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SYNTHESIS AND REACTIVITY OF SUBSTITUTED CHROMONES

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تخليق ونشاطية مشتقات الكرومون

إبراهيم صالح النعيمي و بدرية عبد الوهاب حسين

يتناول هذا البحث تخليق مركبات ٢ ـ ميثيل ـ ٢, ـ ستايريل ـ ٦ ـ برومو ـ ٨,٧ ـ بنزوكرومون و٦,٢ ـ ثنائي ميثيل كرومون ونشاطها تجاه الكواشف الألكتروفيلية والنيوكليوفيلية وتفاعلات الإضافة الحلقية تحت ظروف تفاعل ديلز ـ الدر . ويناقش البحث سبل تكوين وأشكال المركبات الناتجة من هذه التفاعلات باستخدام الأشعة تحت الحمراء ، والرنين النووي المغناطيسي لذرة الهيدروجين ، وطيف الكتلة وتحاليل العناصر .

Key Words: Synthesis, 6-Bromo-7, 8-benzo-2-methylchromone, 2-Styryl-6-bromo-7, 8-benzochromone, 2, 6-Dimethylchromone

ABSTRACT

The synthesis of 2-methyl-and 2-styryl-6-bromo-7, 8-benzochromone and 2, 6-Dimethylchromone and their reactivity towards cyclo-addition reaction under Diels-Alder conditions and towards nucleophilic and electrophilic reagents are studied.

The mode of formation and structure of the various products are reported using IR, ^{1}H NMR, Mass Spectra and elemental analyses.

INTRODUCTION

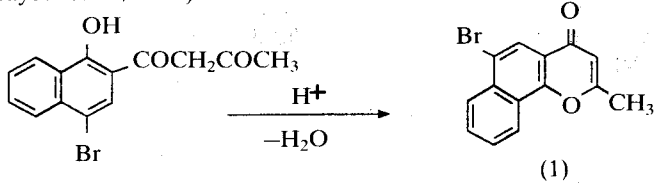
Chromones and their derivatives have been receiving great attention. Some of them proved to be of special importance in medicine as stimulants of the central nervous system (Lami *et al,* 1963), spasmolytic and as cornorary dilators (Bradel-Gay *et al,* 1962). Some were known to inhibit the growth of human cancer cells, reduce blood pressure and act as diurectics (Nakamura *et al,* 1936, Jerome 1964) also some members of the same family are reported to be antiallergic (Umio *et al,* 1974, Pier Giorgio 1978) and antibiotics (Gerhard *et al,* 1984), while other chromone derivatives were found to be active against passive cutaneous anaphylaxis (PCA) in rats (Jadhav and Ingle 1983) and useful as cardiovascular agents.

In the course of the present work several new derivatives containing the chromone moiety were prepared and some of their reactions were investigated. The aim is to show the reactivity of chromone nucleus towards cyclo-addition reactions under Diels-Alder conditions, the behaviour of chromone moiety towards nucleophilic and electrophilic reagents, and thiation.

The structure of the products obtained was confirmed by elemental analysis, infrared spectra, ^{1}H-nuclear magnetic resonance and mass spectra.

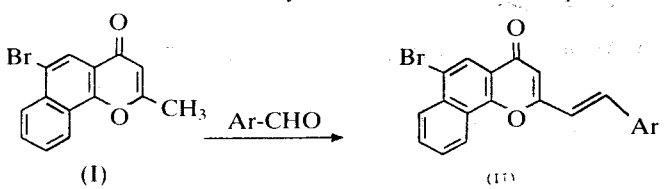
RESULTS

6-Bromo-7,8-benzo-2-methylchromone (I) was prepared via the condensation of 2-acetyl-4-bromo-1-naphthol with acetyl-acetate in the presence of sodium pellets followed by acid-catalysed cyclodehydration of 2-acetoacetyl-4-bromo-naphthol (Sayed *et al,* 1980).



(1)

2-Substituted Styryl-6-bromo-7,8-benzochromones (II_{a-d}) (Heilbron *et al,* 1923, Zaki and Azzam 1943, Schonberg, Fateen and Sammour 1956) were prepared by the treatment of 6-bromo-7,8-benzo-2-methylchromone (I) with the aromatic aldehydes namely; thiophene-2-aldehyde, 2-naphthaldehyde, *p*-chlorobenzaldehyde and veratraldehyde in the presence of sodium ethoxide in dimethylformamide at room temperature.



(I) (II)

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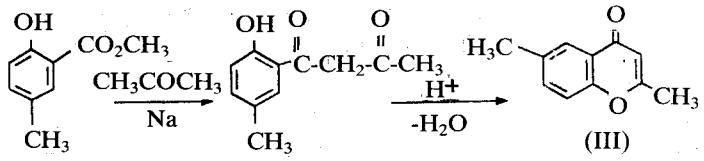
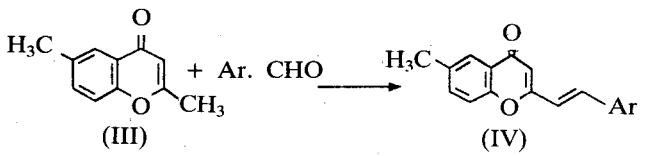
a) Ar = 
b) Ar = -$C_{10}H_7$-2
c) Ar = -C_6H_4Cl-*p*
d) Ar = -C_6H_3 $(OMe)_2$-3, 4

2,6-Dimethyl chromone (III) was prepared via acid catalysed cyclodehydration of 2-acetoacetyl-4-methyl phenol which was prepared from the reaction of methyl (4-methyl) salicylate with acetone in presence of sodium metal.



