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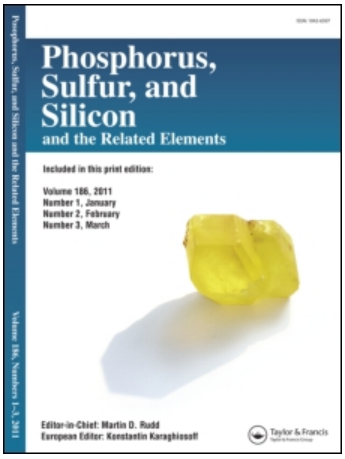

Phosphorus, Sulfur, and Silicon and the Related Elements
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SYNTHESIS OF SOME NEW SPIRO[INDOLINE-3,2'-(THIOCHROMAN)]-2,4'-DIONE DERIVATIVES

Marzoog S. Al-thebeiti[a]
[a] Department of Chemistry, Faculty of Applied Sciences, Umm Al-Qura University, Makkah Almukarramah, Saudi Arabia

To cite this Article Al-thebeiti, Marzoog S.(1998) 'SYNTHESIS OF SOME NEW SPIRO[INDOLINE-3,2'-(THIOCHROMAN)]-2,4'-DIONE DERIVATIVES', Phosphorus, Sulfur, and Silicon and the Related Elements, 141: 1, 89 — 95
To link to this Article: DOI: 10.1080/10426509808033724
URL: http://dx.doi.org/10.1080/10426509808033724

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Phosphorus, Sulfur and Silicon, 1998, Vol. 141, pp. 89-95
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Printed in Malaysia

SYNTHESIS OF SOME NEW SPIRO[INDOLINE-3,2′-(THIOCHROMAN)]-2,4′-DIONE DERIVATIVES

MARZOOG S. AL-THEBEITI*

Department of Chemistry, Faculty of Applied Sciences, Umm Al-Qura University, Makkah Almukarramah, P.O. Box 6876, Saudi Arabia

(Received 14 April, 1998; Revised 8 June, 1998)

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Indole-2,3-diones (**1a, b**) was treated with malonic acid in a mixture of ethanol/pyridine to afford 3-(2-oxoindolinylidene)acetic acid derivatives (**2a, b**) which then reacted with hydrobromic acid to yield 3-bromo-3-(2-oxoindole)acetic acid derivatives (**3a, b**). Compounds **3a, b** were reacted with arylthiols to yield 3-arylmercapto-3-(2-oxoindole)acetic acid derivatives (**4a-f**). Cyclization of compounds **4a-f** with sulfuric acid afforded spiro[indoline-3,2′-(thiochroman)]-2,4′-dione derivatives (**5a-f**).

Keywords: Spiroheterocycles; spirothiochroman-4-ones; cyclization reactions

INTRODUCTION

Several authors have recently reported the syntheses and applications of spirocyclic derivatives.[1–25] In continuation to our interest in this area,[26–32] this work presents a facile route for the synthesis of some new spiro[indoline-3,2′-thiochroman)]-2,4′-dione derivatives.

RESULTS AND DISCUSSIONS

Our precursors indole-2,3-dione **1a** and 1-methylindole-2,3-dione **1b** reacted with malonic acid in a mixture of ethanol/pyridine to yield (Z)

* To whom all correspondence should be addressed.

