H	Cl	H	62	149	52.42 (52.40)	2.81 (2.80)	8.74 (8.72)	9.98 (9.96)
VIIf	Cl	Cl	H	65	193	47.32 (47.30)	2.25 (2.24)	7.89 (7.86)	9.01 (9.00)
VIIIa	H	H	Br	70	236	46.03 (46.00)	2.47 (2.46)	7.67 (7.66)	8.77 (8.76)
VIIIb	OCH_3	H	Br	72	215	45.57 (45.55)	2.79 (2.76)	7.09 (7.00)	8.10 (8.00)
VIIIc	Br	H	Br	70	257	37.84 (37.81)	18.00 (18.00)	6.31 (6.28)	7.21 (7.18)
VIIId	Br	Br	Br	68	247	32.12 (32.00)	1.34 (1.31)	5.35 (5.32)	6.12 (6.10)
VIIIe	H	Cl	Br	64	240	42.05 (42.00)	2.00 (2.00)	7.01 (7.00)	8.01 (8.00)
VIIIf	Cl	Cl	Br	62	228	38.71 (38.69)	1.61 (1.62)	6.45 (6.42)	7.37 (7.36)

II Crystallised from chloroform; III Crystallised from methanol; IV Crystallised from methanol; V Crystallised from methanol; VI Crystallised from acetic acid; VII Crystallised from methanol; VIII Crystallised from methanol.

TABLE II

Spectral data of compounds II, III,[a] IV, V, VI, VII and VIII

Compd	R	R′	X	^{1}H-NMR (δ ppm)	IR (cm^{-1}) —CO—	—C(=O)—NH—	—C=O (Lactone)	C-Br	—NH_2	—SCN
IIa	H	H	—	3.80 (s, 2 H, —$COCH_2SCN$), 6.0–7.0 (m, 4 H, aromatic), 7.7 (s, 1 H, coumarin C_4-H)	1680	—	1720	—	—	2160
IIIa	H	H	—	7.1–7.5 (m, 5 H, aromatic and thiazole 'H'), 7.9 (s, and C_4-H of coumarin)	—	—	1720	—	—	—
IVa	H	H	—	6.8–7.9 (m, 9 H aromatic including 1 H of thiazole) 8.5 (s, 1 H, C_4-H of coumarin)	—	1680	1720	—	—	—
Va	H	H	—	4.95 (br, s, 2 H exchangeable NH_2)	—	—	1705	—	3380	—
				7.26–7.59 (m, 4 H, Ar-H) 7.79 (s, 1 H, C_5-H of thiazole) 8.52 (s, 1 H, C_4-H of coumarin)	—	—	—	—	3160	—
VIa	H	H	Br	—	—	—	1700	760	3370	—
VIc	Br	H	Br	6.7–8.3 (m, 5 H, aromatic and 2 H of NH_2) 8.8 (s, 1 H, C_4-H of coumarin)	—	—	1710	760	3360	—
VIIa	H	H	—	—	—	1680	1710	—	—	—
VIIIa	H	H	Br	—	—	1680	1700	770	—	—

[a]Mass spectrum of **IIIa** (hydrochloride) 299(34.9), 398(7.2), 297(64.1), 270(7.9), 268(11.5), 264(36), 262(100), 208(10.1), 173(47.1) and 145(26.3).

—NH— Protons disappeared on shaking with D_2O.

The structure of **V** was supported by bromination and acetylation to give **VI**, **VII** and **VIII**, respectively (Scheme II). Adopting these procedures, different compounds have been prepared. The structures of all the new compounds were confirmed by analytical and spectral data.

EXPERIMENTAL

All melting points were determined in open capillary tubes using a sulphuric acid bath and are uncorrected. Purity of the compounds was routinely checked by T.L.C. on silica gel plates. IR and PMR spectra were recorded on Perkin-Elmer and Varian 60 MHz spectrometers. The mass spectra were recorded on a Hitachi RUM-6E spectrometer operating at 70 eV.

3-Thiocyanatoacetyl-6,8-disubstituted Coumarin (**II**)—*General Procedure*: To a solution of **I** (0.01 mol) in abs. ethanol was added a saturated ethanolic solution of potassium thiocyanate (0.01 mol) at 60°C, and the reaction mixture was warmed for 10 minutes, kept at room temperature for 2–3 hrs, and these poured into ice-cold water. The solid thus obtained was collected and crystallized from a suitable solvent to give **II** (Table I).

2-Chloro-4-(3-Coumarinyl)thiazole (**III**)—*General Procedure*: To a suspension of **II** (0.01 mol) in dry ether (200 ml) was passed dry HCl gas for 1.5 hr. The solid mass obtained was filtered, washed with liquid ammonia, and crystallized from suitable solvents to give **III** (Table I) after evaporation.

N-(4-2H-1-benzopyran-2-one-2--thiazolyl)phthalimide (**IV**): To a solution of (0.01 mol) in 20 ml of DMF was added 4 ml (excess) of liq. NH_3. The reaction mixture was refluxed for 30 minutes, cooled, and poured over crushed ice. The solid separated was filtered and crystallized from a suitable solvent (Table I).

Bromination of **V** *to give* **VI**: To a solution of 0.01 mol of 2-amino-4-(3-coumarinyl)thiazole in 20 ml acetic acid was added 0.01 mol of bromine in 20 ml of acetic acid with intermittent shaking and warming to decompose an addition product. The mixture was heated for fifteen minutes on a water bath to expel most of the hydrogen bromide. The mixture was cooled and filtered. The solid was washed with ether giving nearly pure product.

Acetylation of **VII**: Compound **VI** (0.01 mol) was dissolved in pyridine (5 ml) heated to 60°C, and acetic anhydride (15 ml) was added. The solution was heated to 70°C for 2 hours with constant stirring. The resulting suspension was cooled to zero°C and then poured over crushed ice. The solid product was collected by filteration and crystallised from a suitable solvent.

Bromination of N-acetyl amino-4-(3-coumarinyl)thiazole (**VIII**): Compound **VII** (0.01 mol) was dissolved in 40 ml of glacial acetic acid, and the solution was heated to 50°C and stirred while 0.01 mole of bromine in a small amount of glacial acetic acid was added. After completing the addition, the mixture was stirred for 10 minutes at 65°C and cooled. The solid product was collected and recrystallised from acetic acid.

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