(III)

2-Styryl-6-methylchromones (IV*a-e*) were prepared by the treatment of 2,6-dimethylchromone (III) with the aromatic aldehydes namely; benzaldehyde, anisaldehyde, *p*-chlorobenzaldehyde, thiophene-2-aldehyde and furfural in the presence of sodium ethoxide in ethanol at room temperature.

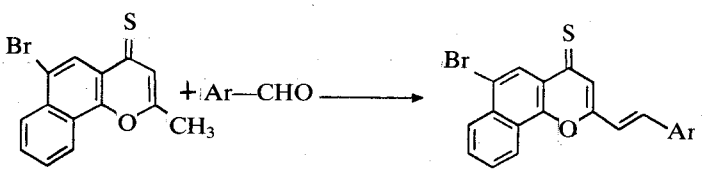


(III) (IV)

a) Ar = C_6H_5
b) Ar = -C_6H_4· OMe-*p*
c) Ar = -C_6H_4· Cl-*p*
d) Ar = 
e) Ar = 

Thiation of the chromone (I) was carried out by use of phosphorus pentasulphide to give 6-bromo-7,8-benzo-2-methyl-4-thiochromone (V).

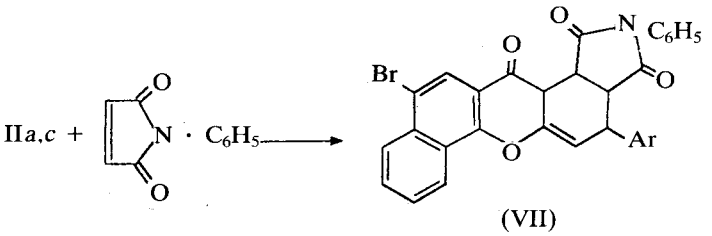
6-Bromo-7,8-benzo-2-methyl-4-thiochromone (V) condensed with aromatic aldehydes namely; thiophene-2-aldehyde, 4-naphthaldehyde, veratraldehyde and *p*-chlorobenzaldehyde in presence of piperidine to yeild the desired 2-styryl derivatives (VI*a-d*) respectively.



(V) (VI)

a) Ar = 
b) Ar = - $C_{10}H_7$ - 2
c) Ar = - $C_6H_3(OMe)_2$ -3,4
d) Ar = - C_6H_4Cl-*p*

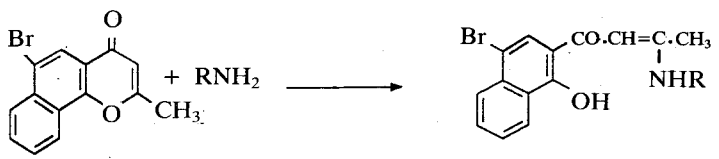
The 2-styryl derivatives (II*a,c*) react as dienes undergoing Diels-Alder reaction (Schonberg *et al*, 1954, 1956, Mustafa and Ali, 1956) with N-phenyl maleimide to give the xanthone derivatives (VII*a,b*).



(VII)

a) Ar = 
b) Ar = -C_6H_4 Cl-*p*

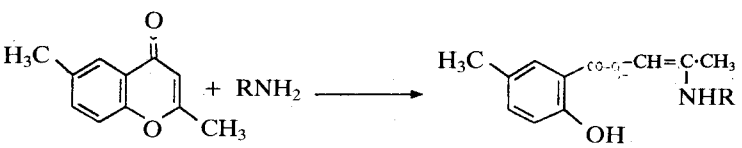
6-Bromo-7,8-benzo-2-methylchromone (I) reacted with aliphatic amines (Sammour 1958, Sammour and Marei 1968) namely; ethylamine and n-butylamine to yield the 2- (β-aminocrotonyl)-4-bromo-1-naphthol derivatives (VIII*a,b*).



(I) (VIII)

a) R = -CH_2CH_3
b) R = -$(CH_2)_3CH_3$

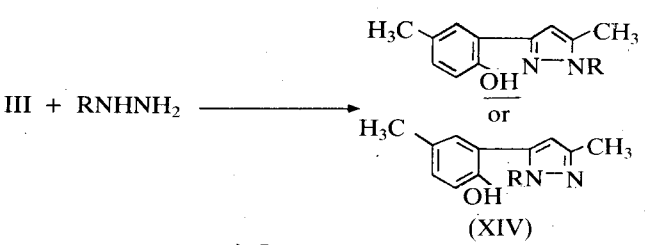
2,6-Dimethylchromone (III) reacted with aliphatic amines namely; ethylamine, n-butylamine and benzylamine in boiling ethanol to give the products (IX*a-c*).



