Chemistry and Application of 4-Oxo-4*H*-1-benzopyran-3-carboxaldehyde

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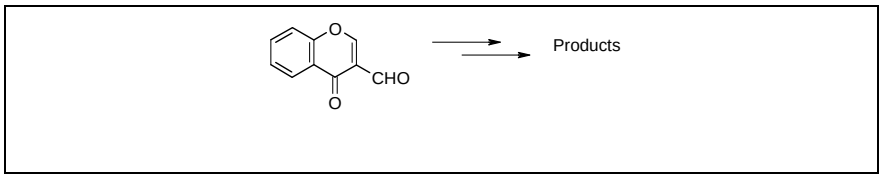

The Chemistry and application of the title aldehyde and some simple derivatives thereof are reviewed.

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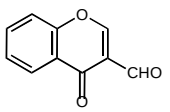
I Introduction.

The first exclusive review on the chemistry and application of the title benzopyran (trivial name: 3-formylchromone) **1** appeared in 1983 [1]. Another review [2], somewhat inexhaustive, compiling mainly the reactions of the chromone **1** itself from literature available to 1994 appeared in 1996. Continuing interest in the title subject to date is vindicated by a spate of publications that warrant a current review. The present article, primarily designed to complement the earlier two reviews [1,2], is a comprehensive survey of the chemistry of 3-formylchromone **1** and utilization of the compounds easily available therefrom for the preparation of different chemical systems. This survey covers the literature available through Sci-Finder till December, 2006. A few earlier works which either remained unmentioned in the previous reviews [1,2] or are helpful for a better understanding of the present write-up are also briefly referred to. Chemistry of the carbonitrile [3] and the acid corresponding to the aldehyde **1** is kept out of the purview. Patented works and the reactions of 2-substituted 4-oxo-4*H*-1-benzopyran-3-carbaldehyde not directly derived from the 2-unsubstituted analogue **1** are not included, and biological properties of the reported compounds are least emphasized. The 4-oxo-4*H*-1-benzopyran-3-yl moiety is abbreviated as 'Chr' so that 1-benzopyran-4-one (chromone) having 'X' substitution at its 3-position is represented by ChrX. Alkyl, alkoxy, halogeno substituents in and heterocyclic moieties linked to or fused with benzene ring of **1** remain unaffected in most of the reactions described here for the unsubstituted 3-formylchromone **1**. The reactions of **1** are described in the following few sections and subsections based on the type of the reactions and the nature of the reagents, and those of its derivatives as and when these appear. The cycloaddition reactions of **1** and its derivatives are, however, clubbed together in a separate section.

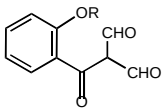
II Synthesis.

The chromone **1** is an intramolecular enol ether of the dialdehyde **2**. So a convenient synthesis of **1** should involve the preparation of **2** or its precursor. Vilsmeier-Haack reaction of 2-hydroxyacetophenone with $POCl_3$-DMF indeed involves the formation of a precursor of **2**, the kinetics and mechanism of the reaction having been studied in details [4]. 2-Hydroxyacetophenone bound to Merrifield resin through ether linkage in the aforesaid reaction gives **3** which may be regarded as a solid

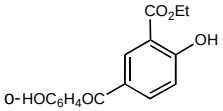


ChrCHO

1



2 : R = H
3 : R = Merrifield resin



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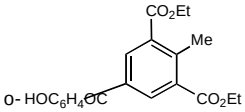

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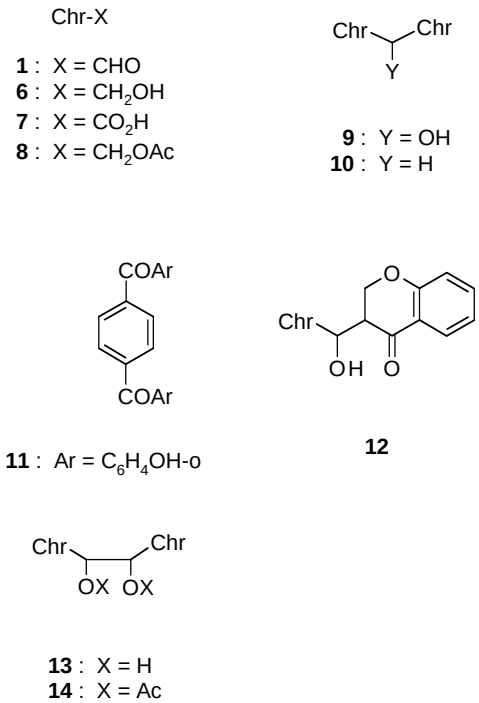
supported synthetic equivalent of **1**. When cleaved from the support by treatment with TFA **3** gives **1** [5]. 2-Hydroxyacetophenone either bound to Wang chloro resin [5] or pretreated with $BF_3.Et_2O$ [6] undergoes mono-formylation at its ketomethyl group by the Vilsmeier reagent. The solid supported ketodialdehyde **3** on reaction with ethyl acetoacetate gives the salicylic ester **4** [7] in contrast to isophthalic ester **5** obtained by treating **1** with two equivalents of ethyl acetoacetate [8].

III Oxidation, Reduction and Reductive Self Coupling.