3-(2-oxoindolinylidene)acetic acid derivatives (**2a, b**).[30] Compounds **2a, b** reacted with hydrobromic acid to afford 3-bromo-3-(2-oxoindole)acetic acid derivatives **3a, b**. Compounds **3a, b** were treated with aromatic thiols in alcoholic sodium hydroxide solution to yield 3-arylmercapto-3-(2-oxoindole)acetic acid derivatives **4a-f** (Scheme I). The structures of compounds **4a-f** were confirmed on the basis of their elemental analyses and spectroscopic data (Table I). The IR spectrum of **4a** showed characteristic broad absorption bands at 2600–3400 cm^{-1} corresponding to the stretching vibration of the hydroxyl group of the carboxyl group, 3200 cm^{-1} for the stretching of the NH group of indole ring, 3000 cm^{-1} aromatic carbon-hydrogen stretching, 2850 cm^{-1} for aliphatic carbon-hydrogen stretching, 1705 cm^{-1} and 1725 cm^{-1} for the carbonyl groups of carboxylic group and indole ring and 740 cm^{-1} for C-S bond. The ^{1}H-NMR spectrum of **4a** (DMSO-d_6) showed the following signals: δ 4.60–4.66 (broad s, the methylene protons of the acetic acid residue), 5.10 (1 H, s, the NH proton of indole ring), 7.70–8.30 (9 H, m, the aromatic protons) and 10.90 (1 H, s, the carboxylic group proton). Reaction of compounds **4a-f** with sulfuric acid yielded the target products, spiro[indoline-3,2′-(thiochroman)]-2,4′-dione derivatives **5a-f** (Scheme I). The structure assignments of compounds **5a-f** were based on their elemental analyses and spectroscopic data (Table I). The IR spectrum of **5a** showed characteristic absorption bands at 3180 cm^{-1} corresponding to the stretching vibrations of NH group of indoline ring, 3060 cm^{-1} for the aromatic carbon-hydrogen stretching, 2950 cm^{-1} for the aliphatic carbon-hydrogen stretching and 1705, 1720 cm^{-1} for the carbonyl groups of indoline and thiochroman rings. The ^{1}H-NMR spectrum of **5a** (DMSO-d_6) showed the following signals : δ 4.40–4.50 (broad s, the methylene protons at C_3 of thiochroman ring). Although these two methylene protons are diastereotopic and should have split each other, under a given instrumental resolution these protons absorb at the same position to give a broad signal[33], as observed in the spectra of compounds **4a-f** and **5a-f**, 5.15 (1 H, s, the NH proton of indoline ring), 7.70–8.40 (8 H, m, the aromatic protons of thiochroman and indoline rings).

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TABLE I Physical data of 3-arylmercapto–3-(2-oxoindole)acetic acid derivatives (**4a-f**) and spiro[indoline-3,2′-(thiochroman)]-2,4′-dione derivatives (**5a-f**)