(III) (IX)

a) R = -CH_2CH_3
b) R = -$(CH_2)_3CH_3$
c) R = -$CH_2C_6H_5$

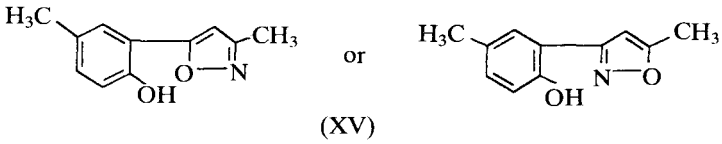
Reaction of 2,6-dimethylchromone (III) with hydrazines (Schonberg *et al*, 1953, 1956) namely; hydrazine hydrate, phenylhydrazine hydrochloride, semicarbazide hydrochloride and thiosemicarbazide took place through cleavage of the pyrone ring and gave the corresponding pyrazole derivatives (XIV*a-d*).



(XIV)

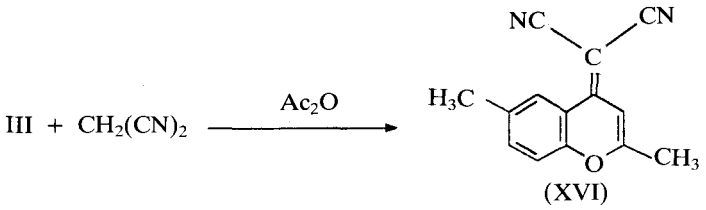
a) R = H
b) R = -C_6H_5
c) R = -$CONH_2$
d) R = -$CSNH_2$

In the same way chromone (III) reacted with excessive hydroxylamine hydrochloride to give the isoxazole derivative (XV).



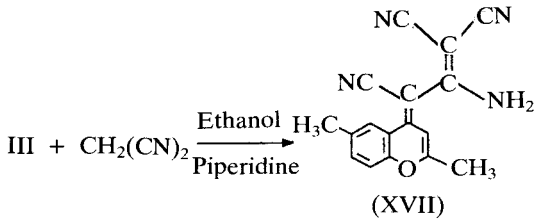
(XV)

Reaction of 2,6-dimethylchromone (III) with malononitrile depends on the reaction conditions, in acetic anhydride it gives compound (XVI) as 1:1 ratio of reactants are consumed.



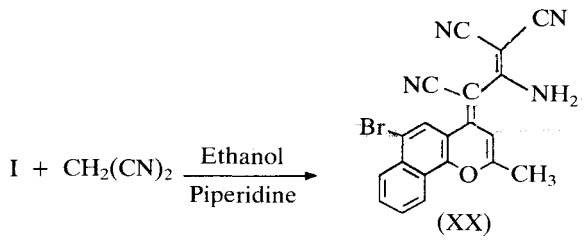
(XVI)

The reaction of the chromone (III) with malononitrile in ethanol and piperidine yields the compound (XVII) as 1:2 ratio of reactants (Chromone III: malononitrile) are reacted.



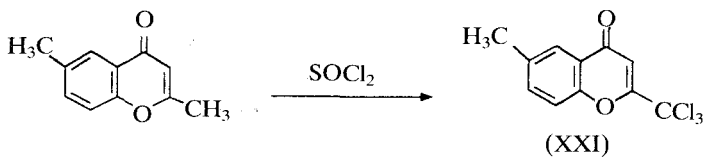
(XVII)

6-Bromo-2-methyl-7,8-benzochromone (I) reaction with malono-nitrile in ethanol and piperidine follows the same pattern and gives (XX) as the only product.



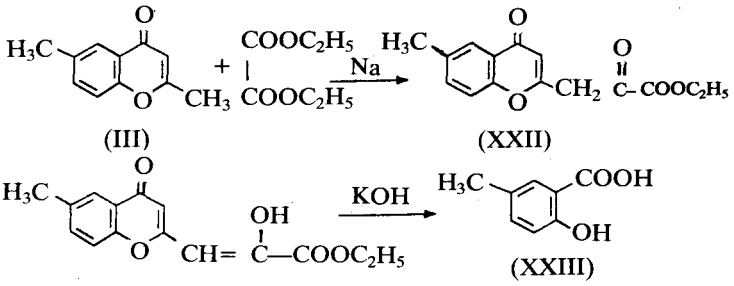
(XX)

The reaction of 2,6-dimethylchromone (III) with thionyl chloride in boiling benzene affords 6-methyl-2-trichloromethyl-chromone (XXI).



(XXI)

Chromone (III) reacts with ethyl oxalate in presence of sodium metal to yield the corresponding pyruvic ester (XXII) which exists in keto-enol tautomers. It is hydrolysed to 5-methylsalicylic acid (XXIII) by the use of 10% aqueous potassium hydroxide.



(III) (XXII)

(XXIII)

EXPERIMENTAL

Melting points reported are uncorrected. IR Spectra in KBr were recorded on a Beckmann IR-20 spectrophotometer and Pye Unicam SP 3-300 spectrophotometer. The ^{1}H NMR Spectra were determined on a Varian T-60. In all NMR experiments the internal standard was TMS. All chemical shifts are in ppm downfield from TMS.