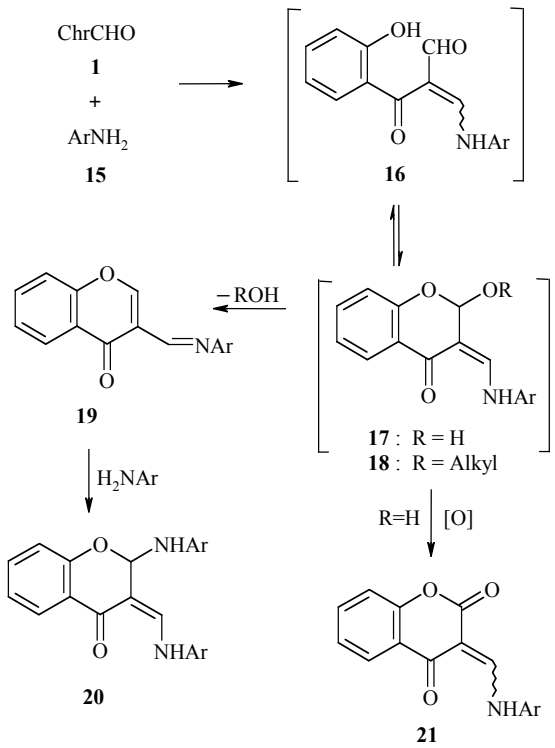
Oxidation of ChrCHO by different reagents has been discussed earlier [1]. Oxidation of 6-ethyl-3-formylchromone with oxone leads to a mixture of 6-ethyl-3-hydroxycarbonylchromone and 6-ethyl-3-hydroxy-chromone [9]. Reduction of **1** with diborane in THF to **6**, cursorily mentioned earlier [1], has been published [10]. Basic alumina selectively reduces the aldehyde group of **1** dissolved in 2-propanol at 75 ºC, the reaction needing no activation process of alumina [11]. Brockmann neutral alumina catalyses disproportionation of the aldehyde **1** to the alcohol **6** and acid **7**, both **1** and **7** undergoing further alumina catalysed condensation with **1** as well as **7** [12]; the aldehyde **1** when refluxed in nitrobenzene containing anhydrous $AlCl_3$ also gives the alcohol **6** together with other self-condensation products (*vide* Section VII.6) [13]. ChrCHO gives the bischromones **9**, **10** and disalicyloylbenzene **11** with sodium naphthalenide, a mixture of **10** and chromanone **12** with zinc in methanol, **6**, **10** and diol **13** with zinc in acetic acid, and acetates **8** and **14** with Zn -Ac_2O - AcONa [14].



IV Nucleophilic Addition of Nitrogenous Nucleophiles.

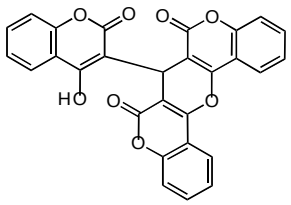
IV.1 Addition of Amines. Reaction of **1** with the aromatic amine **15** (Ar = C_6H_4X-*p*; X = H, Me, OMe) in refluxing benzene in the presence of *p*-toluenesulfonic acid (TsOH) gives a mixture of the Schiff base **19** and the enamine **20** [15]. Because of the 'chemical symmetry' of the formyl carbon and C-2 of **1**, it is very difficult to pinpoint whether a nucleophile is undergoing an initial 1,2- or 1,4-addition to 3-formylchromone. When the reaction between **1** and **15** is mediated by K-10 montmorillonite, chroman-2,4-dione **21** is the exclusive product [16]. The formation of **21** is indicative of an initial 1,4-addition of $ArNH_2$ to the α,β-unsaturated aldehyde **1** with concomitant opening of the pyran ring, the resultant intermediate **16** recyclising to **17** (Scheme **1**); **17** on elimination of water gives **19** and enamine **20** is the 1,4-adduct of **19** with a second molecule of **15**. The dione **21** is formed by oxidation of **17**, Fe (III) present in the clay being the oxidant. The enamine **17** is indeed obtained by reacting **1** with the aromatic carboxylic acid or acid derivative **15** (Ar =C_6H_4X-*p*; X = COOH, $CONHCH_2COOH$) in benzene or toluene containing TsOH at room temperature or under reflux [17]. Pure 3-(aryliminomethyl)chromone **19** can be had by heating **18** obtained by TsOH catalysed condensation of **1** with **15** in an alcohol ROH [18].

Scheme 1



The Schiff base **19** has been reacted with bisnucleophiles like phenylhydrazine, guanidine, thiourea

and 2-aminothiophenol under different experimental conditions [19]. The dione **21** (Ar = C_6H_4X-*p*; X = H, Me, OMe) gives the tricoumarol **22** on acid hydrolysis, and a mixture of 4-arylamino-3-formylcoumarin **23** and 1-benzopyrano[4,3-*b*]quinoline **24** on heating with $POCl_3$ [16]. The Schiff bases of **1** with several aromatic primary amines cause significant decrease in serum cholesterol and triglyceride levels [20].



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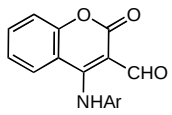

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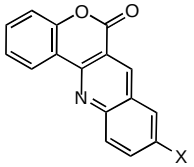

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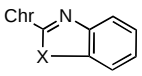
The chromone **1** has been subjected to reaction with several primary amines containing a second nucleophilic center. The reaction of ChrCHO with $H_2NC_6H_4XH$-*o* (X = NH, NPh) ultimately leading to the imidazole **25** has been discussed elsewhere by one of the present authors [21]. That the formation of the dihydrotetraaza[14]annulene **26** by condensing **1** with *o*-phenylenediamine involves the intermediacy of the bischromone **27** has been proved by isolating the latter by using ChrCHO and the diamine in 2:1 molar ratio and subsequently treating it with the diamine [22]. The compound **26** on digestion in acetic acid gives 3-(benzimidazol-2-yl)chromone **25** (X = NH). The dianil of the type **27** derived from 6-formylkhellin and *o*-phenylenediamine forms monomeric or dimeric complexes with Mn (II) and Fe (II, III) whereas that of khellin and *o*-phenylenediamine forms polymeric Mn and Fe complexes [23]. Complexes of the dianils of the type **27** with Co (II), Ni (II) and Cu (II) have also been studied [24]. ChrCHO having different substituents at its phenyl ring has been condensed with 2-aminoaniline [25a] and 2-aminothiophenol [25b] in acetic acid to give the appropriately substituted chromonylbenzimidazole **25** (X = NH) and chromonylbenzthiazole **25** (X = S), respectively. All these results suggest a further scrutiny of the reported condensation of **1** with 2-*N*-alkyl(or aryl)amino-3(or 5)-nitroaniline [26a,b] and 2-aminophenol [26c] in refluxing ethanol giving respectively [1]benzopyrano[2,3-*b*][1,5]-benzodiazepin and benzoxazepin derivatives. Conventional as well as microwave assisted three component condensation involving ChrCHO, $HSCH_2CO_2H$ and 4,5-diamino[2,1,3]benzothiadiazole, however, gives the heterocycle **28** [27].



