Arch. Pharm. Res. **12**(1), 12-16 (1989)

New Synthesis of Chromonopyrroloimidazolinones and Arylidene Thioxoimidazolinones

Study of their antimicrobial activities

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(Received March 6, 1989)

Abstract □ 6-Formyl-5-methoxy-2-methyl chromone derivatives condensed with 2-thiox-4-imidazolinone derivatives to form the corresponding "10-methoxy-7-methyl-3-thioxo-chromono[6,7-b]pyrrolo[1,2-a-]-imidazolin-1-one derivatives **(IIIa-f)** or the 5-arylidene-2-thioxo-4-imidazolinone derivatives **(IVa-f)**. The activity of the NH in the imidazol moiety of **(IIIa)** was confirmed by formation of the Mannich bases **(Va, b)**. Moreover, alkylation of **(IIIa)** was undertaken to give the alkylmercapto derivatives **(VIa, b)**. The antimicrobial activities of compounds **IIIb-e, IVa, IVd** and **IVe** were studied.

Keywords □ Thioxochromonopyrroloimidazolinones, arylidene thioxoimidazolinones, antimicrobial activity.

2-Thioxo-4-imidazolinone derivatives posses anticonvulsant activity[1] and antiasthmatic activity.[2] On the other hand, chromones are known to possess coronary dilator activities.[3] Some derivatives are used in formulations of medicaments for treating eye or skin diseases.[4] Moreover, some chromone derivatives show antispasmodic activity as well as antitumor properties.[5] A compound having both imidazolinone and chromone moieties can be expected to possess marked biological activity. This paper deals with the synthesis of several thioxochromonopyrroloimidazolinone derivatives **(IIIa-f)** and 5-arylidene-2-thioxoimidazolinone derivatives **(IVa-f)** and the results of their preliminary antimicrobial activity.

Chemistry

2-Thioxo-4-imidazolinone **IIa** and 3-phenyl-2-thioxo-4-imidazolinone **IIb** are condensed with 6-formyl-7-hydroxy-5-methoxy-2-methyl chromone derivatives **(Ia-c)** to give **(IIIa-f)**. The reaction products **(IIIa-f)** were formed via the condensation of the formyl group of **Ia-c** with active methylene group of **IIa, b** followed by loss of H_2O due to the presence of the hydrogen atom at position-1 in the thioxoimidazolinone ring in **IIa,b** and the OH group in the chromone derivatives **(Ia-c)**.

Condensation reaction was also extended to the synthesis of a variety of substituted chromone derivatives under similar condition utilizing the chromone derivatives **(Ia-c)** with 1-phenyl-2-thioxo-4-imidazolinone **(IIc)** to give the corresponding 5-[5-methoxy-2-methylchromone-6-yl]methylene-1-phenyl-2-thioxo-4-imidazolinones **(IVa-c)**. In a similar manner condensation of 6-formyl-5,7-dimethoxy-2-methyl chromone **(Id)** with 2-thioxo-4-imidazolinone derivatives **(IIa-c)** afforded the 5-arylidene-2-thioxo-4-imidazolinones **(IVd-f)**. The structure assigned for the cyclyised products **(IIIa-f)** and the arylidene derivatives **(IVa-f)** was established on the basis of elemental analysis and spectral data studies (cf. Tables I and II).

The reactivity of the hydrogen atom of the imino group in imidazoline moiety in the product **IIIa** was confirmed by the Mannich reaction and alkylation reaction. Thus, when **IIIa** was reacted with formaldehyde and the appropriate aromatic amine in ethanol under the Mannich reaction conditions[6], 2-arylaminomethylene derivatives **(Va,b)** were obtained. Also when **IIIa** was treated with alkyl iodide in presence of sodium ethoxide, the alkylmercapto derivatives **(VIa,b)** were obtained. The structures **(Va, b)** and **(VIa, b)** were inferred from both elemental analysis and spectral data studies (cf. Tables I and II). The IR spectra of **VIa,b** showed strong absorption bands for C = N group at 1640 cm^{-1}. This proves that the alkylation reaction takes place at the sulphur atom of the imidazole ring.