The mass spectra were determined on an AEI MS-902 mass spectrometer at 70 ev electron energy.

Formation of 6-bromo-7,8-benzo-2-methyl chromone (I):

2-Acetoacetyl-4-bromo-1-naphthol (10 gm.) was dissolved in glacial acetic acid (40 ml.), then drops of concentrated hydrochloric acid were added. The reaction mixture was refluxed for half an hour, then drops of water were added to the mixture, stirred and left to cool. The solid obtained was filtered off then crystallized from toluene to give the chromone (I) as pale brown crystals (78% yield). It has the following properties m.p. 201-203°C; ^{1}H NMRδ (in ppm) 2.44 (s, 3H), 6.22 (s, 1H), 7.5-8.4 (m, 5H); IRυ, 1100 cm^{-1} (—O—), 1600 cm^{-1} (C = O), 1618 cm^{-1} (C = C), 2980 cm^{-1} (—CH_3); MS, m/e (relative intensity) 289 (20, $M^{+\cdot}$), 288 (100, $M^+ - 1$), 250 (56.5, $M^+ - 39$), 248 (59.5, $M^+ - 41$), 194 (28, $M^+ - 95$), 192 (30, $M^+ - 97$), 152 (24, $M^+ - 137$), 113 (79); Anal. calcd. for $C_{14}H_9BrO_2$:C, 58.13; H, 3.11. Found: C, 57.82; H, 3.09.

Condensation of 6-bromo-7,8-benzo-2-methyl chromone with aromatic aldehydes; Formation of 2-styryl-6-bromo-7,8-benzo chromone (IIa-d):

The chromone (I) (0.01 mole) was dissolved in the least amount of dimethyl formamide and treated at room temperature with an alcoholic solution of sodium ethoxide (0.2 gm. of sodium metal in 10 ml. of absolute ethanol). The appropriate aldehyde (0.01 mole) was then added and the reaction mixture was stirred for 10 minutes, then left to stand at room temperature overnight. The yellow condensation product was filtered off and crystallized from dimethyl formamide to give the 2-styryl chromones (II *a-d*). (cf. Table 1).

Table 1

Physical data of 2-styryl-6-bromo-7,8-benzochromones (II*a-d*)

Compound	m.p. °C	Formula (M. Wt.)	% Yield		Analysis % Calcd.	Found
II*a*	234-36	$C_{19}H_{11}BrSO_2$ (383)	72	C	59.53	59.43
				H	2.87	3.14
II*b*	268-70	$C_{25}H_{15}BrO_2$ (437)	65	C	68.64	69.12
				H	3.43	3.61
II*c*	260-63	$C_{21}H_{12}BrClO_2$ (411.5)	67	C	61.23	60.96
				H	2.91	3.14
II*d*	241-44	$C_{23}H_{12}BrClO_2$ (437)	53	C	63.15	62.90
				H	3.89	4.01

The IR spectra of compounds (II*a-d*) exhibit strong absorption bands at 1650-1630, 1600-1590, 1140-1090 and 3060-3030 cm^{-1} which were attributed to >C = O of pyrone, C= C, —O— and —CH trans respectively.

Compound (II*d*) has the following spectra:

^1H NMRδ (in ppm) 3.55 (s, 6H), 6.34 (s, 1H), 6.8-7.0 (d, 1H), 7.1-7.3 (d, 1H), 7.8-8.45 (m, 8H); MS, m/e (relative intensity) 438 (54.5, M^+ + 1), 437 (25.7, M^+·), 436 (54.5, M^+ − 1), 421 (12, M^+ − 15), 419 (13, M^+ − 17), 250 (18, M^+ − 187), 215 (20, M^+ − 212), 188 (100).

Formation of 2, 6-dimethylchromone (III):

2-Acetoacetyl-4-methyl phenol (2 gm.) was boiled with glacial acetic acid (10 ml.) and few drops of concentrated hydrochloric acid for 5 minutes. The solution was poured into ice/water. The solid obtained was filtered off then crystallized from light petrol (b.p. 60-80°C) to give the chromone (III) as pale yellow crystals (85% yield).

It has the following properties: m.p. 101-102°C; ^1H NMRδ (in ppm) 2.37 (s, 3H), 2.38 (s, 3H), 6.04 (s, 1H), 7.30-7.90 (m, 3H); IRυ 1150cm^{-1} (—O—), 1610cm^{-1} (C = C), 1650cm^{-1} (>C= O pyrone), 2900-3000cm^{-1} (—CH_3); MS, m/e (relative intensity) 175 (44.8, M^+ + 1), 174 (100, M^+·), 173 (32.7, M^+ − 1), 159 (27.5, M^+ − 15), 145 (58.6, M^+ − 29), 134 (82.7, M^+ − 40); Anal. Calcd. for $C_{11}H_{10}O_2$: C, 75.86; H, 5.74, Found: C, 76.01; H, 5.62.

