Some Reactions of 6-Chloro-2-Methyl 4H-1-Benzopyran-4-one (Part II)

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Summary: 6-Chloro-2-methyl-4-H-1-benzopyran-4-one (1) gave the isoxazole derivative (2a) on reaction with hydroxylamine hydrochloride. The action of hydrazine and phenylhydrazine on (1) resulted in pyrazole derivatives (3a) and (3b) respectively. The reactivity of (1) with ethyloxalate and aromatic nitroso compounds have been investigated. Phthalide (8a) derived from the chromone (1) was synthesised and rearranged easily into 1,3-indandione (9) upon refluxing with alcoholic sodium methoxide. Cleavage of (8) with amines and hydrazine hydrate was studied. Thiation of phthalide (8a) with either Lawesson's reagent or phosphorous pentasulphide yielded the corresponding thione (8e)

Introduction

Reaction of 6-chloro-2-methyl-4H-1-benzopyran-4-one (1) with excess of hydroxylamine hydrochloride took place through fission of the pyrone ring and resulted in the formation of the corresponding isoxazole derivative (2a) which was assumed to have the structure (A) or (B). The differentiation between the two formulae appears difficult. Benzoylation of (2a) yielded (2b). In the same way chromone (1) reacted with hydrazines namely; hydrazine hydrate and/or phenylhydrazine to give the pyrazole derivatives (3a) and (3b) respectively.

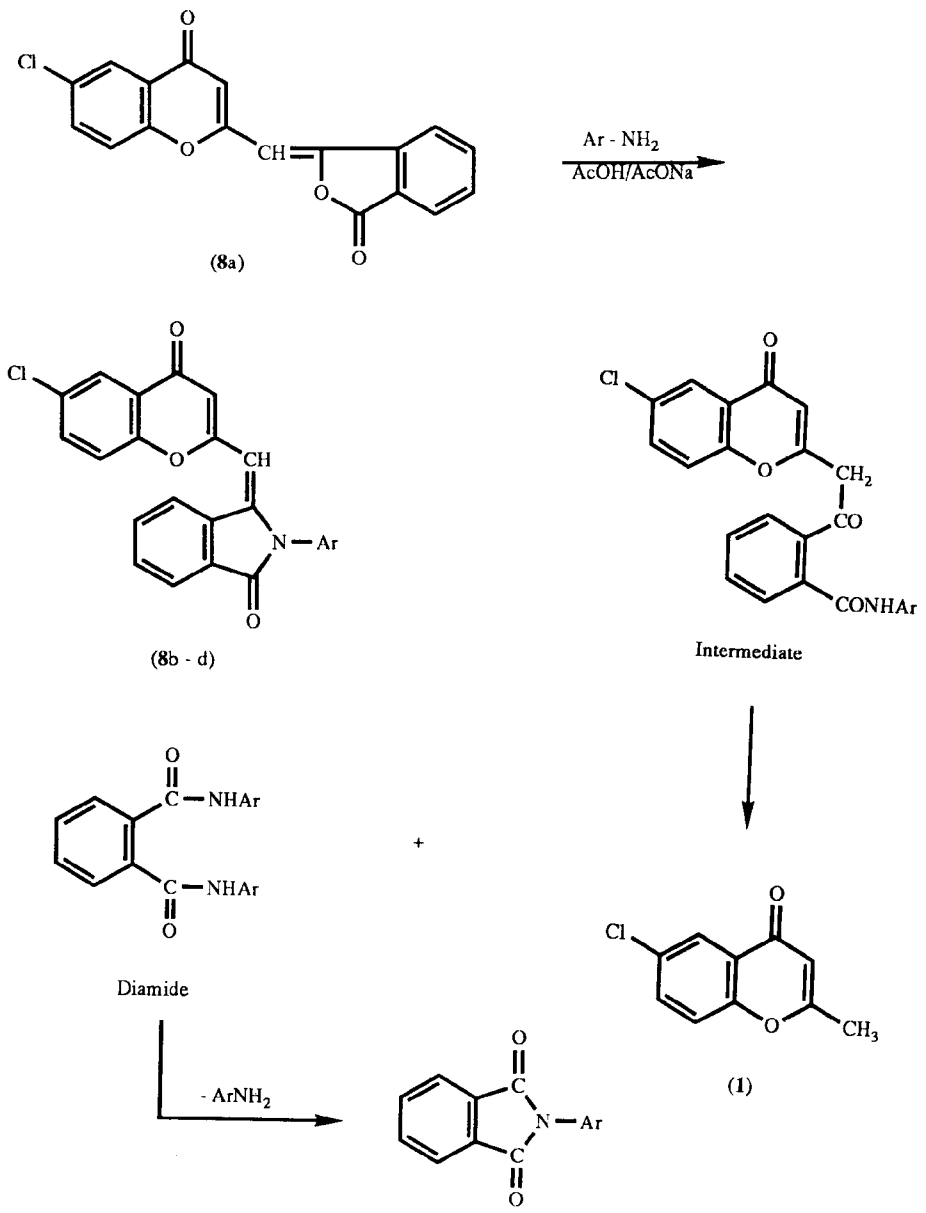
Treatment of (3a) with benzoyl chloride gave the monobenzoyl derivative (3c) and/or dibenzoyl derivative (3d) depending on the conditions of the reaction.