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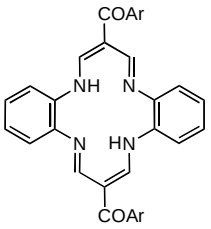
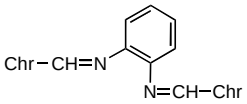


26 : Ar = C_6H_4OH-o



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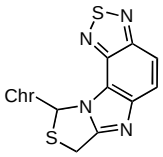

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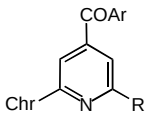
Reaction of **1** with α-aminoacetonitrile and unsubstituted as well as α-substituted glycine ester has been studied in detail [28]. For example, treatment of **1** with $H_2NCH_2CO_2Et$ in refluxing toluene containing TsOH gives a mixture of pyridine **29** (R = CO_2Et) and pyrrole **30** (R = H, R^1 = CO_2Et). Similar treatment of **1** with NH_2CH_2CN gives **29** (R = CN) whereas that with ethyl 2-aminopropanoate as well as ethyl 2-amino-2-phenylethanoate gives the pyrrole **31** [28]. 1-(2-Aminophenyl)pyrrole and **1** together in refluxing ethanol containing catalytic amount of HOAc give 4,5-dihydropyrrolo[1,2-*a*]quinoxaline **32** [29]. The reaction between **1** and an aliphatic secondary amine like dimethylamine and piperidine leading to an enamino-ketone had been previously discussed [1,2]. ChrCHO gives with *N*-methylglycine the pyrrole **30** (R = Me, R^1 = H) [28].



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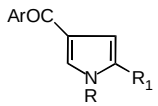

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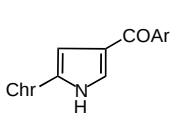

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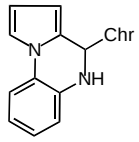

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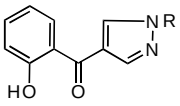
For **29**-**31** : Ar = C_6H_4OH-o

Triethylamine in an alcohol brings about deformylation in addition to other transformations of ChrCHO [30].

IV.2 Addition of Hydrazines. ChrCHO has been reacted with NH_2NHR (R = H, Ph) under both conventional heating [31] and microwave irradiation [32] to give the pyrazole **33**; **33** (R = H) is also obtained by heating under reflux an ethanolic solution of **1** with thiosemicarbazide, the reaction undergoing *via* the corresponding thiosemicarbazone **34** (X = S, R = H) [33]. *N*-Glycosyl-*N*-iminothiourea, derived from glycosylisothiocyanate and anhydrous hydrazine, gives with **1** the semicarbazone **34** (X = S, R = β-glycosyl) [34]. Cytotoxicities of the hydrazones **34** (X = S, R = OH) [35] and **34** (X = NH, R = OH) [36] against tumor cells have been studied. Acylhydrazone **35** is formed from **1** and $H_2NNHCOAr$ (Ar = aryl, hetaryl). Antimicrobial activities of **35** [Ar = (1-phenyl, 3-phenyl or -thien-2-yl)pyrazol-4-yl] have also been investigated [37]. Benzoylhydrazone of 3-formyl-6-hydroxychromone has been used as a ligand in forming complexes such as $[Ln(L)_2(NO_3)_2]NO_3$ where L stands for the ligand and Ln for the rare earth elements as Eu, Sm, Tb and Dy [38].

Condensation of **33** with ethyl cyanoacetate leads to a coumarin derivative **36** [39]. The thiosemicarbazone **34** (X = S, R = H) undergoes cyclisation with $BrCH_2CO_2Et$ and $ClCH_2COMe$ to give the thiazole derivatives **37** (X = OH, keto form), and **37** (X = Me), respectively [40].



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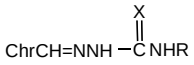

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ChrCH=NNHCOAr

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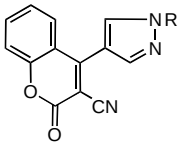

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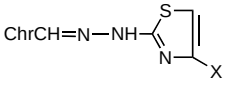

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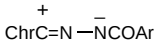

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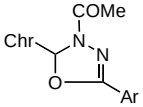

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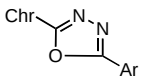

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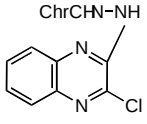

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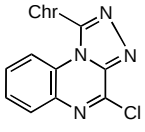