Condensation of 2,6-dimethylchromone (III) with aromatic aldehydes; Formation of 2-styryl-6-methyl chromone (IVa-e):

0.01 mole of 2, 6-dimethylchromone was dissolved in a small quantity of ethanol (20 ml.) and treated at room temperature with an alcoholic solution of sodium ethoxide (0.2 gm. of sodium metal in 10 ml. of absolute ethanol). The appropriate aldehyde (0.01 mole) was then added and the reaction mixture was stirred for 10 minutes, then left to stand at room temperature for 24 hrs. The condensation product was filtered off and crystallized from ethanol to give 2-styryl-6-methyl chromones (IV*a-e*). (cf. Table 2).

Table 2
Physical data of 2-styryl-6-methyl chromones (IV*a-e*)

Compound	m.p. °C	Formula (M. Wt.)	% Yield		Analysis % Calcd.	Found
IV*a*	133-35	$C_{18}H_{14}O_2$ (262)	82	C	82.44	83.01
				H	5.34	5.74
IV*b*	156-58	$C_{19}H_{16}O_3$ (292)	76	C	78.08	78.11
				H	5.47	5.60
IV*c*	189-91	$C_{18}H_{13}ClO_2$ (296.5)	80	C	72.84	73.10
				H	4.38	4.66
IV*d*	143-45	$C_{16}H_{12}O_2S$ (268)	63	C	71.64	72.01
				H	4.47	4.70
IV*e*	160-62	$C_{16}H_{12}O_3$ (252)	65	C	76.19	76.61
				H	4.76	5.01

The IR spectra of compounds (IV*a-e*) exhibit strong absorption bands at 1090-1130, 1610-1615, 1628-1640, 2930 and 3060-3090 cm^{-1} which is attributable to >C= O pyrone, C = C, —O—, —CH_3 and —CH trans respectively. Compound IVb has the following spectra:

^1H NMRδ (in ppm) 2.42 (s, 3H), 3.83 (s, 3H), 6.30 (s, 1H), 6.50-6.78 (d, 1H), 6.82-7.10 (d, 1H), 7.40-8.00 (m, 7H); MS, m/e (relative intensity) 293 (50, M^+ + 1), 292 (87.5, M^+ ·), 291 (81.25, M^+ − 1), 277 (48.5, M^+ − 15), 276 (68.7, M^+ − 16), 185 (53, M^+ − 107), 159 (100, M^+ − 133).

Thiation of 6-bromo-7,8-benzo-2-methyl chromone (I); Formation of 6-bromo-7,8-benzo-2-methyl-4-thiochromone (V):

A mixture of chromone (I) (1 gm.) and phosphorous pentasulphide (1 gm.) was refluxed in dry benzene (50 ml.) for 2 hrs. The reaction mixture was filtered off while hot, left to cool at room temperature and the red solid that deposited was collected and crystallized from toluene to give (V) (93% yield).

It has the following properties: m.p. 233-234°C; IRυ 1180 cm^{-1} (—O—); 1360 cm^{-1} (C = S), 1610 cm^{-1}, (C= C), MS, m/e (relative intensity) 306 (66.6, M^+ + 1), 305 (18.2, M^+·), 304 (72.7, M^+ − 1), 225 (13.6, M^+ − 80), 197 (16.6, M^+ − 108), 55 (84.8), 41 (100); Anal. Calcd. for $C_{14}H_9BrOS$: C, 55.08; H, 2.95. Found: C, 54.93; H, 2.88.

Condensation of 6-bromo-7,8-benzo-2-methyl-4-thiochromone (V) with aromatic aldehydes; Formation of (VIa-d):

A mixture of thiochromone (V) (0.005 mole), dimethyl formamide (20 ml.) and an equimolecular amount of the appropriate aldehyde was treated with 4 drops of piperidine and heated for 4 hrs. on a water bath, the condensation products were separated upon cooling, and crystallized from dimethyl formamide to give the styryl derivatives (VIa-d) as dark violet crystals (cf. Table 3).

Table 3
Physical data of 2-styryl-6-bromo-7,8-benzo-4-thiochromone (VI*a-d*)

Compound	m.p.°C	Formula (M. Wt.)	% Yield		Analysis % Calcd.	Found
VI*a*	235-37	$C_{19}H_{11}BrOS_2$ (399)	61	C	57.14	56.86
				H	2.75	2.76
VI*b*	272-74	$C_{25}H_{15}BrOS$ (443)	43	C	67.72	67.38
				H	3.38	3.38
VI*c*	244-46	$C_{23}H_{17}BrO_3S$ (453)	52	C	60.42	59.98
				H	3.75	3.75
VI*d*	272-73	$C_{21}H_{12}BrClOS$ (427.5)	75	C	58.94	58.72
				H	2.80	3.05

The IR spectra of compounds (VI*a-d*) exhibit well defined absorption bands at 1360-1350, 1620-1610, 1120-1110 and 3040-3020 cm^{-1} which were attributable to C = S, C = C, —O— and CH— trans respectively.

Compound (VI*a*) has the following spectra: ^1H NMRδ (in ppm) 6.85 (s, 1H), 7.10-7.21 (d, 1H), 7.27-7.35 (d, 1H), 7.65-8.40 (m, 8H); MS, m/e (relative intensity) 400 (54.5, M^+ + 1), 399 (44, M^+·), 398 (53, M^+ − 1), 367 (21.2, M^+ − 32), 319 (11, M^+ − 80), 290 (13, M^+ − 109), 266 (27. 2, M^+ − 133), 134 (30.3), 113 (48.5), 70 (54.5), 41 (100).