Ethyloxalate reacted with the chromone (1) in the presence of sodium metal to give the corresponding pyruvic ester (4a) which exists as keto-enol tautomers [1,2]. The oxo form is the predominant structure of (4a) this result was concluded via the fusion of the pyruvic ester (4a) with benzaldehyde in presence of piperidine to give the corresponding chalcone analogue (4b) while hydrolysis of (4a) by 10% KOH gave 5-chlorosalicylic acid.

Treatment of chromone (1) with nitroso aromatic compounds namely, nitrosobenzene and p-nitroso-N,N-dimethylaniline in presene of sodium ethoxide gave α-(2'-chromonyl) nitrone derivatives (5a) and (5b) respectively. The reaction occurs through the active methyl group in the 2-position of chromone nucleus. The behaviour of nitrone derivative (5b) towards some nucleophilic reagents such as hydrazine hydrate and hydroxylamine hydrochloride has been investigated and found to yield the product (6a) and (6b) respectively. Also (5b) reacts as a diene under Diels-Alder reaction conditions with N-phenylmaleimide to give the expected adduct (7).

When 6-chloro-2-methylchromone (1) was allowed to react with phthalic anhydride at elevated temperature in the presence of sodium acetate, it yielded 2-(3'-phthalidenemethylene)-6- chlorochromone (8a) which rearranged readily under the influence of alcoholic sodium methoxide to afford the corresponding 1,3- indandione, 2-(6-chloro-2'-chromonyl)-1,3-indandione (9). While the alkaline hydrolysis of (8a) gave 5-chlorosalicyclic acid.

Aromatic and aliphatic amines namely; aniline, p-toluidine and benzylamine reacted with (8a) in boiling acetic acid-sodium acetate mixture (1:1 molar ratio) to give a mixture of N-arylphthalimidine derivatives (8b-d), N-arylphthalimides and the starting 6-chloro-2-methylchromone (1). This result is explained via the formation of ω-(2-chromonyl)-2-arylcarboxyamide acetophenone as an intermediate which is easily converted into chromone (1) and diamide deriva-



tive, the latter was cyclised with deamination to give N-arylphthalimides as isolated products.

Aromatic amines namely; aniline and p-toluidine reacted with (**8a**) in boiling n-butanol (2:1 molar ratio) to give N-arylphthalimide together with chromone (**1**). The previous explanation can also be used to interpret the formation of the above products. With more basic amines namely; benzylamine in boiling ethanol the phthalide (**8a**) underwent complete cleagave to give N,N-dibenzylphthalamide together with 4-chloro-2-(β-benzylamino-crotonyl) phenyl (**10**). The reaction of hydrazine hydrate with (**8a**) depends on the temperature at which the reaction was conducted. At room temperature, (**8a**) reacted with hydrazine hydrate in ethanol to give the phthalazinone derivative (**11**) which probably exists in a lactam-lactim dynamic equilibrium. In boiling ethanol hydrazine hydrate reacted with (**8a**) in similar way to its reaction with aliphatic amines and gave a mixture of 1,4-phthalazindione and 3-methyl-5-(5'-chloro-2'-hydroxy-phenyl or 5-methyl-3-(5'-chloro-2'-hydroxyphenyl) pyrazoles (**3a**) [3]. In both cases the for-

mation of these two products could be explained by the complete cleavage of (8a) to phthalic anhydride and chromone moieties. Both moieties react with the reagent to yield the above products. Also, the differentiation between the two isomeric formulae given for the pyrazole derivatives (3a) appears difficult. Alkaline hydrolysis of (8a) gave 5-chlorosalicylic acid. Thiation of the phthalide (8a) was carried out by the use of either 2,4-bis (4'-methoxyphenyl) 1,3,2,4-dithiadiphosphetane-2,4-disulphide (Lawesson's reagent) [4] or phosphorous pentasulphide to give 2-(3'-phthalidenemethylene)-6-chlorocromen-4-thione (8e). The former reagent has the advantage of high yield of the product and time saving.

The structures of the new synthetic products were elucidated and confirmed by elemental analysis, infrared spectra, ^{1}H and ^{13}C- nuclear magnetic resonance spectral data listed in Tables 1 and 2 [5,6].

Experimental

Melting points reported are uncorrected. IR spectra in KBr were recorded on a Beckman IR-20 spectrophotometer and Pye Unicam SP 3-300 spectrophotometer. The ^{1}H-NMR spectra were determined on a Varian T-60 or Jeol FX 90 spectrometer. In all NMR experiments the internal standard was TMS and the solvent was $CDCl_3$. All chemical shifts are in ppm downfield from TMS. The ^{13}C-NMR spectra were determined on a Jeol FX 90 Q fourier Transform instrument operating at 22.50 MHz, 8192 data points were collected and a sweep width of 5000 Hz, i.e. digital resolution of 0.6 Hz (0.03 ppm). Pulse intervals of 5 seconds or more were used to achieve resonable signal-to-noise ratios especially for the signals of carbons of long relaxation times, e.g., C=O and C=N.

