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Studies on the Synthesis of Some Substituted Flavonyl Thiazolidinedione Derivatives-I

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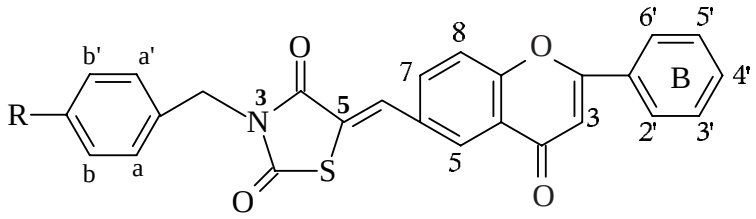
Synthesis and some physico-chemical properties of five flavonyl thiazolidinedione derivatives are described. These products were synthesized by Knoevenagel condensation from flavone-6-carboxaldehyde and 3-substituted 2,4-thiazolidinediones.

Introduction

Penicillin derivatives with important roles in antibacterial chemotherapy contain a thiazolidine ring system. Thiazolidinediones represent a class of chemical products with interesting pharmacological activities including antibacterial, antifungal[1–3] and antidiabetic[4–6]. The present paper reports the synthesis of some derivatives containing a flavone ring system, already known to have antibacterial[7] and antidiabetic[8] activity at the 5 position of thiazolidinedione ring (Figure 1).



R=H, CI, Br, F, NO_2

Figure 1.

Experimental

Melting points were determined with a Buchi SMP 20 capillary melting point apparatus and were uncorrected. The IR spectra were recorded on a Jasco FT/IR 420 spectrometer as potassium bromide discs. Instrumental analysis was performed by TUBITAK. ^{1}H NMR spectra were recorded with a Bruker GmbH DPX-400, 400 MHz instrument using TMS internal standard and DMSO-d_6. All chemical shifts were reported as δ (ppm) values. Mass spectra were recorded on a VG Platform II LC-MS spectrometer (70eV) with EI (electron ionisation) methods. Elementary analysis was performed on a Leco 932 CHNS-O analyser.

All the chemical reagents used in the synthesis were purchased from E. Merck (Darmstadt, FRG) and Aldrich (Milwaukee, WI, USA). To reach the molecules that were planned to be synthesized, the starting materials were synthesized as given in the literature (3, 9, 10)(Scheme 1).

I. Synthesis of 6-formyl flavone (Ie)

2-benzoyloxy-5-methylacetophenone(Ia)

A mixture of benzoyl chloride (10ml, 0.0086mol) and 2-hydroxy-5-methylacetophenone (10g, 0.066mol) was heated in 25ml pyridine at 60°C for 30 min. The product was crystallized from ethanol. m.p:63°C (Lit.9 m.p:65°C).

2-hydroxy-5-methyldibenzoylmethane(Ib)

2-benzoyloxy-5-methylacetophenone (5g, 0.0196mol) was treated with 15g KOH in 25ml pyridine and heated at 100°C for 30 min., acidified with ice cold 6N HCl. The product crystallized from petroleum ether in yellow shining plates. m.p:94°C (Lit.10 m.p:96°C).

6-methylflavone(Ic)

2-hydroxy-5-methyldibenzoylmethane (2.5g, 0.098mol) was stirred in 12.5ml conc.H_2SO_4 at room temperature for 30 min. The product was obtained crystallized from petroleum ether in white woolly needles. m.p:118-120°C (Lit.10 m.p:122-123°C).

6-bromomethylflavone(Id)

A mixture of N-bromosuccinimide (1.2g, 0.00672mol) and 6-methylflavone (1g, 0.0042mol) was dissolved in 40ml hot benzene (35ml) and benzoylperoxide (0.1g) was added. The reaction mixture was refluxed for 6 hours. The product was crystallized from benzene. m.p:173°C (Lit.10 m.p:175°C).

6-formylflavone(Ie)

A mixture of 6-bromomethylflavone (1g, 0.00317mol) and hexamethylenetetramine (4g, 0.028mol) in 20ml acetic acid (%50,v/v) was refluxed for 15 min. HCl:H_2O (1:1, 10ml) was added and refluxed for another 10 min. The product which separated on dilution of the reaction mixture with water, was crystallized from acetic acid in tiny pale yellow needles. m.p:184°C (Lit.10 m.p:186°C).