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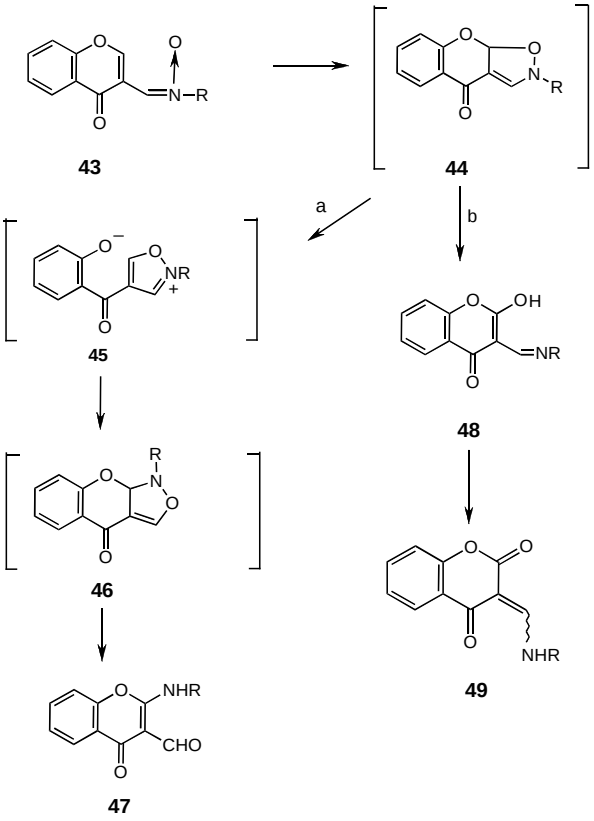
The hydrazone **35** with Ac_2O gives 2,3-dihydro-1,3,4-oxadiazole **38**, the reaction being completed in a much shorter time under microwave irradiation than in conventional heating [41,42]. The hydrazone, derived from **1** and *p*-$RC_6H_4OCH_2CONHNH_2$ (R = H, Me, Cl, Br) on refluxing in Ac_2O gives **38** (Ar = $CH_2OC_6H_4R$-*p*) [43]. The nitrilimine **39**, generated from **35** by treatment with Br_2 - AcONa, cyclises to 3-(5-aryl-1,3,4-oxadiazol-2-yl)-chromone **40** [44, 45]. The hydrazone **41**, derived from **1** and 2-chloro-3-hydrazinoquinoxaline, gives the 1,2,4-triazolo[4,3-*a*]quinoxaline **42** on treatment with DDQ [46].

IV.3 Reaction with Hydroxylamine. The oxime ChrCH=NOR (R = H or alkyl), derived from **1** and hydroxylamine or the appropriate *O*-alkyl (or aryl)-hydroxylamine undergoes acid catalysed dehydration to ChrCN [3,47]. ChrCH=NOH when heated under reflux in MeCN containing NaI also affords ChrCN [48]. A one pot synthesis of ChrCN from 2-hydroxyacetophenone involves treatment of the latter at room temperature first with DMF-$POCl_3$ and then with $NH_2OH.HCl$, the chloroiminium salt $[Me_2N^+=CHCl]Cl^-$ presumably bringing about dehydration of the intermediate oxime [49].

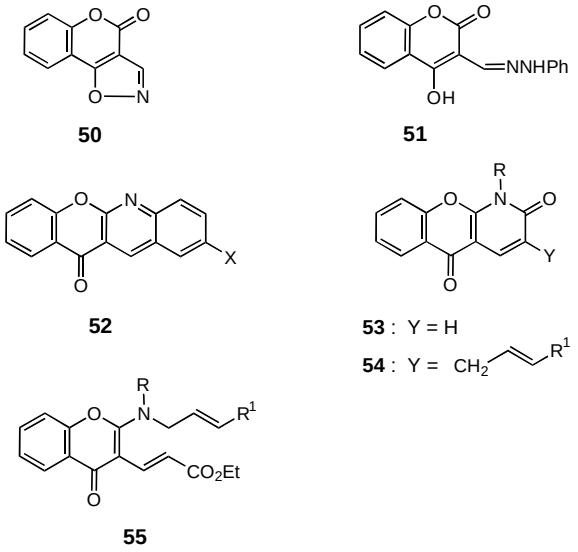
C-(4-Oxo-4*H*-1-benzopyran-3-yl)-*N*-phenyl-nitrone **43** (R = Ph) is obtained in *Z*-isomeric form by condensing **1** with PhNHOH in dry ethanol [50,51]. The nitrone **43** (R = alkyl or aryl) can also be prepared by treatment of a mixture of **1** and an aliphatic or aromatic nitrocompound with zinc in ethanol-acetic acid [52]. Heating a solution of **43** (R = Ph) in ethanol under reflux affords 2-substituted 3-formylchromone **47** (70%) and a stereoisomeric mixture of **49** (25%) [50]. Arylnitrone **43** (R = aryl), however, remains unaffected under reflux in MeOH whereas the aliphatic nitrone **43** (R = alkyl) rearranges to **47** under similar conditions [53]. Ghosh and Bandyopadhyay [54] have shown that rearrangement of **43** (R = aryl or alkyl) is dependent on the reaction medium, polar solvents facilitating the formation of **47** whereas non-polar ones allowing the formation of both **47** and **49**. No reaction between ChrCHO, nitroarene or nitroalkane and zinc powder in THF at ambient temperature takes place; but addition of a saturated aqueous solution of NH_4Cl in the mixture induces the reaction, a nitroalkane giving **47** (R = alkyl) whereas a nitroarene the nitrone **43** (R = aryl) as the major product along with (**49**, R = Ar) (≡ **21**) [52]. The rearrangement of **43** to **47** and **49** has been explained in the following way. 1,5-Electrocyclisation of **43** gives the fused isoxazoline **44** as an intermediate. Rearrangement of **44** by pyran ring opening (→ **45**) and recyclisation gives **46**, which leads to **47** by a 1,5-hydrogen shift (Scheme 2 – path *a*). Alternatively, **44** by a sequential 1,5-hydrogen shift (→ **48**) and prototropy gives **49** (path *b*) [50].