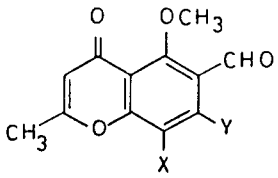
Table I. Condensation products (IIIa-f), (IVa-f), Mannich bases (Va,b) and alkylmercapto derivatives (VIa,b)

Compound	M.P	Yield %	Formula	Elemental analysis %									
				Calcd.					Found				
				C	H	N	S	Br	C	H	N	S	Br
IIIa	280	80	$C_{15}H_{10}N_2O_4S$	57.32	3.18	8.91	10.19		57.1	3.0	8.6	10.0	—
IIIb	273-4	75	$C_{21}H_{14}N_2O_4S$	64.61	3.58	7.17	8.20	—	64.4	3.3	7.4	8.0	—
IIIc	288-9	78	$C_{15}H_9N_3O_6S$	50.13	2.50	11.69	8.91	—	50.5	2.2	11.5	8.6	—
IIId	225-7	73	$C_{21}H_{13}N_3O_6S$	57.93	2.98	9.65	7.35	—	57.6	3.0	9.8	7.1	—
IIIe	306-8	70	$C_{15}H_9N_2O_4SBr$	45.80	2.29	7.12	8.14	20.35	45.5	2.5	7.4	8.0	20.6
IIIf	220	76	$C_{21}H_{13}N_2O_4SBr$	53.73	2.77	5.97	6.82	17.05	54.0	2.9	5.6	6.4	17.2
IVa	235-6	78	$C_{21}H_{16}N_2O_5S$	61.76	3.92	6.86	7.84	—	61.4	3.6	6.6	8.1	—
IVb	150	75	$C_{21}H_{15}N_3O_7S$	55.62	3.31	9.27	7.06	—	55.4	3.5	9.6	6.8	—
IVc	190	77	$C_{21}H_{15}N_2O_5SBr$	51.74	3.08	5.74	6.57	16.42	51.4	3.3	5.5	6.8	16.2
IVd	270	82	$C_{16}H_{14}N_2O_5S$	55.49	4.04	8.09	9.24	—	55.7	3.8	8.3	9.0	—
IVe	230-2	81	$C_{22}H_{18}N_2O_5S$	62.55	4.26	6.63	7.58	—	62.2	4.0	6.4	7.8	—
IVf	215-6	88	$C_{22}H_{18}N_2O_5S$	62.55	4.26	6.63	7.58	—	62.3	4.5	6.5	7.8	—
Va	205	90	$C_{22}H_{17}N_3O_4S$	63.00	4.05	10.02	7.63	—	63.3	3.9	9.8	7.8	—
Vb	222-3	83	$C_{23}H_{19}N_3O_4S$	63.74	4.38	9.69	7.39	—	63.5	4.5	9.5	7.1	—
VIa	232-3	75	$C_{16}H_{12}N_2O_4S$	58.53	3.65	8.53	9.75	—	58.3	3.5	8.7	9.5	—
VIb	210	69	$C_{17}H_{14}N_2O_4S$	59.64	4.09	8.18	9.35	—	60.0	3.8	8.0	9.1	

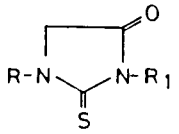
Compounds **IIIa**, **IVc** and **IVd** were crystallised from AcOH and the other products from EtOH.