II. Synthesis of 2,4-thiazolidinedione (II)

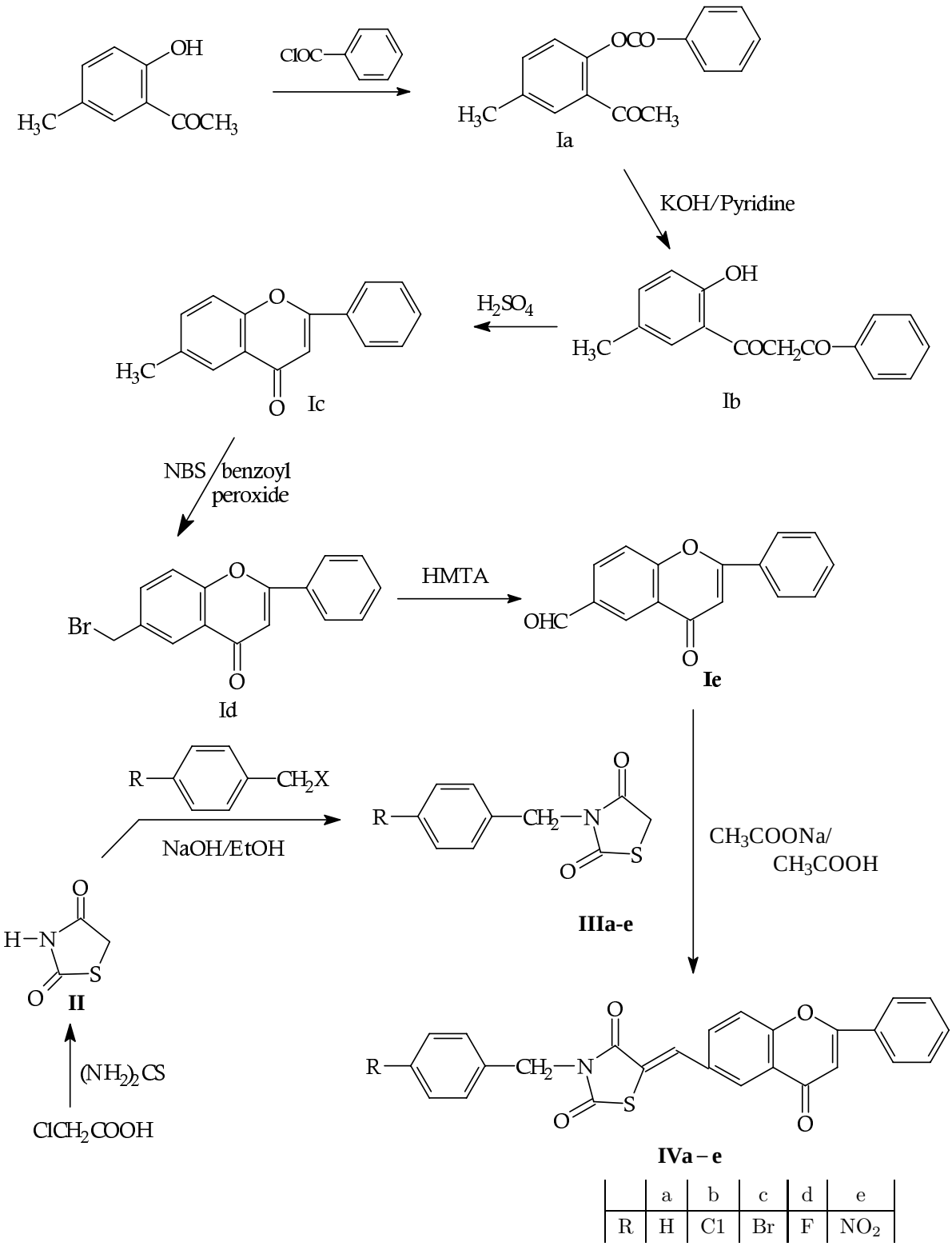
A mixture of $ClCH_2COOH$ (10g, 0.106mol) and thiourea (8.055g, 0.106mol) in 10ml water was heated for 40 hours. The product was crystallized from water. m.p:125°C (Lit.3 m.p:125°C).