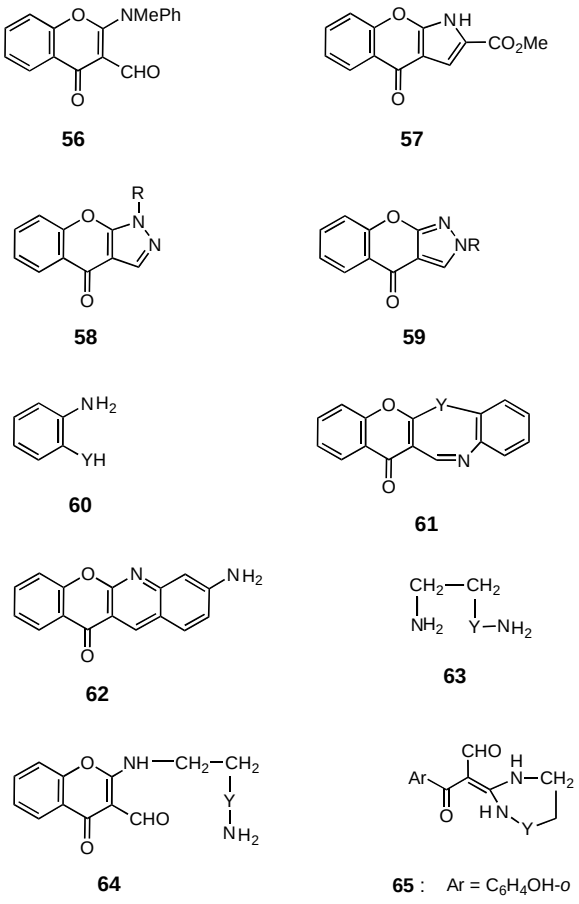
Scheme 2



The nitrones **43** (R = alkyl) and **43** (R = Ar) give respectively $ChrCO_2H$ and ChrCHO on hydrolysis with 70% sulfuric acid [53]. The chromandione **49** (R = alkyl) gives the fused isoxazole **50** with hydroxylamine and the coumarin derivative **51** with phenylhydrazine [54]. A few reactions of **49** (R = Ar) are mentioned in Section IV.1. On heating with 70% sulfuric acid **47** (R = Me, Et) undergoes deformylation whereas **47** (R = C_6H_4X-*p*, X = H, OMe) undergoes cyclodehydration to benzazaxanthone **52** [50,52]. The chromone **47** has been extensively used for the synthesis of various heterocycles fused with the 2,3-bond of the chromone moiety. For example, **47** (R = Ph, CH_2Ph) on being refluxed with $Ph_3P{=}CHCO_2Et$ in benzene gives the azaxanthone derivative **53** by cyclisation of the initially formed Wittig reaction product [55]. The chromone **47** (R = Ph, CH_2Ph) on sequential treatment with allyl bromide in refluxing acetone – K_2CO_3 and the phosphorane $Ph_3P{=}CHCO_2Et$ in refluxing benzene gives **55**. A xylene solution of **55** on being heated in a sealed tube at 220-230 ºC gives the azaxanthone **54** [55].

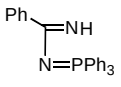
The chromone **56**, obtained by methylation of **47** (R = Ph), possesses a highly nucleofugal *N*-methylanilino group and it has been reacted with bisnucleophiles to obtain several heterocycles fused with the 2,3-bond of chromone as well as macrocycles having intact chromone moieties at the periphery. For example, **56** gives the pyrrole **57** with methyl glycinate, a mixture of pyrazoles **58** and **59** with NH_2NHR (R = H, Ph), and seven membered heterocycle **61** with 2-substituted aniline **60** (Y = NH, O, S) [56]. An equimolar mixture of **56** and *m*-phenylenediamine gives 1-benzopyrano[2,3-*b*]quinoline **62** in refluxing MeCN - H_2O





but a [2+2]macrocycle in refluxing dry MeCN. 3-Aminophenol and **56** when refluxed together in xylene produce a [3+3]macrocycle [56]. The aliphatic diamine **63** (Y = bond, CH_2) behaves differently from an aromatic primary diamine towards **56**. The intermediate **64** initially formed from **56** by displacement of *N*-methylaniline with **63** undergoes intramolecular 1,4-addition with concomitant opening of the pyran ring to give the imidazole or pyrimidine derivative **65** [57a]; no attempt to cyclise **65** to 3-hetarylchromone has been done. Heterocyclic amines like pyrrolidine, piperidine, morpholine, piperazine and *N*-methylpiperazine bring about nucleophilic substitution of *N*-methylanilino moiety of 6-chloro(or fluoro)-3-formyl-2-*N*-methylanilino-chromone, the resultant 2-cyclamino derivatives showing anticancer activity to some extent [57b].

IV.4 Addition of Amidines. The reaction of **1** with formamidine and some *C*-substituted formamidines leading to either 5-salicyloyl-pyrimidine or 5-hydroxy-5*H*-[1]benzopyrano[4,3-*d*]-pyrimidine or both had been previously discussed [1,2]. The iminophosphorane **66**, equivalent to benzamidine, undergoes an aza-Wittig reaction with the aldehyde function of 6-methyl-3-formylchromone followed by electrocyclic ring closure of the intermediate 1,3-diazatriene with concomitant opening of the pyran ring to give 5-(2-hydroxy-5-methylbenzoyl)-1-phenylpyrimidine [58]. In its reaction with **1**, thiourea behaves like guanidine to give the chromenopyrimidine **67** (Y = OH, X = SH, thioxo form) [59]. $H_2NC(=NH)SMe$ gives with **1** in EtOH-NEt_3, a mixture of 2-thiomethyl-5-salicyloyl-pyrimidine and the chromenopyrimidine **67** (X = SMe, Y = OH) [60] whereas $H_2NC(=NH)X$ where X stands for OMe [61] and NR^1R^2 (R^1R^2 = CH_2CH_2-Z-CH_2CH_2; Z = bond, CH_2, O) [62] gives only the fused pyrimidine **67** (Y = OH). $TiCl_4$ catalysed reaction of **67** (X = OMe, SMe, NR^1R^2; Y = OH) with NHR^1R^2 (R^1 = H, R^2 = cyclopropyl, *t*-butyl etc; R^1R^2 = CH_2CH_2 Z CH_2CH_2; Z = bond, CH_2, O) gives the corresponding 2-substituted pyrimidine **67** (Y = NR^1R^2) [60-62]. The pyrimidines



