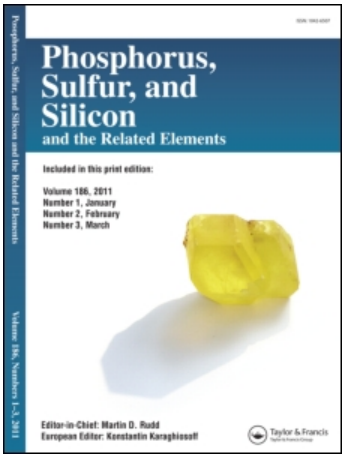

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SYNTHESIS OF THE BIOLOGICALLY ACTIVE 5-(INDOLYL-3-METHYLENE) THIAZOLIDINE-2,4-DIONE DERIVATIVES

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The cycloaddition reaction of the biologically active 5-(indolyl-3-methylene) derivatives of thiazolidinone-4-thiones **2a-c** to acrylonitrile, ethyl acrylate, *N*-phenylmaleimides and dimethyl fumarate has been evaluated.

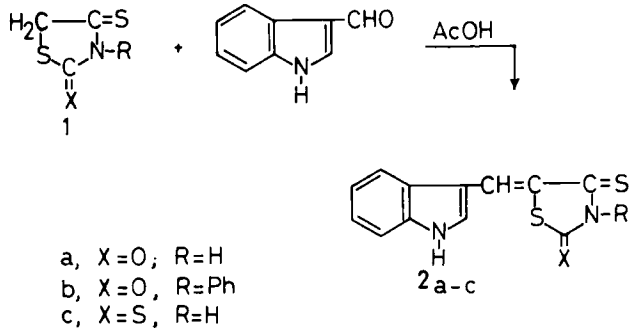
Key words: Cycloaddition; 5-(Indolyl-3-methylene)-2-thiazolidinone-4-thiones

INTRODUCTION

In recent years, an increasingly large number of pharmacologically active agents have been investigated which contain an indole ring system. Besides, indole subunit is present in many classes of alkaloids,[1] some of them exhibiting important biological activities. In continuation of our program aiming at the synthesis of biologically active compounds of thiazolidinone series,[2-5] we wish to report in this paper the preparation of new indolyl-3-methylene thiazolidine-2,4-dione derivatives and the cycloaddition reaction with some electron poor-dienophiles.

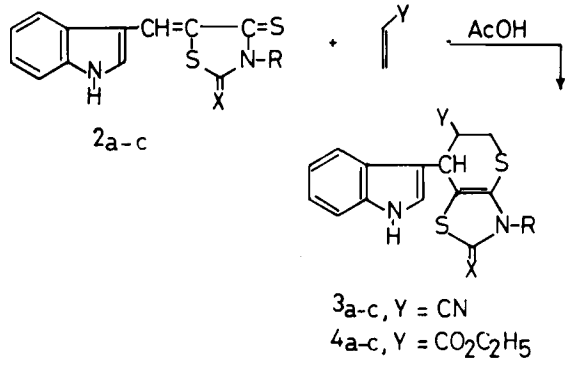
RESULTS AND DISCUSSION

Thus, the reaction of indole-3-carboxaldehyde with 2-thiazolidinone-4-thiones, **Ia,b** and thiazolidine-2,4-dithione **1c** in glacial acetic acid and in the presence of anhydrous sodium acetate afforded the 5-(indolyl-3-methylene) derivatives **2a-c** in good yields. The structure of **2** was supported by elemental and spectral data.



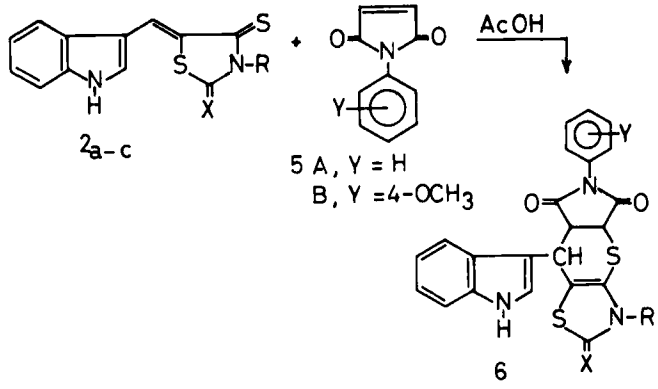
Scheme 1

We initially tried an intramolecular Diels-Alder reaction, of the C=C bond of the indole moiety and the α,β-unsaturated thiocarbonyl system, but **2** was recovered unchanged as indicated by TLC. When **2a-c** were refluxed with acrylonitrile and or ethyl acrylate in glacial acetic acid, the colourless 6-cyano- and or 6-carbethoxy-7-(3-indolyl)-tetrahydrothiopyrano-7H[2,3-*d*]-thiazoles **3a-c** and **4a-c** were obtained, respectively. The assigned structure for **3** and **4** is established from elemental and spectral data. Furthermore, this type of cycloaddition has already been described for the 5-arylidene derivatives of **1a-c** by Kassab et al.[5]