The physical data of the new synthesised products are listed in Table 1 while the spectral data listed in Table 2.

Reaction of excessive hydroxylamine hydrochloride with chromone (1); Formation of 3-methyl-5-(5'-chloro-2'-hydroxyphenyl) isoxazole or 5-methyl-3(5-chloro-2'-hydroxyphenyl) isoxazole (2a)

A solution of hydroxylamine hydrochloride (0.4 mol, 2.4 g., assay 96%) in distilled water (4 ml.) was added to a solution of chromone 1 (0.01 mole, 1.9 g) in pyridine (40 ml.). The reaction mixture was heated under reflux for 4 hrs. The cold mixture was diluted with cold water and the solid that precipitated was filtered off and crystallized from the proper solvent to give isoxazole derivative (2a).

Benzoylation of (2a); Formation of (2b)

To a solution of (2a) (1 g.) in 10% aqueous sodium hydroxide (20 ml.) benzoyl chloride (1.2 g; 1 ml.) was added. The mixture was vigorously shaked for 45 minutes. The solid was separated out and crystallized from the suitable solvent to yield the benzoylated product (2b).

Action of excessive hydrazine on chromone (1); Formation of (3a) and (3b)

To a solution of 1 (0.01 mol; 1.9 g) in ethanol (30 ml.), hydrazine hydrate and/or phenylhydrazine (10 g.) in warm ethanol (20 ml) was added. After adding few drops of glacial acetic acid, the reaction mixture was heated under reflux for 4 hrs, cooled, diluted with water and the solid that separated out was collected and crystallised from the proper solvent, to give the products (3a) and (3b) respectively.

Benzoylation of (3a); Formation of (3c,d)

(A) Monobenzoyl derivative (3c)

A mixture of (3a) (1g.) in pyridine (10 ml.) and 0.5 g. of benzoyl chloride (1:1 mol.) was heated on a water bath for 2 hrs. the cooled mixture was poured into cold dilute hydrochloric acid and the solid which deposited was filtered off, washed with water, dried and crystallized from the proper solvent to give the monobenzoylated product (3c)

Dibenzoyl derivative (3d)
Method (i)

To a solution of (3a) (1 g.) in pyridine (20 ml.) 1g. of benzoyl chloride was added (1:2 mol) and the reaction mixture was heated on a water bath for 2 hrs, left overnight at room temperature and poured into diluted hydrochloric acid. The solid mixture that precipitated was collected and fractionally crystallised from light petrol (80-100°C) to give (3d) in a minute yield then from ethanol to give (3c) respectively.

Table 1: Physical data of new synthesised products

Compd. No.	M.p.°C (colour)	Solvent of crystallisation	M.P. (M.W.)	Analysis Calcd./Found C%	H%	N%
1	139-140 (Deep purple)	Benzene + L.P (80-100°C) (92)	$C_{10}H_7ClOS$ (210.5)	57.00 56.98	3.32 3.41	
2a	241-242 (Colourless)	Benzene + Ethanol (91)	$C_{10}H_8ClNO_2$ (209.5)	57.28 57.40	3.82 3.65	6.68 6.70
2b	122-123 (Colourless)	Ethanol (75)	$C_{17}H_{12}ClNO_3$ (314.5)	64.86 64.69	3.81 3.73	4.45 4.42
3a	166-167 (Colourless)	B + L.P(80-100°C) (23)	$C_{10}H_9ClN_2O$ (208.5)	57.55 57.80	4.32 4.29	13.43 13.58
3b	173-174 (Pale yellow)	B + L.P(80-100°C) (78)	$C_{16}H_{13}ClN_2O$ (284.5)	67.48 67.41	4.56 4.63	9.84 9.92
3c	160-161 (Colourless)	Aqeuous ethanol (83)	$C_{17}H_{13}ClN_2O_2$ (312.5)	65.28 65.30	4.16 4.15	8.96 8.94
3d	117-119 (Colourless)	L.p(80-100°C) (86)	$C_{24}H_{17}ClN_2O_3$ (416.5)	69.14 69.26	4.08 4.10	6.72 6.70
4a	225-226 (Bright yellow)	Ethyl acetate (88)	$C_{14}H_{11}ClO_5$ (294.5)	57.04 56.98	3.73 3.68	-
4b	273-274 (Intense yellow)	L.p(80-100°C) Benzene (57)	$C_{21}H_{15}ClO_5$ (382.5)	65.88 65.70	3.92 3.94	
5a	199-200 (Deep brown)	Benzene + Ethanol (52)	$C_{16}H_{10}ClNO_3$ (299.5)	64.10 63.95	3.33 3.28	4.67 4.80
5b	220-221 (decomp.) (Deep orange)	Butan-1-ol (66)	$C_{18}H_{15}ClN_2O_3$ (342.5)	63.06 63.28	4.37 4.48	8.17 8.16
6a	248-249 (Greenish-) brown	Butan-1-ol (28)	$C_{18}H_{17}ClN_4O$ (340.5)	63.40 63.62	4.98 4.78	16.40 16.28
6b	260-263 (decomp.) (Brown)	Benzene (32)	$C_{18}H_{16}ClN_3O_2$ (341.5)	63.02 63.00	4.70 4.68	12.30 12.49
7	130-132 (decomp.) (Intense brown)	Ethyl acetate (71)	$C_{28}H_{21}ClN_3O_4$ (498.5)	67.40 67.72	4.20 4.18	8.40 8.32
8a	318-319 (Brownish-(yellow)	Anisole (59)	$C_{18}H_9ClO_4$ (324.5)	66.56 66.47	2.77 - 2.83	
8b	268-269 (Yellow)	Dil acetic acid (72)	$C_{24}H_{14}ClNO_3$ (399.5)	72.09 72.21	3.50 3.44	3.50 3.63
8c	288-290 (Yellow)	Acetic acid (80)	$C_{25}H_{16}ClNO_3$ (413.5)	72.55 72.84	3.86 3.79	3.38 3.40
8d	228-230 (Yellow)	Ethanol (75)	$C_{25}H_{16}ClNO_3$ (413.5)	72.55 72.83	3.86 3.80	3.38 3.34
8e	289-290 (Brick-red	Anisole (84)	$C_{18}H_9ClO_3S$ (340.5)	63.44 63.26	2.64 2.58	-
9	>360°C (Golden) yellow)	Pyridine (83)	$C_{18}H_9ClO_4$ (324.5)	66.56 66.20	2.77 2.83	
10	154-155 (Yellow)	L.p(100-120°C) (61)	$C_{17}H_{16}ClNO_2$ (301.5)	67.66 68.13	5.30 5.36	4.64 4.55
11	303-304 (Pale yellow)	Ethanol (47)	$C_{18}H_{11}ClNO_2O_3$ (338.5)	63.8 63.74	3.24 3.28	8.27 8.31