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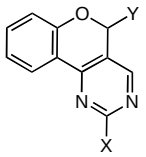

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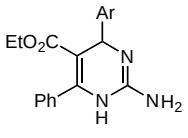

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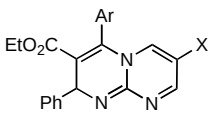
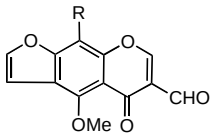


69 : X = COC_6H_4OH-*o*

having the same or different cyclamino substitutents at their 2- and 5-position show *in vitro* antiplatelet activity [62]. It is relevant to mention here that the pyrimidine **67** (X = NH_2; Y = NHAr) is obtained by treating **19** with guanidine [19a]. The 2-amino-1,4-dihydropyrimidine **68**, derived from the three component condensation of ArCHO (Ar = phenyl, *p*-tolyl, *p*-anisyl, *p*-chlorophenyl, 2-thienyl), $PhCOCH_2CO_2Et$ and guanidine, can be regarded as an *N,N´*-disubstituted guanidine and it reacts with **1** giving 2*H*-pyrimido[1,2-*a*]pyrimidine **69** [63].

IV.5 Reaction with 1,2-Diimine. When ChrCHO is reacted with a 1,2-diketone in the presence of NH_4OAc, the diketone is first converted to the corresponding 1,2-diimine that reacts with the aldehyde function of **1** giving an imidazole linked to the 3-position of chromone. Thus, 3-formylchromone **1** [64] and 6-formylkhellin **70** (R = OMe) [20] give with benzil and NH_4OAc in refluxing AcOH 3-(4,5-diphenyl-imidazol-2-yl)chromone and 6-(4,5-diphenyl-imidazol-2-yl)khellin, respectively. Similar condensation of **1** with 1,10-phenanthroline-5,6-dione gives 3-(1*H*-imidazolo-[4,5-*f*][1,10]phenanthrolin-2-yl)-4-oxo-4*H*-1-benzopyran (abbreviated as ipbp) **71** [65]. 2,2´-Bipyridyl and 1,10-phenanthronyl complexes of Ru (II) like $[Ru(bpy)_2Cl_2]$ and $[Ru(phen)_2Cl_2]$ form with ipbp respectively $[Ru(bpy)_2(ipbp)]Cl_2$ and $[Ru(phen)_2(ipbp)]Cl_2$ that bind with calf thymus DNA in an intercalative mode [65].



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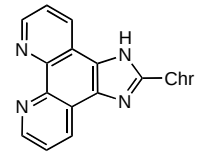

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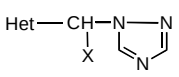
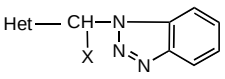
IV.6 Reaction with Heterocyclic NH. 1*H*-1,2,4-Triazole (or 1*H*-benzotriazole) has been condensed with the aldehyde group of several substituted 3-formyl-chromones (Het-CHO) to give **72** (or **74**), the latter forming **73** (or **75**) by reaction with $RCONH_2$ (R = alkyl or aryl). The heterocycles **72** and **74** have been reacted with oxygen, sulfur and nitrogen nucleophiles [66].



72 : X = OH
73 : X = NHCOR

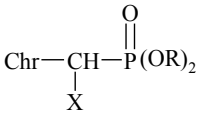


74 : X = OH
75 : X = NHCOR

V Addition of Phosphorus Nucleophiles.

Treatment of **1** with dialkyl phosphite $HOP(OR)_2$ and 1,2-drops of trialkyl phosphite $P(OR)_3$ (R = Me, Et, $CHMe_2$, Bu, Ph) gives the phosphonate **76** [67]. Abdou *et*

al. [68] have reported the formation of the phosphonates **76** and **77** by condensing **1** with dialkyl phosphonate $HPO(OR)_2$ and trialkylphosphite $P(OR)_3$, respectively. The compound **76** (R = Me, Et) is also obtained by condensing **1** with $P(OR)_3$ under microwave irradiation mediated by TMSCl under solvent free conditions; TMSCl presumably acts as a trapping agent and prevents intramolecular dealkylation [69]. The phosphonate **78** has been obtained by refluxing an equimolar mixture of **1**, $P(OPh)_3$ and $H_2NCO_2CH_2Ph$ in glacial AcOH [70]. Reaction of **76** (R = Me) with HBr in AcOH gives **79** that can be reduced by red P - HI in hot HOAc to **80** [67].

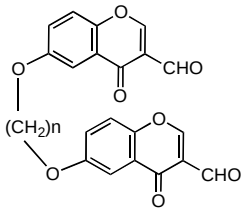


76 : X = OH, R = alkyl
77 : X = OR^1, R^1 = R = alkyl
78 : X = $HNCO_2CH_2Ph$, R = Ph
79 : X = OH, R = H
80 : X = R = H

VI Addition of Oxygen and Sulfur Nucleophiles.