Scheme 2

The cycloaddition reaction of 5-(indolyl-3-methylene) derivatives of **1a-c** in glacial acetic acid or benzene with *N*-phenylmaleimides **5A,B** gave, in each case, one product as evidenced by TLC analysis in almost quantitative yield. The assigned structure of the cycloadducts **6** isolated was supported by analytical and spectral data. The ^{1}H NMR spectra of the cycloadducts **6** were characterised, in each case, by the presence of two doublets and one *dd* corresponding to H5, H7, H6 at δ 4.8, 4.1 and 3.8, respectively.



a, X=O, R=Y=H
b, X=O, R=H, Y=OCH3-p
c, X=O, R=Ph, Y=H
d, X=O, R=Ph, Y=OCH3-p
e, X=S, R=Y=H
f, X=S, R=Ph, Y=OCH3-p

Scheme 3

TABLE 1

Characterization data of compounds **2-4, 6** and **7**

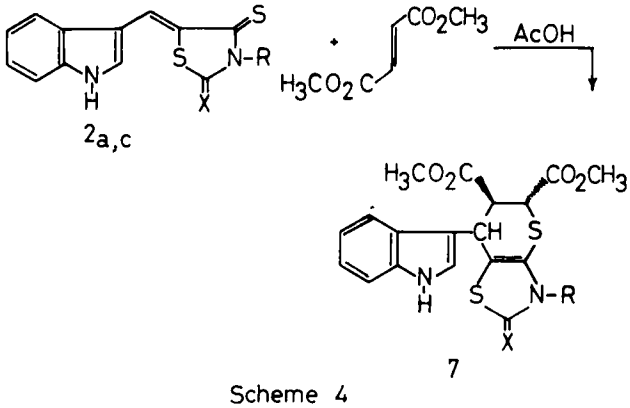
Compd	M.P. C	Yield %	Mol. form.	% Analysis cald./found C	H	N
			C H N S O	55.4	3.10	10.7
2a	300	80	12 8 2 2	55.0	3.00	10.3
			C H N S O	64.3	3.60	8.3
2b	255	85	18 12 2 2	63.9	3.45	8.1
			C H N S	52.2	2.92	10.1
2c	275	80	12 8 2 3	51.9	2.75	10.0
			C H N S O	57.5	3.54	13.4
3a	215	70	15 11 3 2	57.2	3.35	13.1
			C H N S O	65.4	3.92	18.2
3b	250	75	21 15 3 2	65.2	3.80	18.0
			C H N S	54.7	3.37	12.7
3c	235	77	15 11 3 3	54.4	3.21	12.5
			C H N S O	56.7	4.47	7.8
4a	145	65	17 16 2 2 3	56.4	4.35	7.7
			C H N S O	63.3	4.62	6.4
4b	190	60	23 20 2 2 3	63.2	4.51	6.2
			C H N S O	54.3	4.29	7.4
4c	185	70	17 16 2 3 2	54.1	4.15	7.2
			C H N S O	60.9	3.49	9.7
6a	208	75	22 15 3 2 3	60.6	3.27	9.6
			C H N S O	59.6	3.70	9.1
6b	240	70	23 17 3 2 4	59.4	3.70	9.0
			C H N S O	66.0	3.76	8.2
6c	170	65	28 19 3 2 3	65.8	3.56	8.1
			C H N S O	64.5	3.92	7.8
6d	175	70	29 21 3 2 4	64.4	3.75	7.7
			C H N S O	58.8	3.36	9.3
6e	225	75	22 15 3 3 2	58.6	3.27	9.1
			C H N S O	57.6	3.57	8.7
6f	213	70	23 17 3 3 3	57.5	3.41	8.5
			C H N S O	53.5	3.99	6.9
7a	180	75	18 16 2 2 5	53.2	3.90	6.8
			C H N S O	51.4	3.84	6.7
7c	165	65	18 16 2 3 4	51.2	3.74	6.6