Table II. IR and ^1H NMR spectra of the compounds IIIa-f, IVa,d,e, Va and VIa, b

Compound	IR [cm^{-1}]	^1H NMR [δ_{ppm}]
IIIa	3370(NH); 1720, 1660 (2C=O) and 1200(C=S).	2.3(s, 3H, CH_3); 3.9(s, 3H, OCH_3); 6, 6.5, 6.8(3s, 3H, 3CH=C) and 12.5(s, br, 1H, NH exchangable with D_2O).
IIIb	1730, 1660(2C=O) and 1210(C=S)	2.3(s, 3H, CH_3); 3.9(s, 3H, OCH_3); 6, 6.6, 6.8(3s, 3H, 3CH=C) and 7.3-7.6(m, 5H, aromatic protons).
IIIc	3380(NH); 1715, 1660 (2C=O); 1530, 1350(NO_2) and 1200(C=S)	2.4(s, 3H, CH_3); 3.9(s, 3H, OCH_3); 6.1, 6.6(2s, 2H, 2CH=C) and 12.0(s, br, 1H, NH exchangable with D_2O).
IIId	1730, 1670(2C=O); 1520, 1350(NO_2) and 1205(C=S)	2.3(s, 3H, CH_3); 3.8(s, 3H, OCH_3); 6.2, 6.7(2s, 2H, 2CH=C) and 7.3-7.5(m, 5H, aromatic protons).
IIIe	3350(NH); 1720, 1660 (2C=O); 1200(C=S) and 660(C-Br).	
IIIf	1725, 1670(2C=O); 1210(C=S) and 660(C-Br)	2.3(s, 3H; CH_3); 3.9(s, 3H, OCH_3); 6.2, 6.6(2s, 2H, 2CH=C) and 7.2-7.5(m, 5H, aromatic protons).
IVa	3400(NH), 3200(broad OH); 1730, 1660(2C=O) and 1200(C=S)	2.3(s, 3H, CH_3); 3.8(s, 3H, OCH_3); 6, 6.5, 6.9(3s, 3H, 3CH=C); 7.4-7.6(m, 5H, aromatic protons) and [10.2 (s, 1H, NH), 11.5(s, br, 1H, OH) exchangable with D_2O].
IVd	3410, 3380(2NH); 1720, 1660(2C=O) and 1210(C=S)	2.3(s, 3H, CH_3); 3.7, 3.9(2s, 6H, $2OCH_3$); 6, 6.6, 6.8 (3s, 3H, 3CH=C) and 10.8, 11.5(2s, 2H, 2NH).
IVe	3390(NH); 1725, 1660(2C=O) and 1205(C=S)	2.2(s, 3H, CH_3); 3.7, 3.9(2s, 6H, $2OCH_3$); 6.1, 6.6, 6.8(3s, 3H, 3CH=C); 7.3-7.5(m, 5H, aromatic protons) and 10.5 (s, 1H, NH).
Va	3380(NH), 1720, 1660(2C=O) and 1205(C=S)	2.3(s, 3H, CH_3); 3.8(s, 3H, OCH_3); 4.1(s, 2H, N-CH_2-N); 6.1, 6.5, 6.8(3s, 3H, 3CH=C); 7.2-7.4(m, 5H, aromatic protons) and 10.7(s, 1H, NH).
VIa	1710, 1660(2C=O) and 1640(C=N)	2.2(s, 3H, CH_3); 2.6(s, 3H, S-CH_3); 3.8(s, 3H, OCH_3) and 6, 6.6, 6.8(3s, 3H, 3CH=C).
VIb	1720, 1660(2C=O) and 1640(C=N).	

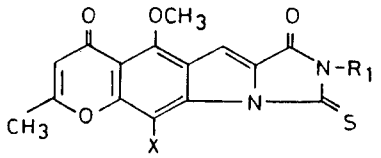


Ia, X= H ; Y= OH
b, X= NO_2 ; Y= OH
c, X= Br ; Y= OH
d, X= H ; Y= OCH_3

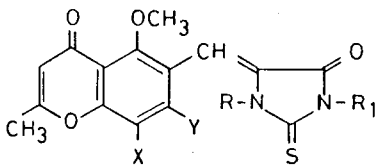


IIa, R= R_1 = H
b, R= H ; R_1= C_6H_5
c, R= C_6H_5 ; R_1= H

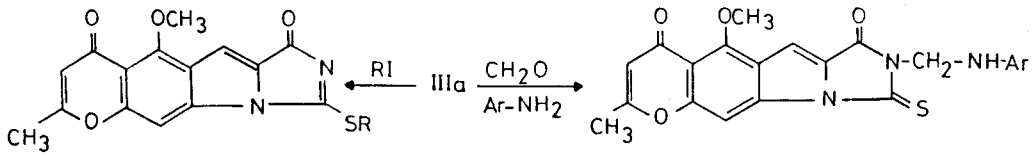
Ia-c + II a,b ⟶



IIIa, X= R_1= H
b, X= H ; R_1= C_6H_5
c, X= NO_2 ; R_1= H
d X= NO_2 ; R_1= C_6H_5
e, X= Br ; R_1= H
f, X= Br ; R_1= C_6H_5



IVa, X= R_1= H ; Y= OH ; R= C_6H_5
b, X= NO_2 ; Y= OH ; R= C_6H_5 ; R_1= H
c, X= Br ; Y= OH ; R= C_6H_5 ; R_1= H
d, X= R= R_1= H ; Y= OCH_3
e, X= R= H ; Y= OCH_3 ; R_1= C_6H_5
f, X= R_1= H ; Y= OCH_3 ; R= C_6H_5



VI a, R= CH_3
b, R= CH_2CH_3

V a, Ar= C_6H_5
b, Ar= $C_6H_4CH_3$-p

RESULTS AND DISCUSSION

Antimicrobial activity

Table III shows the effect of compounds **IIIb-e** and **IVa,d,e** on the micro-organisms tested. All the compounds were in active against gram-ve bacteria.