3-Formylchromone **1** can be crystallised from methanol; on prolonged (22-25 hr) heating in dry methanol under reflux, however, undergoes complete acetalisation. In contrast, complete acetalisation with methanol of both the aldehyde functions of the bischromone **81** (n = 3-5) takes place within 6 hr under the same conditions, the faster acetalisation in this case being not rationalized [71]. TsOH catalysed condensation of **1** with ethane-1,2-dithiol [72] and the diol $HOCH_2XCH_2OH$ (X = bond, CH_2, CMe_2) [72,73] in refluxing benzene under azeotropic conditions gives **82** and **83**, respectively. Thioacetalisation of **1** has been achieved in excellent yield at room temperature using thiols and dithiols in aqueous hydrobromic acid [74]. Ti(IV) exchanged montmorillonite efficiently catalyses the acetalisation of **1** with ethane-1,2-diol as well as propane-1,3-diol in refluxing toluene [75]. Silica supported metallic sulfates as $Ce(SO_4)_2$, $MgSO_4$, $NaHSO_4$ are efficient catalysts for the protection of the aldehyde function of **1** as the 1,3-dioxalone under microwave solvent free conditions [76]. Acetalization of ChrCHO has been achieved in basic media too. For example, 6-substituted 3-formylchromone on refluxing in ROH (R = Me, Et) containing catalytic amount of NEt_3 gives the corresponding acetal (22-34%) in addition to several other products (see Section VII.6) [30] whereas **84** (R = Me) is the sole product obtained by $TiCl_4$ catalysed acetalisation of **1** in MeOH in the presence of NH_3 or NEt_3 [77]. Ac_2O in the presence of $AlCl_3$ at room temperature converts **1** to the acylal **84** (R= Ac), which can be reconverted to **1** by treatment also at room temperature by $AlCl_3$ in CH_2Cl_2 [78]. The formation of **84** (R = Ac) from **1** and Ac_2O at room temperature is also catalysed by ceric ammonium nitrate (CAN) [79] as well as 1,3-dibromo-5,5-dimethylhydantion (DBH) [80]; CAN in aqueous MeCN at 70 ºC can deprotect the aldehyde group in **84** (R = Ac) [79].

The acetal **83** (Y = bond) gives with nitrogen nucleophiles the same products as are obtained from the aldehyde **1** [72]. The acetal **83** after lithiation at its pyran 2-position is reacted with electrophiles like TMSCl, $ClCO_2Et$, MeCHO and PhCOCN *etc*. to form the corresponding 2-substituted analogue of **83**, the 2-substituted products from **83** (Y = CH_2) being always accompanied by the dimer **85** [73]. Ammonium formate and palladized charcoal in refluxing methanol brings about hydrogenation of the pyran 2,3-olefinic bond of **83** (Y = bond) [81].



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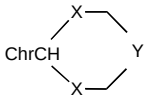
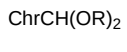


82 : X = S, Y = bond
83 : X = O



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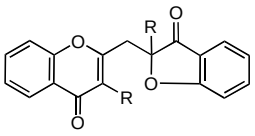
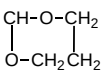
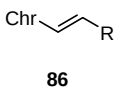


85 : R = 

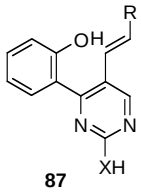
VII Addition of Carbon Nucleophiles.

VII.1 Condensation with Active Methyl or Methylene Group Linked to an Arene or Hetarene : Formation of 3-[2-Aryl(or hetaryl)vinyl]chromone. Condensation of ChrCHO with 2,4-dinitrotoluene in refluxing pyridine [82] and with 4-nitrotoluene in pyridine under ultrasonic irradiation [83] yields *E*-3-(2-arylvinyl)chromones **86** (R = 2,4-dinitrophenyl) and **86** (R = 4-nitrophenyl), respectively. Methyl group of 3-aryl-2-methylquinazolin-4(3*H*)-one is active so as to condense with ChrCHO [84]. 3-Methyl-1-phenylpyrazolin-5-one condenses with **1** under base catalysis to give a small amount of **86** (R = 5-oxo-1-phenylpyrazolin-3-yl) in addition to the major product arising from the condensation of aldehyde function of **1** with the methylene group of the said pyrazolinone [85]. Knoevenagel condensation of ChrCHO with active methylene group of several aryl(or hetaryl)acetic acids is always accompanied by decarboxylation so as to give the title chromone **86** of *E*-sterochemistry. For example, a mixture of ChrCHO and phenylacetic acid having a chloro,

nitro or trifluoromethyl substituent at its *ortho*- or *para*-position in pyridine under reflux [86] or in pyridine under ultrasonic irradiation [83] or in pyridine containing *t*-BuOK under classical heating conditions as well as microwave irradiation [87] gives the corresponding *E*-3-styrylchromone, Knoevenagel condensation with decarboxylation being faster under microwave irradiation. Coumarin-4-ylacetic acid [88] and 6,8-dimethylcoumarin-4-ylacetic acid [89] with ChrCHO in boiling pyridine form the corresponding *E*-3-(2-hetarylvinyl)chromone, the former acid being also condensed with **1** under microwave irradiation [90]. *p*-Nitro(or ethoxy)benzylidenetriphenylphosphorane, obtained by treatment of the appropriate benzyl bromide with triphenylphosphine followed by a base, gives with **1** an isomeric mixture of 3-[4'-nitro(or ethoxy)styryl]chromone, *Z*-isomer being most abundant independent of having electron withdrawing or electron donating group at the phenyl ring of the benzylidene moiety [89]. The styrylchromone **86** reacts with urea (or thiourea) in alcoholic KOH yielding 2-hydroxy (or sulfhydryl) pyrimidine **87** (X = O or S) [83].