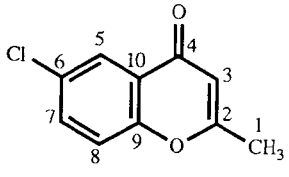
Table 2: Spectral data of new synthesised products

Compd. No.	IR spectra (KBr) ν(cm^{-1})		^{1}H-NMR δ-value	No. of H (spliting)	Group
1	1680	C=O pyrone	3.38	3H(s)	-CH_3
	1610	C=C	6.1	1H(s)	-CO-CH=C
	1150	-O-	7.3-7.6	3H(m)	aromatic
	2870	-CH_3			protons
2a	1620	C=N			
	1605	C=C			
	3450	OH	- -	- -	- -
	(intramolecular)				
	no C=O of chromone				
2b	1720	C=O of ester	2.14	3H(s)	-CH_3
	1625	C=N	6.25	1H(s)	Olefinic proton of isoxazole ring.
	1605	C=C	7.34-8.72	8H(m)	Ar-protons
		no ν OH			
3a	1620	C=N			
	1600	C=C			
	3180	NH			
	3450	OH	- -	- -	- -
	no ν C=O chromone				
	no ν C=O lactone				
3b	1625	C=N			
	1600	C=C	- -	- -	- -
	3430	OH			
	no ν C=O chromone				
3c	1680	C=O			
	1620	C=N			
	1600	C=C	- -	- -	- -
	3480	-OH			
3d	1735	C=O ester	2.74	3H(s)	-CH_3
	1665	C=O	6.56	1H(s)	olefinic proton of pyrazole.
	1625	C=N			
	1605	C=C			
			6.92-8.0	13H(m)	Ar protons.
4a	1730	α-keto ester			
	1640	C=O chromone			
	1615	C=C			
	2980, 1420	-CH_2-C=O	- -	- -	- -
	3430	chelated			
	intramolecular H-bonded				
		-OH			
4b	1740	C=O ester	1.4-1.65	3H(t)	-CH_3
	1640	C=O chromone	4.2-4.4	2H(q)	-CH_2-
	1610	C=C	5.62	1H(s)	olefinic proton of pyrone ring.
	1090	-O-	6.24	1H(s)	-C = CH-
			7.6-8.35	8H(m)	aromatic protons
5a	1640	C=O chromone			
	1620	C=N			
	1600	C=C			
	1320, 970	N→O	- -	- -	- -
	1120	-O-			
5b	1645	C=O chromone			
	1615	C=N			
	1600	C=C	- -	- -	- -
	1360, 940	N→O			
	1080	-O-			