Diels-Alder adducts of 2-styryl chromones (IIa,c) with N-phenylmaleimide; Formation of (VII a,b):

A mixture of 2-styrylchromones (0.002 mole), N-phenylmaleimide (0.004 mole) and dry xylene (20 ml.) was refluxed for 15 hrs. The solid deposited after cooling was filtered off and crystallized from dioxane to give the desired adducts (VII*a, b*). (cf. Table 4).

Table 4
Reaction products of 2-styryl chromones (II*a,c*) with N-phenylmaleimide; Formation of (VII*a,b*).

Compound	m.p.°C	Formula (M. Wt.)	% Yield		Analysis % Calcd.	Found
VII*a*	289-91	$C_{29}H_{18}BrNSO_4$ (556)	35	C	62.58	61.31
				H	3.23	3.41
				N	2.51	2.74
VII*b*	326-28	$C_{31}H_{19}BrNClO_{10}$ (584.5)	42	C	63.64	64.02
				H	3.25	3.32
				N	2.39	2.58

The IR spectra of compounds (VII *a,b*) show characteristic bands at 1740-1730 and at 1660-1650 cm^{-1} which appear as doublet due to >C = O imide, >C = O pyrone at 1650-1630 cm^{-1} and C= C at 1600 cm^{-1}.

Action of primary aliphatic amines on 6-bromo-7,8-benzo-2-methylchromone (I); Formation of (VIII a,b):

A mixture of 6-bromo-7,8-benzo-2-methyl chromone (I) (2 gm.) in dimethyl formamide (20 ml.) and the appropriate amine, ethylamine and/or n-butylamine was refluxed for 3 hrs. on a steam bath, and kept overnight at room temperature. The yellow solid that separated was filtered off and crystallized from light petrol (b.p. 100-120°C) to give compounds (VIII *a,b*). They gave a green colour with alcoholic ferric chloride solution. (cf. Table 5).

Table 5
Action of aliphatic amines on (I); Formation of (VIII *a,b*).

Compound	m.p.°C	Formula (M. Wt.)	% Yield		Analysis % Calcd.	Found
VIII*a*	164-65	$C_{16}H_{16}BrNO_2$ (334)	64	C	57.48	57.09
				H	4.79	4.75
				N	4.19	3.95
VIII*b*	103-104	$C_{18}H_{19}BrNO_2$ (361)	58	C	59.85	60.02
				H	5.26	5.45
				N	3.88	3.93

Compounds (VIII*a,b*) show the following IR spectra (υ): 1600-1610 cm^{-1} (C = C), 1675-1689 cm^{-1} (C = O), 3240 cm^{-1} (N—H), 3300-3450 cm^{-1} (O — H); Compound (VIII *a*) has the following spectra: ^1H NMRδ (in ppm) 1.25 (t, 3H), 2 (s, 3H), 3.28 (p, 2H), 5.52 (s, 1H), 7.30-8.30 (m, 5H); MS, m/e (relative intensity).335 (58.7, $M^+ + 1$), 334 (39, $M^{+\cdot}$), 333 (45, $M^+ - 1$), 319 (37, $M^+ - 15$), 290 (35, $M^+ - 44$), 196 (39, $M^+ - 138$), 86 (100), 71 (52).

Reaction of 2,6-dimethylchromone (III) with primary aliphatic amines; Formation of (IXa-c):

0.006 mole of the chromone (III) (1.04 gm.) was dissolved in 25 ml. of ethanol, then 0.04 mole of aliphatic amine was added. The solution was refluxed on a water bath for 3 hrs. The solid that obtained upon cooling was filtered off, dried, and crystallized from ethanol to give products (IX*a-c*), (cf. Table 6).

Table 6
Physical data of the products (IX*a-c*).

Compound	m.p.°C	Formula (M. Wt.)	% Yield		Analysis % Calcd.	Found
IX*a*	122-23	$C_{13}H_{17}NO_2$ (219)	76	C	71.23	71.62
				H	7.76	8.08
				N	6.39	7.01
IX*b*	85-86	$C_{15}H_{21}NO_2$ (247)	74	C	72.87	73.09
				H	8.50	9.03
				N	5.66	6.08
IX*c*	124-25	$C_{18}H_{19}NO_2$ (281)	69	C	76.86	76.41
				H	6.76	6.15
				N	4.98	5.14

Compounds (IX*a-c*) show the following IR spectra (υ): 1600-1610 cm^{-1} (C = C), 1675-1680 cm^{-1} (C = O), 3250 cm^{-1} (N−H), 3450 cm^{-1} (O − H), Compound (IX *c*) has the following spectra: ^1H NMRδ (in ppm) 2.16 (s, 3H), 2.30 (s, 3H) 4.6 (d, 2H), 5.8 (s,1H), 6.75-7.58 (m, 8H); MS, m/e (relative intensity) 282 (37.3, $M^+ + 1$), 281 (71.1, $M^{+\cdot}$), 264 (57.7, $M^+ - 19$), 175 (48.8, $M^+ - 106$), 147 (66.6, $M^+ - 134$), 107 (48.8), 92 (100).