III. Synthesis of 3-benzyl substituted 2,4-thiazolidinediones (IIIa-e)

A mixture of 2,4-thiazolidinedione (2.34g, 0.02 mol), substituted benzyl halide (0.02mol) and sodium hydroxide (0.8g, 0.02 mol) solution (EtOH/H_2O: 50%, 20ml) was refluxed for 18 hours. The crude product was crystallized from EtOH. (**IIIa** m.p:60°C (Lit.11 m.p:60.3-61°C), **IIIb** m.p:95°C (Lit.2 m.p:96°C), **IIIc** m.p:91°C (Lit.12 m.p:90-91°C), **IIId** m.p:83°C (Lit.3 m.p:82°C), **IIIe** m.p:117°C (Lit.13 m.p:117°C)).

IV. Synthesis of substituted flavonyl thiazolidinedione derivatives (IVa-e)

A mixture of 6-formylflavone (**Ie**) (0.4 mmol) and corresponding 3- substituted benzyl 2,4-thiazolidinedione (**IIIa-e**) (0.4 mmol) was heated at 140-150°C in the presence of 1ml acetic acid glacial and sodium acetate (0.4 mmol) for 12 hours. The crude product was crystallized from DMF.



	a	b	c	d	e
R	H	C1	Br	F	NO_2

Scheme 1. Synthesis of Some Substituted Flavonyl Thiazolidinedione Derivatives

3-benzyl-5-[2-phenyl-4H-4-oxo-1-benzopyran-6-yl)methylenyl]-2,4-thiazolidinedione (IVa)

Yield: 80%, m.p:219°C

IR cm^{-1}:1654 (γ-pyron CO), 1685, 1746 (thiazolidinedione ring CO) ^{1}H-NMR (DMSO-d_6) (δ ppm): 4.90 (s, 2H, CH_2), 7.12 (s, 1H, 3-H), 7.30-7.40 (m, 5H, C_6H_5), 7.58-7.65 (m, 3H, 3',4',5'-H), 7.90 (d,1H, 8-H), 8.05-8.18 (m, 3H, 7,2',6'-H), 8.25 (dd, 1H, =CH), 8.28 (dd, 1H, 5-H) Mass, EI 70eV: *m/z* (%): 439 (M^+) (24.85), 278 (38.71), 221 (1.02), 120 (23.62), 102 (12.61), 92 (6.15), 91 (100), 63 (8.10)

Anal. for $C_{26}H_{17}NO_4S.\ 0.3H_2O$
Calcd. C:70.20, H:3.96, N:3.15, S:7.20
Found C:70.23, H:4.12, N:3.44, S:7.29

3-(4-chlorobenzyl)-5-[2-phenyl-4H-4-oxo-1-benzopyran-6-yl) methylenyl]-2,4-thiazolidinedione (IVb)

Yield: 84.5%, m.p:249°C

IR cm^{-1}:1636 (γ-pyron CO), 1673, 1736 (thiazolidinedione ring CO) ^{1}H-NMR (DMSO-d_6) (δ ppm): 4.87 (s, 2H, CH_2), 7.15 (s, 1H, 3-H), 7.40 (dd, 4H, a,a',b,b'-H), 7.58-7.65 (m, 3H, 3',4',5'-H), 7.98 (d,1H, 8-H), 8.08-8.18 (m, 4H, 7,2',6'=CH), 8.28 (dd, 1H, 5-H) Mass, EI 70eV: *m/z* (%): 473.5 (M^+) (20.90), 278 (42.58), 221 (1.88), 125 (100), 120 (39.45), 102 (22.27), 91.3 (1.61), 63 (5.00)

Anal. for $C_{26}H_{16}ClNO_4S$
Calcd. C:65.89, H:3.38, N:2.96, S:6.76
Found C:66.42, H:3.53, N:3.26, S:6.83

3-(4-bromobenzyl)-5-[2-phenyl-4H-4-oxo-1-benzopyran-6-yl) methylenyl]-2,4-thiazolidinedione (IVc)

Yield: 65.2%, m.p:265°C

IR cm^{-1}:1637 (γ-pyron CO), 1678, 1743 (thiazolidinedione ring CO) ^{1}H-NMR (DMSO-d_6) (δ ppm): 4.85 (s, 2H, CH_2), 7.15 (s, 1H, 3-H), 7.30 (d, 2H, a,a'-H), 7.55-7.65 (m, 5H, b,b',3',4',5'-H), 7.99 (d,1H, 8-H), 8.08-8.18 (m, 4H, 7,2',6'=CH), 8.30 (s, 1H, 5-H) Mass, EI 70eV: *m/z* (%): 518 (M^+) (5.67), 278 (100), 221 (4.20), 171 (80.99), 169 (77.82), 120 (73.59), 92 (3.72), 63 (40.85)