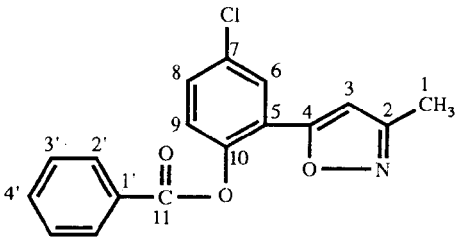
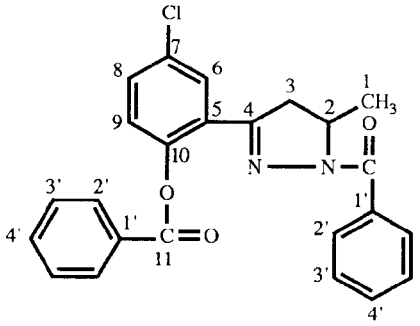
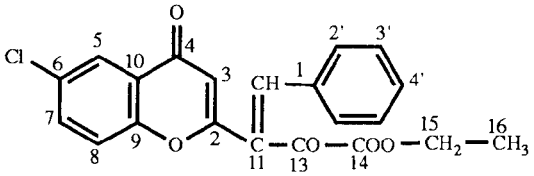
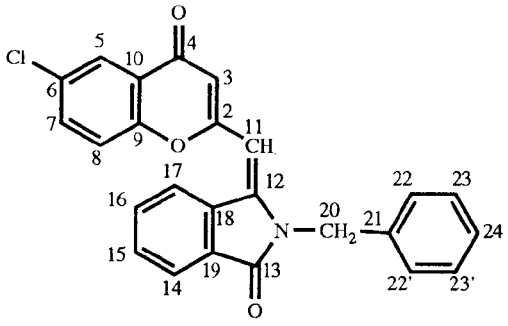
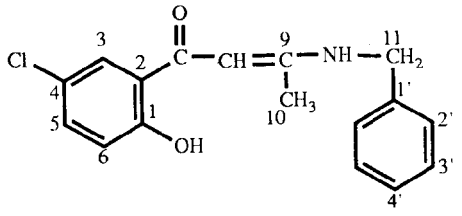
Table 2: Condt.,

Compd. No.	IR spectra (KBr) $\nu(cm^{-1})$		δ-value	^{1}H-NMR No. of H (spliting)	Group
6a	1610	C=N			
	1600	C=C			
	3180	-NH	– –	– –	– –
	3260 (broad)	intramolecular -OH (broad)			
6b	1610	C=N			
	1590	C=C	– –	– –	– –
	3170	-NH			
	3280	intramolecular -OH (broad)			
7	1720 }				
	1670 }	C=O imide	– –	– –	– –
	1645	C=O chromone			
	1605	C=C			
	1130	-O-			
8a	1810	C=O lactone			
	1650	C=O chromone	– –	– –	– –
	1610	C=O			
	1130	-O-			
8b	1720-1710	C=O	– –	– –	– –
8c	1660-1640	C=O chromone	– –	– –	– –
8d	1615-1605	C=C	5.1	2H(s)	$-CH_2$
			5.9	1H(s)	-CH=C- of pyrone ring.
			6.4	1H(s)	oxo CH=C-
			7.3-8.2	12H(m)	Ar protons.
8e	1790	C=O lactone			
	1610	C=C			
	1350	C=S	– –	– –	– –
	1170	-O-			
	no C=O chromone				
9	1700	C=O indandione			
	1635	C=O chromone			
	1610	C=C	– –	– –	– –
	1190-	-O-			
	3450	-OH			
10	1680	C=O	2.11	3H(s)	$-CH_3$
	1610	C=C	4.5-4.6	2H(d)	$-CH_2$-
	3240	NH	6.8-6.9	1H(t)	NH
	3450	-OH	5.7	1H(s)	-CH=C-
			7.3-7.6	8H(m)	Ar-protons
11	1690	C=O phthalazinone			
	1650	C=O chromone			
	1630	C=N			
	1610	C=C	– –	– –	– –
	3320	NH			
	3450	-OH			

Table 2(cont.) ^{13}C-NMR of some new synthesised products

Compd. No.	Structural formula	^{13}C-NMR Carbon atom	δ-value (ppm)
1		19.8,165.6,134.8 176.4,127.8,125.1 133.6,119.7,153.0 and 123.4	C_1,C_2,C_3, C_4,C_5,C_6, C_7,C_8,C_9 and C_{10}

Tabl 2: contd.

Compd. No.	Structural formula	^{13}C-NMR Carbon atom	δ-value (ppm)
2b		11.3, 134.6,114.8, 145.7,122.2,127.9 124.9,134.1,120.2, 160.2,164.2,130.1 128.8,127.8 131.8	C_1,C_2,C_3, C_4,C_5,C_6 C_7,C_8,C_9, C_{10},H_{11},C_1, and $C_{2'}$,$C_{3'}$, and $C_{4'}$,
3d		11.2, 132.8,113.6 142.2,118.1,125.9 123.2,132.1,118.1 154.5,165.2,165.2, 130.1,128.6,125.9 and 131.4.	C_1,C_2,C_3,C_4, C_5,C_6,C_7,C_8, C_9,C_{10},C_{11}, C_{12},$C_{1'}$,$C_{2'}$, $C_{3'}$, and $C_{4'}$,
4b		164.1,1.134,176.08, 129.5,127.3,134.7 119.5,154.1,125.3 139.9,124.2,164.8, 192.1,63.2,14.1, 1324.7,125.1,128.3 and 127.7	C_2,C_3,C_4, C_5,C_6,C_7,C_8, C_9,C_{10},C_{11}, C_{12},C_{13},C_{14}, C_{15},C_{16},$C_{1'}$, $C_{2'}$,$C_{3'}$, and $C_{4'}$,
8d		161.0,135.6,176.2,130.1, 127.8,134.1,119.3,154.4, 125.2,112.5,142.4,166.8 131.1,132.6,132.6,131.1, 135.6,134.1,143.5,120.9, 129.0,124.1,120.5.	from C_2 To C_{24} respectively.
10		160.6,126.7,129.0 127.8,133.0,119.6, 175.7,126.7,136.9 19.8,48.2,121.5 129.0,123.6 127.8	C_1,C_2,C_3,C_4, C_5,C_6,C_7,C_8, C_9,C_{10},C_{11}, $C_{1'}$,$C_{2'}$,$C_{3'}$, and $C_{4'}$,