Action of hydrazine hydrate on 2,6-dimethylchromone (III); Formation of (XIVa):

To a solution of the chromone (III) (0.0025 mole) in ethanol (20 ml.), a solution of hydrazine hydrate (excess 2.5 gm.) in warm ethanol (15 ml.) was added. The reaction mixture was heated for 15 min., cooled, diluted with water and the solid which separated was crystallized from light petrol (b.p. 100-120°C) to give the pyrazole derivative (XIV*a*) (78% yield).

It has the following properties: m.p. 105-107°C; IRυ: 1600-1620 cm^{-1} (C = C) , 1625-1640 cm^{-1} (C = N), 3400-3450 cm^{-1} (O−H); Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.21; H, 6.38; N, 14.89. Found: C, 70.61; H, 6.81; N, 14.91.

Action of phenylhydrazine hydrochloride on 2,6-dimethylchromone (III); Formation of (XIVb):

A mixture of the chromone (III) (0.0025 mole), pyridine (10 ml.) and phenylhydrazine hydrochloride (0.003 mole) in water (3 ml.) was refluxed for 4 hrs. The cooled mixture was acidified with dilute acetic acid and the product filtered off to give the pyrazole derivative (XIV*b*) which crystallized from light petrol (b.p. 100-120°C) (68% yield).

It has the following properties: m.p. 178-179°C; IRυ: 1600-1620 cm^{-1} (C=C), 1625-1640 cm^{-1} (C = N), 3400-3450 cm^{-1} (O−H); ^1H NMR δ (in ppm) 2.18 (s, 3H), 2.38 (s, 3H), 6.3 (s, 1H) 6.72-7.28 (m, 8H); MS, m/e (relative intensity) 264 (100, $M^{+\cdot}$), 263 (52, $M^+ - 1$), 249 (37.5, $M^+ - 15$), 247 (40, $M^+ - 17$), 235 (35.5, $M^+ - 29$), 118 (36), 92 (40), 78 (42); Anal. Calcd. for

$C_{17}H_{16}N_2O$: C, 77.27; H, 6.06; N, 10.60. Found: C, 87.38; H, 6.36; N, 11.08.

Action of semicarbazide hydrochloride and thiosemicarbazide on the chromone (III); Formation of (XIV c,d):

A mixture of the chromone (III) (0.0025 mole), pyridine (10 ml.) and semicarbazide hydrochloride or thiosemicarbazide (0.003 ml.) in water (3 ml.) was refluxed for 4 hrs. The solid that was obtained upon cooling was filtered off and crystallized from ethanol to give the products (XIV *c, d*) respectively, (cf. Table 7).

Table 7
Physical data of the products (XIV *c,d*).

Compound	m.p.°C	Formula (M. Wt.)	% Yield		Analysis % Calcd.	Found
XIV*c*	251-52	$C_{12}H_{13}N_3O$ (215)	62	C	66.97	66.70
				H	6.04	6.23
				N	19.53	19.72
XIV*d*	176-77	$C_{12}H_{13}N_3S$ (231)	60	C	62.33	62.21
				H	5.62	5.71
				N	18.18	18.07

The IR spectra of (XIV) exhibit strong absorption bands at 1600-1620, 1625-1640 and 3400-3450 cm^{-1} which was attributable to C = C, C = N and O − H respectively.

Action of hydroxylamine hydrochloride on 2,6-dimethylchromone (III); Formation of (XV):

A mixture of the chromone (III) (0.0025 mole), pyridine (10 ml.) and hydroxylamine hydrochloride (excess 0.06 mole) in water (5 ml.) was refluxed for 4 hrs. The cooled mixture was acidified with dilute acetic acid and the solid deposited was filtered off and crystallized from toluene to give the isoxazole derivative (XV) (74%, yield).

It has the following properties: m.p. 184-185°C; IRυ: 1605 cm^{-1} (C = C), 1620 cm^{-1} (C = N), 3450 cm^{-1} (O − H); ^{1}H NMRδ (in ppm) 2.44 (s, 3H), 2.48(s, 3H), 6.62 (s, 1H), 6.8-7.6 (m, 3H); MS, m/e (relative intensity) 189 (100, $M^{+\cdot}$), 188 (47, $M^+ - 1$), 160 (45.5, $M^+ - 29$), 134 (61.5, $M^+ - 55$), 118 (70.5, $M^+ - 71$), 91 (64.5), 55 (76.5); Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.84; H, 5.82; N, 7.40. Found: C, 70.12; H, 6.06; N, 7.24.

Reaction of 2,6-dimethylchromone (III) with malononitrile:

A. Formation of (XVI):

A mixture of the chromone (III) (0.01 mole), malononitrile (0.01 mole) and acetic anhydride (25 ml.) were heated under reflux for one hour. The mixture was left to cool. The excess of acetic anhydride was aspirated off and the residue was washed with (50 ml.) of hot water, then crystallized from ethanol to give (XVI) (78% yield).