Compd. No.	*Yield (%)*	*MP (°C)*	*Molecular Formula (solvent of crystallization)*	*Anal. Calcd/(Found) %*					*IR (KBr), cm^{-1}*	*^1H NMR (DMSO-d_6), δ (TMS)ppm*
				C	*H*	*N*	*S*	*Cl*		
4a	80	325–327	$C_{16}H_{13}NO_3S$ (acetic acid/water) 4 : 1	64.20 (64.00)	4.38 (4.20)	4.68 (4.50)	10.71 (10.65)		2600–3400 (OH), 3200 (NH), 3000(CH arom), 2850(CH aliph), 1725, 1705 (C=O), 740 (C-S).	4.60–4.66(2 H, broad s), 5.10(1 H, s), 7.70–8.30 (9 H, m), 10.90(1 H, s).
4b	85	330–332	$C_{17}H_{15}NO_3S$ (acetic acid/water) 3 : 2	65.16 (65,10)	4.82 (4.75)	4.47 (4.40)	10.23 (10.20)		2600–3400 (OH), 3180 (NH), 3000 (CH arom), 2950 (CH aliph), 1720, 1705 (C=O), 740 (C-S).	2.30 (3 H, s), 4.60–4.66 (2 H, broad s), 5.10(1 H, s), 7.70–8.30 (8 H, m), 10.90 (1 H, s).
4c	80	> 350	$C_{16}H_{12}NO_3SCl$ (acetic acid/water) 4 : 1	57.57 (57.50)	3.62 (3.57)	4.20 (4.18)	9.60 (9.50)	10.62 (10.50)	2600–3400(OH), 3200 (NH), 3000 (CH arom), 2940 (CH aliph), 1720, 1695 (C=O), 740 (C-S).	4.60–4.66(2 H, broad s), 5.10(1 H, s), 7.70–8.30 (8 H, m), 10.90(1 H, s).
4d	85	110–112	$C_{17}H_{15}NO_3S$ (acetic acid)	65.16 (65.10)	4.82 (4.75)	4.47 (4.45)	10.23 (10.20)		2600–3400 (OH), 3060 (CH arom), 2940 (CH aliph), 1720, 1690 (C=O), 740 (C-S).	3.25 (3 H, s), 4.70–4.75 (2 H, broad s), 7.70–8.40 (9 H, m), 10.90(1 H, s).
4e	87	140–142	$C_{18}H_{16}NO_3S$ (acetic acid)	66.24 (66.20)	4.94 (4.87)	4.29 (4.15)	9.82 (9.79)		2600–3400 (OH), 3060 (CH arom), 2950 (CH aliph), 1720, 1700 (C=O), 740 (C-S).	2.30 (3 H, s), 3.30 (3 H, s), 4.70–4.75 (2 H, broad s), 7.70–8.30 (8 H, m), 10.90(1 H, s).
4f	82	130–132	$C_{17}H_{14}NO_3SCl$ (acetic acid)	58.71 (58.65)	4.06 (4.00)	4.03 (4.00)	9.22 (9.15)	10.19 (10.10)	2600–3400 (OH), 3060 (CH arom), 2940 (CH aliph), 1725, 1700 (C=O), 740 (C-S).	3.25 (3 H, s), 4.60–4.66 (2 H, broad s), 7.70–8.40 (8 H, m), 10.90(1 H, s).