Anal. for $C_{26}H_{16}BrNO_4S.\ 0.35H_2O$
Calcd. C:59.50, H:3.19, N:2.67, S:6.10
Found C:59.53, H:3.29, N:2.96, S:6.09

3-(4-fluorobenzyl)-5-[2-phenyl-4H-4-oxo-1-benzopyran-6-yl) methylenyl]-2,4-thiazolidinedione (IVd)

Yield: 79.3%, m.p:253°C

IR cm^{-1}:1650 (γ-pyron CO), 1686, 1741 (thiazolidinedione ring CO) ^{1}H-NMR (DMSO-d_6) (δ ppm): 4.82 (s, 2H, CH_2), 7.15 (s, 1H, 3-H), 7.20 (dd, 2H, a,a'-H), 7.40 (dd, 2H, b,b'-H), 7.60-7.64 (m,3H, 3',4',5'-H), 7.90 (d, 1H, 8-H), 8.08-8.18 (m, 4H, 7,2',6'=CH), 8.26 (d, 1H, 5-H) Mass, EI 70eV: *m/z* (%): 457 (M^+) (14.32), 278 (21.68), 221 (0.89), 136 (6.70), 120 (20.73), 109 (100), 102 (11.57), 93 (2.37)

Anal. for $C_{26}H_{16}FNO_4S.\ 0.15H_2O$
Calcd. C:67.87, H:3.54, N:3.05, S:6.96
Found C:67.89, H:3.13, N:3.34, S:7.11

3-(4-nitrobenzyl)-5-[2-phenyl-4H-4-oxo-1-benzopyran-6-yl)methylenyl]-2,4-thiazolidinedione (IVe)

Yield: 39.0%, m.p: 296°C

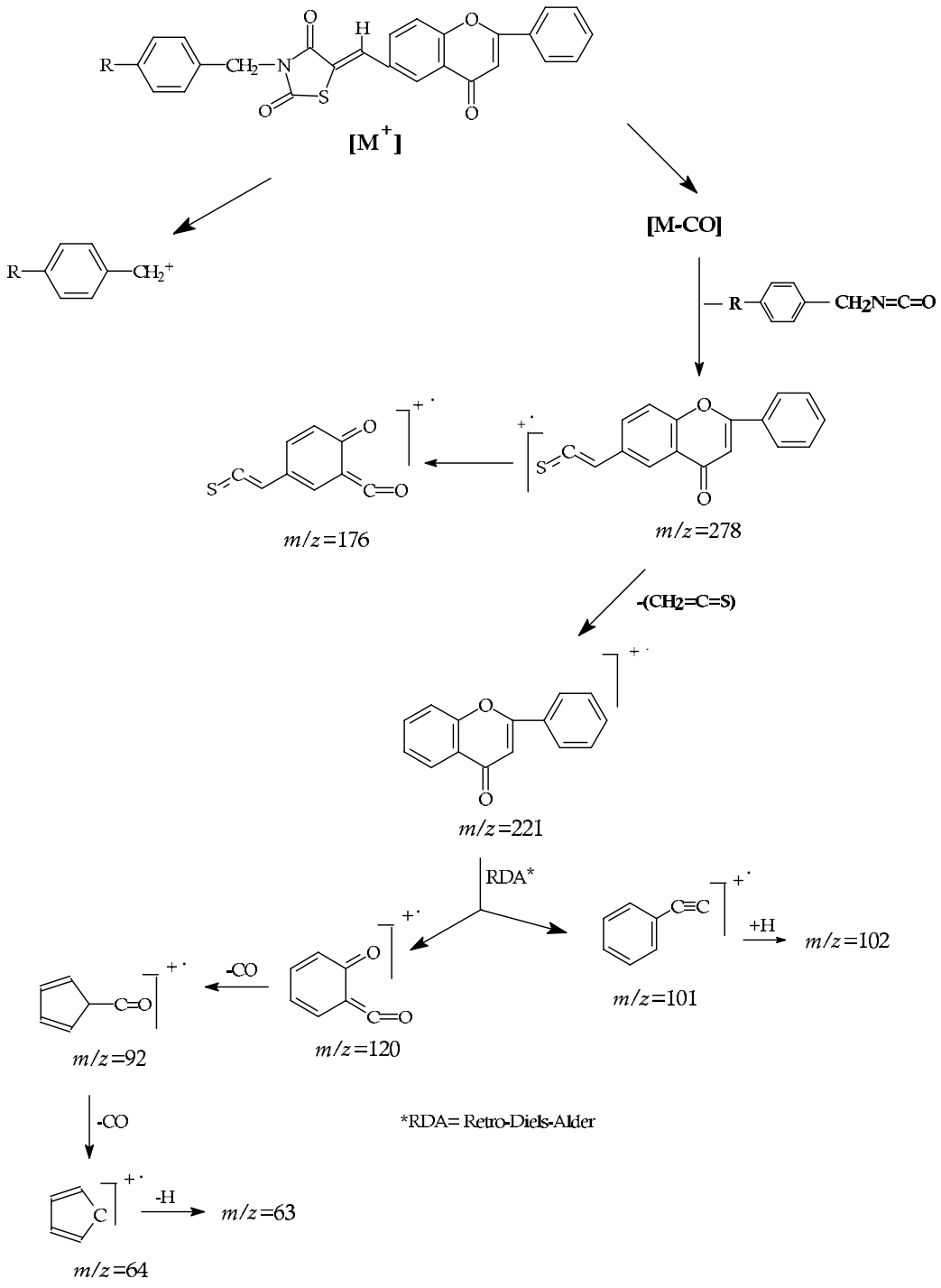
IR cm^{-1}:1635 (γ-pyron CO), 1676, 1737(thiazolidinedione ring CO) ^{1}H-NMR (DMSO-d_6) (δ ppm): 5.10 (s, 2H, CH_2), 7.15 (s, 1H, 3-H), 7.30 (d, 2H, a,a'-H), 7.55-7.65 (m, 5H, b,b',3',4',5'-H), 7.99 (d,1H, 8-H), 8.08-8.18 (m, 4H, 7,2',6'=CH), 8.30 (s, 1H, 5-H) Mass, EI 70eV: *m/z* (%): 484 (M^+) (47.71), 278 (100), 221