It is of interest to note that the most active compound is **IVa,** this is probably due to the presence of the free OH and NH groups.

The disappearance of the OH group by cyclization diminished the activity as in **IIIc** and **IIIe.**

It is obvious that the introduction of a phenyl group in **IIIb** and **IIId** gave a further decreases in activity. Furthermore the presence of the methoxy

Table III. The antimicrobial activity of compounds IIIb-e and IVa,d,e

Compound	Bacillus subtilis	Staphylococcus aureus	Pseudomonas putida	Serritia species	Fusarium oxysporum	Cephalosporium maydis	Monilia species
IIIb	+	+	−	−	+	+	+
IIIc	+ +	+ +	−	−	+ +	+	+
IIId	+	+	−	−	−	+	+
IVa	+ + +	+ + +	−	−	+ +	+ +	+ +
IVd	−	−	−	−	−	−	−
IVe	−	−	−	−	−	−	−

group in **IVd** and **IVe** abolished the activity.

EXPERIMENTAL

All m.p.'s are incorrected. The IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer. ^{1}H NMR were obtained on a Varian EM-390-90 MHz NMR spectrometer with $SiMe_4$ as internal standard. Elemental analysis were done by the microanalytical laboratory at Cairo University.

General synthetic procedure for the preparation of IIIa-f and IVa-f:

To a mixture of (0.01 mole) of chromone derivatives (**Ia-b**)[7] and (0.01 mole) of the active methylene-2-thioxo-4-imidazolinone derivatives (**IIa-c**)[8-10] in 30 m*l* absolute ethanol was added 3 drops of triethylamine. The reaction mixture was refluxed for 2 hours. The solvent mixture was evaporated under vaccum and the solid so obtained was crystallized from the appropriate solvent (cf. Table I). All the products are coloured compounds ranging from yellow to brown.

Mannich bases of IIIa

To a suspension of **IIIa** (0.01 mole) and the appropriate amine (0.011 mole) in ethyl alcohol (50 m*l*) was added 30% aqueous formaldehyde (1.1 m*l*). The reaction mixture was refluxed on water bath for 3 hours, and left aside overnight. It was concentrated to 20 m*l* by evaporation and left to cool at room temperature. The obtained solid was crystallised from ethanol as yellow crystals of **Va,b.**

Action of alkyl iodide on IIIa

To a mixture of **IIIa** (0.01 mole) in 0.01 sodium ethoxide (prepared from 0.23 g of sodium metal in 50 m*l* absolute ethanol) was added the appropriate alkyl iodide (0.011 mole). The reaction mixture was stirred for 2 hrs and left overnight at room temperature. The obtained solid was collected and crystallised from ethanol as pale yellow crystals of **VIa,b.**

Antimicrobial activity

The following microbial strains were used as target organisma. *Bacillus subtilis, Staphylococcus aureus* (gram + ve bacteria), *Pseudomonas putida* and *Serritia species* (gram − ve bacteria), *Fusarim oxysporum, Cephalosporium* maydis and *Monilia* species (Fungi).

The compounds under investigation were insoluble in water, therefore they were dissolved in acetone 2 g/*l* and filtered through bacterial membrane filter (0.45 um).

The antimicrobial effect of the compounds was determined by the whole plate method.[11] A spore suspension of the test organisms were prepared and inoculated onto the surface of the solidified plate medium (pH = 7). 400 μg of each compound (dissolved in 0.2 m*l* of acetone), were added to each pit.

Incubation temperature was 35-37 °C for bacteria and 27-30 °C for fungi. The toxicity was measured after 24 and 48 hrs for bacteria and 5-7 days for fungi and it was estimated as follows:

− ve no inhibition zone
+ ve slight inhibition zone
+ + ve moderate inhibition zone
+ + + ve extensive inhibition zone

The above estimation was based on the diameter of the inhibition zone formed. A control experiment with acetone was also performed.

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