TABLE 2

IR and ^{1}H NMR data of compounds **2–4, 6** and **7**

Compd	IR (cm^{-1})	^{1}H NMR (δ ppm)
2a	3200 (NH), 3400 (indole NH) and 1680 (C=O)	—
2b	3400 (indole NH) and 1680 (C=O)	10.8 (*s*, 1H, NH), 7.4–6.8 (*m*, 10H), and 7.65 (*s*, 1H, –CH=)
2c	3225 (NH), 3420 (indole NH) and 1175 (C=S)	—
3a	3200 (NH), 3420 (indole NH), 2220 (C≡N) and 1680 (C=O)	11.1, 10.9 (*s*, 2H, 2NH), 7.2–6.8 (*m*, 5H), 4.75 (*d*, 1H, H-7), 2.7 (*d*, 1H, H-5), 3.52 (*d*, 1H, H-5) and 4.0–3.5 (*m*, 1H, H-6)
3b	3420 (indole NH), 2220 (C≡N) and 1690 (C=O)	—
3c	3200 (NH), 3400 (indole NH) and 2210 (C≡N)	11.1, 10.8 (*s*, 2H, 2NH), 7.4–6.8 (*m*, 5H), 4.7 (*d*, 1H, H-7), 2.75 (*d*, 1H, H-5), 3.5 (*d*, 1H, H-5) and 4.1–3.65 (*m*, 1H, H-6)
4a	3220 (NH), 3420 (indole NH), 1720, 1680 (ester and ring C=O)	—
4b	3400 (indole NH), 1720, 1690 (ester and ring C=O)	11.8 (*s*, 1H, NH), 7.2–6.8 (*m*, 10H), 2.8 (*d*, 1H, H-5), 3.55 (1H, H-5), 3.9–3.6 (*m*, 1H, H-6), 4.7 (*d*, 1H, H-7), 4.4 (*q*, 2H, CH2CH3) and 1.4 (*t*, 3H, CH2CH3)
4c	3200 (NH), 3400 (indole NH) and 1720 (ester C=O)	11.1, 10.9 (*s*, 2H, 2NH), 7.3–6.9, 5H), 2.8 (*d*, 1H, H-5), 3.55 (*d*, 1H, H-5), 3.9–3.6 (*m*, 1H, H-6), 4.7 (*d*, 1H, H-7), 4.4 (*q*, 2H, CH2CH3) and 1.4 (*t*, 3H, CH2CH3)
6a	3200 (NH), 3420 (indole NH), 1740, 1680 (amide and ring C=O)	11.1, 10.89 (*s*, 2H, 2NH), 7.4–6.82 (*m*, 10H), 4.8 (*d*, J = 8Hz), H-5), 4.1 (*d*, J = 5Hz, H-7) and 3.8 (*dd*, J = 8Hz, H-6)
6b	3200 (NH), 3420 (indole NH), 1740, 1680 (amide and ring C=O)	—
6c	3420 (indole NH), 1740, 1680 (amide and ring C=O)	—
6d	3420 (indole NH), 1740, 1680 (amide and ring C=O)	10.9 (*s*, 1H, NH), 7.44–6.8 (*m*, 14H) 4.8 (*d*, J = 8Hz, H-5), 4.1 (*d*, J = 5Hz, H-7) 3.85 (*dd*, J = 8Hz, H-6) and 3.7 (*s*, 3H, OCH3)
6e	3220 (NH), 3400 (indole NH), 1740 (amide C=O)	11.2, 10.8 (*s*, 2H, 2NH), 7.4–6.85 (*m*, 10H), 4.82 (*d*, 1H, H-5), 4.1 (*d*, 1H, H-7) and 3.8 (*dd*, 1H, H-6)
6f	3220 (NH), 3400 (indole NH), and 1740 (amide C=O)	—
7a	3220 (NH), 3420 (indole NH), 1740 and 1690 (ester and ring C=O)	11.1, 10.8 (*s*, 2H, 2NH), 7.3–6.8 (*m*, 5H), 4.7 (*d*, 1H, H-5), 3.55 (*dd*, 1H, H-6) and 4.3 (*d*, 1H, H-7)
7c	3200 (NH), 3420 (indole NH) and 1740 (ester C=O)	—

The reaction of **2** with dimethyl fumarate, when carried out in similar manner, gave the corresponding thiopyrano[2,3-*d*]thiazole derivatives **7**. ^{1}H NMR spectra of **7** exhibit in each case signals at δ 4.7 (*d*, *J* = 4Hz, 1H) 3.55 (*dd*, *J* = 4Hz, 1H) and 4.3 (*d*, *J* = 4Hz, 1H) assignable to H-5, H-6 and H-7, respectively. Thus, the cycloadducts **7** could be assigned the indicated trans-configuration.



Scheme 4

EXPERIMENTAL

The melting points are uncorrected. The infrared spectra (KBr) were recorded on a Perkin-Elmer 257 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian EM-390 90 MHz spectrometer in DMSO-d_6 as a solvent and TMS as an internal standard. Chemical shifts are expressed as δ ppm units. Elemental analyses were performed at the microanalytical unit of Cairo University.

Preparation of **5***-(indolyl-3-methylene)-thiazolidine-2,4-dione derivatives* **2a-c**. Equimolecular amounts (0.01 mole) of **1a-c** and indole-3-carboxyaldehyde in glacial acetic acid and in presence of anhydrous sodium acetate (0.01 mole) were stirred on a water bath for 1.5 h and left to cool, to afford the coloured **2a-c**. The crude products were crystallised from glacial acetic acid. The physical and spectral data of the products are listed in Tables 1 and 2.

General procedure for the reaction of **2a-c** *with acrylonitrile, ethyl acrylate, N-phenylmaleimides and dimethyl fumarate to give the cycloadducts* **3, 4, 6** *and* **7**. A solution of equimolecular amounts (0.01 mole) of each of **2a-c** and the appropriate dienophiles in glacial acetic acid (30 ml) was refluxed for 2 h and then left overnight. The white solid so formed was filtered off and crystallised from ethanol or glacial acetic acid. The cycloaddition products **3, 4, 6** and **7** and their physical constants are listed in Tables 1 and 2.

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