Method (ii)

0.01 mol, 2 g. of (**3a**) was dissolved in dry acetone (50 ml.) then 0.04 mole, 5 ml of benzoyl chloride and anhydrous potassium carbonate (0.04 mol, 5.6 g) were added and the reaction mixture was refluxed for 15 hrs. on a water bath. Excess of acetone was removed by distillation and the reaction mixture was diluted with water. The solid deposited was filtered of and crystallized from suitable solvent to give (**3d**) in high yield.

*Reaction of chromone (**1**) with ethyl oxalate; Formation of pyruvic ester derivative (**4a**)*

To a mixture of the chromone (1.5 g) and ethyl oxalate (4.5 ml) in dry ether (75 ml) was added sodium metal (0.6 g. 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 yellow pyruvic ester derivative (**4a**).

*Hydrolysis of (**4a**) to 5-chlorosalicyclic acid*

Pyruvic ester derivative (**4a**) (0.005 mol, 1.5 g.) 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 benzene to give 5-chlorosalicyclic acid m.p. 174°C as a colourless crystalline solid. It gave positive acidity test and deep violet colouration with aqueous ferric chloride.

*Fusion of (**4a**) with benzaldehyde; Formation of (**4b**)*

A mixture of the ester (**4a**) (0.005 mol, 1.5 g.), benzaldehyde (0.005 mol, 0.5 ml.) and 5 drops of piperidine was fused for two hrs. at 200-210°C using an electric mantle.

The reaction mixture was treated with cold 5 % hydrochloric acid and the solid obtained was collected and crystallized from the proper solvent to yield the desired product (**4b**)

*Reaction of chromone (**1**) with nitroso-aromatic compounds; Formation of the nitrone derivatives (**5a,b**)*

The chromone (**1**) (0.01 mol, 1.9 g.) was mixed with nitrosobenzene and/or p-nitroso-N,N-dimethyl aniline (0.03 mol) in a minimum amount of absolute ethanol. An alcoholic sodium ethoxide solution (0.23 g of sodium metla in 20 ml. of absolute ethanol) was added to the reaction mixture which was shaked well to obtain a deep brown-orange solid. The reaction mixture was left overnight at room temperature and the crystals that separated out were filtered off and crystallized from the proper solvent to give the nitrone derivatives (**5a,b**) respectively.

*Action of hydrazine hydrate on (**5b**); Formation of (**6a**)*

A mixture of (**5b**) (0.006 mole, 2 g.) and hydrazine hydrate (0.006 mol, 0.4 ml.) in 20 ml of glacial acetic acid was heated under reflux for 4 hrs. The solid that separated out was crystallized from the suitable solvent yielding (**6a**) as greenish yellow needles.

*Action of hydroxylamine hydrochloride on (**5b**); Formation of (**6b**)*

To a solution of hydroxylamine hydrochloride (0.006 mol, 0.4 g.) containing fused sodium acetate (0.006 mol) in ethanol (50 ml.) the nitrone (**5b**) (0.006 mol, 2 g.) was added and the reaction mixture was refluxed for 4 hrs. The mixture was cooled then the solid deposited was crystallized from the proper solvent to give (**6b**)

*Reaction of nitrone derivative (**5b**) with N-phenylmaleimide; Formation of (**7**)*

In dry phenetole (50 ml.), a mixture of (0.006, mol, 2 g.) (**5b**) and (0.012 mol, 2.1 g.) of N-phenylmaleimide was added and refluxed for 2 hrs. The solid obtained was collected and crystallized from the suitable solvent to give (**7**).

*Action of phthalic anhydride on 6-chloro-2-methyl-4H-1- benzopyran-4-one (**1**); Formation of 6-chloro-2-(3'- phthalidenemethylene) chromone (**8a**)*

A mixture of chromone 1 (2 g), phthalic anhydride (6 g.) and anhydrous sodium acetate (3 g., powder) was heated at 260-270°C for 2 hrs. using an electric mantle. After cooling, the reaction mixture was triturated with diluted sodium bicarbonate solution and the solid obtained was washed several times with boiling ethanol, collected then crystallized from anisole to give the desired

phthalidenemethylene chromone (8a) as brownish yellow crystals.