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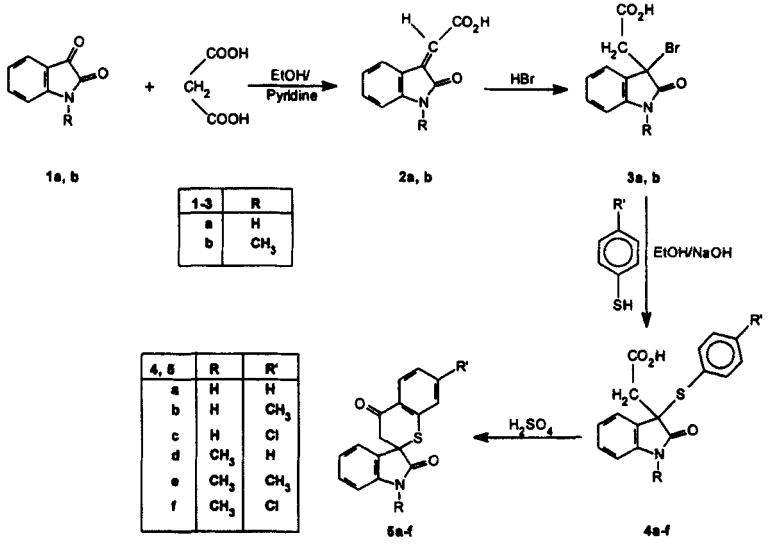
Compd. No.	*Yield (%)*	*MP (°C)*	*Molecular Formula (solvent of crystallization)*	*Anal. Calcd/(Found) %*					*IR (KBr), cm^{-1}*	*^1H NMR (DMSO-d_6), δ (TMS)ppm*
				C	*H*	*N*	*S*	*Cl*		
5a	57	128–130	$C_{16}H_{11}NO_2S$ (dioxane)	68.31 (68.25)	3.94 (3.85)	4.98 (4.90)	11.40 (11.28)		3180(NH), 3060(CH arom), 2950 (CH aliph), 1720, 1705 (C=O), 730 (C-S).	4.40–4.66(2 H, broad s),5.15(1 H, s), 7.70–8.40 (8 H, m).
5b	59	160–162	$C_{17}H_{13}NO_2S$ (dioxane)	69.13 (69.10)	4.44 (4.37)	4.74 (4.70)	10.83 (10.80)		3180 (NH), 3050 (CH arom), 2950 (CH aliph), 1720, 1705 (C=O), 740 (C-S).	2.30(3 H, s), 4.40–4.66 (2 H, broad s), 5.20(1 H, s), 7.70–8.30(7 H, m).
5c	55	125–127	$C_{16}H_{10}NO_2SCl$ (dioxane)	60.86 (60.80)	3.19 (3.15)	4.44 (4.40)	10.15 (10.10)	11.23 (11.20)	3180 (NH), 3060 (CH arom), 2950 (CH aliph), 1720, 1700 (C=O), 740 (C-S).	4.40–4.66(2 H, broad s), 5.20 (1 H, s), 7.70–8.40 (7 H, m).
5d	52	172–174	$C_{17}H_{13}NO_2S$ (dioxane)	69.13 (69.10)	4.44 (4.35)	4.74 (4.70)	10.83 (10.80)		3060 (CH arom), 2950 (CH aliph), 1720, 1705 (C=O), 740 (C-S).	3.25 (3 H, s), 4.45–4.66(2 H, broad s), 7.75–8.40 (8 H, m).
5e	55	220–222	$C_{18}H_{15}NO_2S$ (dioxane)	69.88 (69.85)	4.89 (4.85)	4.53 (4.45)	10.34 (10.30)		3060 (CH arom), 2950 (CH aliph), 1720, 1705 (C=O), 740 (C-S).	2.30 (3 H, s), 3.25 (3 H, s), 4.40–4.66 (2 H, broad s) 7.80–8.40 (7 H, m).
5f	50	> 300	$C_{17}H_{12}NO_2SCl$ (dioxane)	61.91 (61.85)	3.67 (3.60)	4.25 (4.20)	9.72 (9.70)	10.75 (10.70)	3060 (CH arom), 2950 (CH aliph), 1720, 1705 (C=O), 730 (C-S).	3.20 (3 H, s), 4.40–4.66 (2 H, broad s), 7.70–8.30 (7 H, m).



SCHEME 1

EXPERIMENTAL

The time required for completion of the reaction was monitored by thin layer chromatography (TLC). Melting points are uncorrected, ^{1}H-NMR spectra were measured on EM-360 90-MHz spectrophotometer. IR spectra were recorded on a Pye-Unicam Sp 200-G spectrophotometer. Elemental analyses were determined on a Perkin-Elmer 240 C microanalyser.

Preparation of 3-(2-Oxoindolinylidene)acetic acid derivatives (2a, b)

These Compounds were prepared according to our reported method.[29]

Preparation of 3-Bromo–3-(2-oxoindole)acetic acid derivatives (3a, b)

These compounds were prepared according to our reported method.[30]

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Synthesis of 3-Arylmercapto-3-(2-oxoindole)acetic acid derivatives (4a-f). General Procedure

Each aromatic thiol (0.01 mole) was dissolved in alcoholic sodium hydroxide solution (0.02 mole in 50 ml ethanol) and reacted with the calculated amount of **3a, b**. The reaction mixture was refluxed for 6 hrs, then cooled to room temperature acidified with dilute HCl whereby the target product was precipitated. It was filtered off and crystallized from the proper solvent (Table I).

Synthesis of Spiro[indoline-3,2′-(thiochroman)]–2,4′-dione derivatives (5a-f). General Procedure

Each compound **4a-f** (0.001 mole) was treated with 5 ml conc. sulfuric acid, then the reaction mixture was heated on water bath for 6 hrs. The reaction mixture was cooled to room temperature, poured into 50 ml of sodium carbonate solution (10%) whereby the target spiro derivatives **5a-f** were precipitated. The products were filtered off, washed with water and crystallized from the proper solvent (Table I).

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