It has the following properties: m.p. 176-177°C; IRυ: 1140 cm^{-1} (—O—), 1640 cm^{-1} (C = C), 2210 cm^{-1} (C ≡ N), 2865-3000 cm^{-1} (—CH_3); ^{1}H NMRδ (in ppm) 2.44 (s, 3H), 2.46 (s, 3H), 6.68 (s, 1H), 7.30-7.64 (m, 3H); Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.67; H, 4.50; N, 12.61. Found: C, 76.02; H, 4.41; N, 12.50.

B. Formation of (XVII):

A mixture of the chromone (III) (0.01 mole), malononitrile (3 ml.) in ethanol (25 ml.) and piperidine (3 ml.) was refluxed for 4 hrs. The solid that obtained upon cooling was filtered off and crystallized from dimethylformamide to give (XVII) (67% yield).

It has the following properties: m.p. 355-357°C; IRυ: 1120 cm^{-1} (—O—), 1580-1640 cm^{-1} (C = C), 2200 cm^{-1} (C ≡ N), 2820 cm^{-1} (—CH_3), 3280-3330 cm^{-1} (—NH_2); Anal. Calcd. for $C_{17}H_{12}N_4O$: C, 70.83; H, 4.16; N, 19.44. Found: C, 70.71; H, 4.27; N, 19.20.

Reaction of 6-bromo-7,8-benzo-2-methylchromone (I) with malononitrile; Formation of (XX):

A mixture of chromone (I) (0.01 mole), malononitrile (3 ml.) in ethanol (25 ml.) and piperidine (3 ml.) was refluxed for 4 hrs. The solid that separated upon cooling was filtered off and crystallized from dimethylformamide to give (XX) (65% yield).

It has the following properties: m.p. 355°C; IRυ: 1100 cm^{-1} (—O—), 1600-1610 cm^{-1} (C = C), 2220 cm^{-1} (C ≡ N), 2940-2980 cm^{-1} (—CH_3), 3200-3340 cm^{-1} (—NH_2); MS, m/e (relative intensity) 405 (71.5, $M^+ + 2$), 403 (72, $M^{+\cdot}$), 374 (24, $M^+ - 29$), 323 (38, $M^+ - 80$), 282 (33, $M^+ - 121$), 244 (30), 232 (49), 220 (53.5), 182 (100), 170 (96), 132 (91.5), 120 (90.5), 102 (56); Anal. Calcd. for $C_{20}H_{11}BrN_4O$: C, 59.55; H, 2.72; N, 23.89. Found C, 60.07; H, 2.61; N, 13.72.

Action of thionyl chloride on 2,6-dimethylchromone (III); Formation of (XXI):

The chromone (III) (0.02 mole, 3.48 gm.) was dissolved freely in benzene (50 ml.), then thionyl chloride (0.08 mole, 7 ml.) was added and the reaction mixture was refluxed for 3 hrs. on a water bath. The solid obtained after concentration under fuming cupboard was collected and crystallized from dimethylformamide to give (XXI) (85% yield).

It has the following properties: m.p. 300°C; IRυ: 1180 cm^{-1} (—O—), 1605 cm^{-1} (C = C), 1640 cm^{-1} (C = O); Anal. Calcd. for $C_{11}H_7Cl_3O_2$: C, 47.46; H, 2.52. Found: C, 47.81; H, 2.37.

Reaction of 2,6-dimethylchromone (III) with ethyl oxalate; Formation of pyruvic ester derivatives (XXII):

To a mixture of the chromone (III) (0.007 mole) and ethyl oxalate (0.003 mole) in dry ether (75 ml.) was added sodium metal (0.6 gm. pellets). After stirring, a vigorous reaction took place. The reaction was left 1 hr. for completion then stoppered and left overnight at room temperature. Acidification with dilute acetic acid gave the pyruvic ester derivative (XXII), which crystallized from dimethylformamide (87% yield).

It has the following properties: m.p. 218-220°C; IRυ: 1620 cm^{-1} (C = C), 1660 cm^{-1} (C = O Chromone), 1750 cm^{-1} (C = O ketoester), 1420, 2980 cm^{-1} (CH_2 — C), 3440 cm^{-1} (O− H); ^{1}H NMRδ (in ppm) 0.82 (t, 3H), 2.00 (s, 3H), 3.36 (s, 2H), 3.98 (q, 2H), 7.2 (s, 1H), 7.24-7.64 (m, 3H); Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.11. Found: C, 66.01; H, 5.03.

Hydrolysis of the pyruvic ester (XXII) to 5-methylsalicylic acid (XXIII):

Pyruvic ester derivative (XXII) (0.005 mole) was refluxed for 4 hrs. in (30 ml.) of 10% aqueous potassium hydroxide. The cold

solution was poured into dilute hydrochloric acid, and the solid that separated out was filtered off and crystallized from light petrol (b.p. 60-80°C) to give 5-methylsalicylic acid (XXIII) (97% yield) as colourless crystalline solid. It gave positive acidity test and deep violet colouration with aqueous ferric chloride.

It has the following properties: m.p. 150-151°C; Anal. Calcd. for $C_8H_8O_3$: C, 63.15; H, 5.26. Found: C, 63.41; H, 5.07.

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