Alkaline hydrolysis of the phthalide (8a)

0.004 mol of the phthalide (8a) was refluxed in ethanol (50 ml) and 10% aqueous sodium hydroxide (50 ml.) for 4 hrs. The cold reaction mixture was distilled to remove alcohol and acidified with dilute sulphuric acid. The solid that separated out was collected and crystallized from benzene to give 5- chlorosalicylic acid as colorless crystals (m.p. 174°C). The mother liquor was extracted with ether, washed with cold water several times and dried over molecular sieves. After the removal of ether, the solid obtained was crystallized from distilled water to give phthalic acid as colourless crystals (m.p. 210- 211°C).

Rearrangement of phthalide (8a) a into phthalone; Formation of 2-(6'-chloro-2'-chromonyl)-1,3-indandione (9)

To a suspension of the phthalide (8a) (2 g.) in absolute methanol (40 ml.) alcoholic sodium methoxide solution [(from sodium metal 2 g. and absolute methanol (40 ml.)] was added. The mixture was heated under reflux for one hour. The resulting deep orange solution was cooled, diluted with water, then acidified with cold diluted sulphuric acid, the rearrangement product obtained was crystallized from pyridine to give the desired phthalone (9) as golden yellow crystals.

Reaction of phthalide (8a) with amines in acetic acid- sodium acetate mixture; Formation of phthalimidine derivatives (8b-d)

a) Aromatic amines

A mixture of the phthalide (8a) (0.004 mol, 1.3 g.) and the appropriate aromatic amine namely, aniline and p-toluidine (0.008 mol. 0.8 ml.) in glacial acetic acid (5 ml) containing anhydrous sodium acetate (0.4 g.) was heated under reflux for 9 hurs. After most of acetic acid had been evaporated by air-evaporation under funming cupboard, a mixture of the phthalimidine (7 b,c) and the corresponding N-arylphthalimide were obtained. The latter was obtained in minor yield. The two products were isolated in the pure state by fractional crystallization.

b) Aliphatic amines

A mixture of the phthalide (8a) (0.004 mol, 1.3 g.) and benzylamine (0.012 mol, 1.3 ml) in glacial acetic acid and anhydrous sodium acetate (0.4 g.) was refluxed for 9 hrs. The solid deposited was collected and crystallized from ethanol to give the phthalimidine (8d) as yellow fluffy solid. The mother liquor upon concentration gave a solid which was filtered off and crystallized from petroleum ether (100-120°C) to give N- benzylphthalimide in minor yield. Evaporation of the filtrate left an oily material responding to the colour reactions of 2- methyl-chromones.

Reaction of the phthalide (8a) with aromatic amines in n- butanol

The phthalide (8a) (0.004 mol, 1.3 g) and the appropriate aromatic amines namely, aniline and p-toluidine (0.008 mole) in 60 ml. of n-butyl alcohol were heated under reflux for 6 hrs. After the removal of the solvent the solid mixture deposited was collected and the two products were isolated by fractional crystallization using petroleum ether 80-100°C to give 6-chloro-2-methylchromone (1) and then ethanol to yield N-phenylphthalimide and N-p- tolylphthalimide respectively.