(2.36), 120 (52.29), 102 (23.20), 92 (1.59), 63 (10.95)

Anal. for $C_{26}H_{16}N_2O_6S.\ 0.35H_2O$

Calcd. C:63.63, H:3.41, N:5.71, S:6.53

Found C:63.68, H:3.44, N:5.86, S:6.80



Scheme 2. Mass fragmentation of the flavonyl thiazolidinedione compounds

Results and Discussion

The general method which is known as Baker-Venkataraman was used to prepare 6-methyl flavone. The methyl group of the flavone was converted to bromomethyl and then this group was changed into carboxaldehyde. The methylenyl group linker between the flavone and the 2,4-thiazolidinedione derivative was synthesized by Knoevenagel condensation of the 6-flavone carboxaldehyde and 2,4-thiazolidinedione ring. Sodium acetate/gl. acetic acid were generally used as the reagents in this condensation.

The formula, melting points, yields, ^{1}H-NMR spectra and mass spectral values of the compounds are listed in the Experimental section. All spectral data were in accordance with assumed structures. In ^{1}H-NMR spectra: C-3, C-5, C-7 and C-8 protons of 4H-benzopyran ring and flavone B ring protons were seen between 7.12-8.30 ppm. Benzylic protons were observed 4.82-5.10 ppm as a singlet. All the compounds have a molecular ion (M^+), M+1 and M+2 peaks (Scheme 2). Ion peak (m/z=278) is a base peak for R=Br (IIc) and R=NO_2 (IIe); benzyl cation peak is a base peak for R=H (IIa) (m/z=91), R=Cl (IIb) (m/z=125) and R=F (IId) (m/z=109). Other fragments appeared at the expected m/z values.

Substituted 5-arylidene-2,4-thiazolidinediones are theoretically able to exist in the Z and E configurations. However, in the literature, in reactions using unsubstituted imidazolidinediones and benzaldehyde in acidic medium, the main product was the Z isomer [14]. The coupled ^{13}C NMR study given the vicinal coupling constant of the ethylenic proton and the carbonyl group show that arylidene thiazolidinediones was also in the Z configuration [15,16]. In this study only one isomer was obtained. However, due to the low solubility of the compounds and the difficulties in getting suitable crystals for X-Ray analysis, the isomer could not be structurally analysed in detail.

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