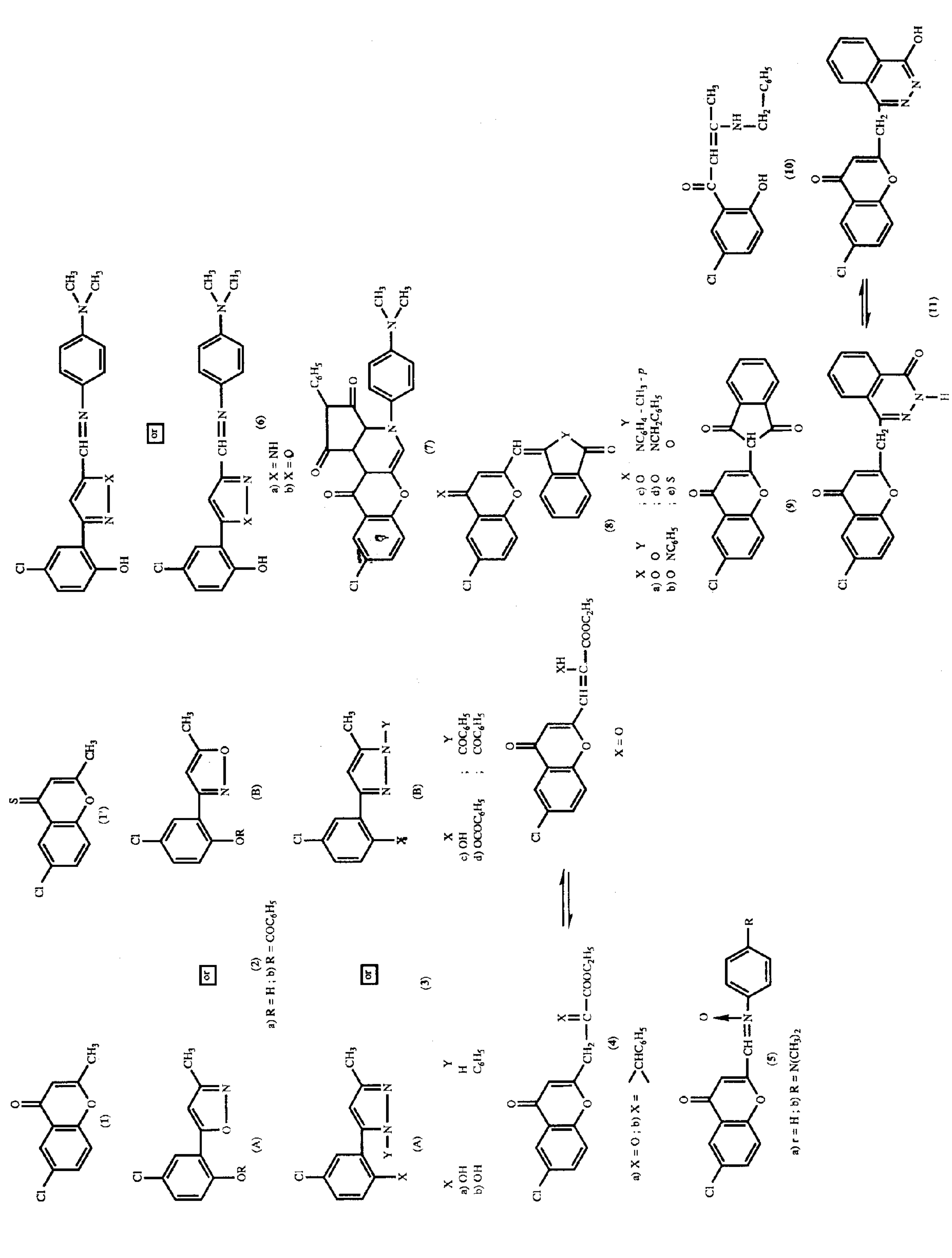
Action of aliphatic amines on phthalide (8a) in ethanol; Formation of 4-chloro-2-(β-benzylaminocrotonyl) phenol (10)

A mixture of the phthalide (8a) (0.004 mol, 1.3 g.) benzylamine (0.012, mol, 1.3 ml) and ethanol (20 ml.) was heated under reflux for 2 hrs. The solid that separated out was filtered off and crystallized from benzene to give N,N-dibenzylphthalamide (m.p. 178-179°C). The mother liquor was extracted with chloroform and the solid obtained after evaporating the solvent to dryness was crystallized from petroleum ether (100-120°C) to give 4-chloro-2- (β-benzyl-aminocrotonyl) phenol (10)

Action of hydrazine hydrate on phthalide (8a); Formation of (11) and (3a)

A) At room temperature

A mixture of the phthalide (8a) (0.004 mole, 1.3 g.) hydrazine hydrate (0.7 ml., 85% assay), ethanol (40 ml.) and drops of glacial acetic acid was



stirred constantly at room temperature for 24 hrs. The reaction mixture was poured into cold water containing few milliliters of conc. HCl and the solid obtained was filtered off and crystallized from aqueous ethanol (50%) to give (11) as a pale yellow crystals.

B) In boiling ethanol

A mixture of the phthalide (8a) (0.004 mol; 1.3 g.) hydrazine hydrate (1.3 ml, 85% assay), ethanol (40 ml) and few drops of glacial acetic acid was refluxed for 4 hrs. The solid obtained after cooling of the reaction mixture was collected and fractionally crystallized from the proper solvents to give 1,4- phthalazindione and pyrazole derivative (3a).

Thiation of the phthalide (8a) by Lawesson's Reagent (L.R.); Formation of (8e)

Method (A)

A mixture of the phthalide (8a) (0.004 mol, 1.3 g.) and Lawesson's Reagent (0.004 mol, 1.6 g.) was heated under reflux in sodium dried toluene (30 ml.) for 30 minutes. The reaction mixture was left to cool and the crude solid deposited was filtered off and crystallized from the suitable solvent to give (8e)

Method (B)

A solution of phthalide (8a) (2 g.) and purified phosprous pentasulphide (4 g.) was refluxed in dry xylene for 4 hrs., filtration process took place while the mixture still hot, the filtrate was concentrated, left to cool at room temperature then the solid that separated out was filtered off, washed several times with water, dried and then crystalized from the proper solvent to yield a product which was found to be identical with (8e), the yield % of the product is less than in method (A).

Action of phthalic anhydride on 6-chloro-2-methyl-4H-1- benzopyran-4-thione (i); Formation of (8c)

A mixture of thiochromone (i) (2 g.), phthalic anhydride (6 g.) and anhydrous sodium acetate (3 g.) was heated at 150 - 160°C for 2 hrs. After cooling the reaction mixture was triturated with diluted sodium bicarbonate solution and the solid obtainted was filtered off, washed several times with water and ethanol, dried and then crystallized from anisole to give the product (8e).

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