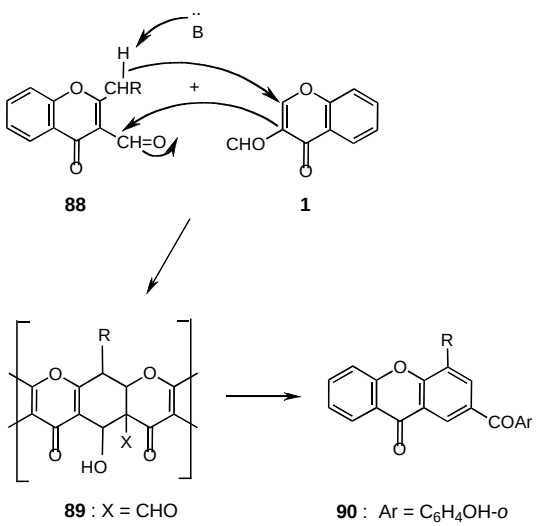
86



87

3-Formyl-2-methylchromone **88** (R = H) does not give any Aldol condensation product with **1** under base catalysis; instead, a Michael initiated ring closure reaction is involved and the intermediate **89** ultimately gives the xanthone **90** (R = H) by water elimination and deformylative pyran ring opening (Scheme 3) [91].

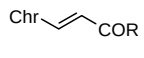
Scheme 3



88 **1**

89 : X = CHO **90** : Ar = C_6H_4OH-*o*

VII.2 Reaction with Methyl Ketones, and Acylic and Alicylic Compounds Having an Active Methylene Group. Aldol condensation involving methyl group of RCOMe (R = Me, aryl, hetaryl) with the formyl group of ChrCHO gives **91** in *E*-isomeric form [92-95] which has been reacted with various nucleophiles; for example, **91** (R = aryl) gives the 1,5-benzothiazepin **92** with 2-aminobenzenethiol. Reactions of **91** (R = Me, Ar) with hydrazine and hydroxylamine have been studied [94,95].



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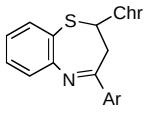
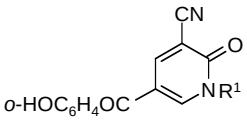


92

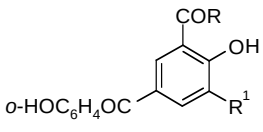
Formation of ChrCH = CXY by base catalysed condensation of **1** with XCH_2Y where both X and Y are electron withdrawing groups is well known; the initially formed condensates may undergo further transformation depending on the nature of X and Y groups [1,2]. The same condensation has been carried out under varying conditions. Based catalysed reaction of ChrCHO with cyanoacetamide gives the cyanopyridone **93** accompanied by other products [96,97]. The best reaction conditions for getting pyridone **93** in high yield are by heating **1** with $R^1NHCOCH_2CN$ (R^1 = H, CH_2Ph, CH_2Me, cyclohexyl) in DMF in the presence of TMSCl as a promoter and water scavenger [98a]. 6-Methyl-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde when simply heated with $NCCH_2COZ$ (Z = OH, NH_2) in distilled water without catalyst at 90 ºC for 12h, however, gives the corresponding ylidene nitrile in quantitative yield [98b]. Base catalysed condensation of some 6-formyl-furochromones **70** with cyanoacetamide, cyanothioacetamide, malononitrile, malonic acid, ethyl acetoacetate, acetylacetone, ethyl benzoylacetate [97], dimedone, indanone [99] and 1,3-indandione [100] has been reported. 6-Substituted 3-formylchromones have been condensed with dimedone and biindone under heating, as well as in a microwave oven [101].

$ArCOCH_2X$ (X = NO_2, SO_2Ar^1) has been condensed with **1** [102]. The formation of the benzophenone **94** (R = Me, R^1 = H) and $ChrCH=C(COMe)_2$ by reaction of **1** with $CH_2(COMe)_2$ in AcOH containing a few drops of HCl has been rationalized [103]. The domino Michael-retro-Michael-Wittig reaction of the phosphorane **95** (R = $OCHMe_2$, OMe, OEt, NH_2, 1-pyrrolidinyl) with ChrCHO in refluxing THF in the presence of NaH also gives the benzophenone **94** (R^1 = H) [104]. ChrCHO gives the benzo[*b*]furan **96** with chloroacetone in acetone containing anhydrous K_2CO_3 and a catalytic amount of iodine but gives **97** in dichloromethane in the presence of Brockmann neutral alumina [105]. Horner-Wadsworth-Emmons reaction of ChrCHO with $(EtO)_2P(=O)CH_2CO_2Et$ affords the electron deficient diene **91** (R = OEt)

[106]. ChrCHO and benzimidazol-2-acetonitrile **98** together in refluxing ethylene glycol form the pyrido-[1,2-*a*]imidazole **99** [107].



93



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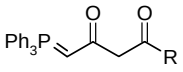

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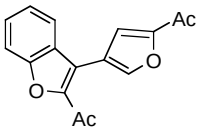

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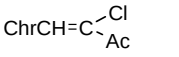

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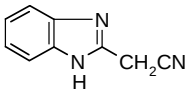

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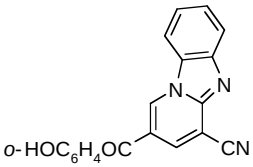

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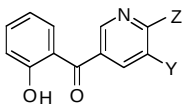
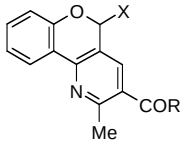
ChrCHO in the presence of ammonia gives the pyridines **100**-**102** respectively with acetylacetone, diethyl malonate and ethyl cyanoacetate; the formation of these pyridines involves Knoevenagel condensation of the active methylene compounds with **1** and the subsequent reactions of the condensates with ammonia [108]. In contrast, ethyl acetoacetate and ammonia under similar conditions, and acetylacetone pretreated with ammonia condense with **1** giving the pyranopyridines **103** (R = OEt, X = OH) and **103** (R = Me, X = OH), respectively [108]. 6-Formylkhellin **70** (R = OMe) on condensation with malononitrile in the presence of ammonium acetate gives the 1,4-dihydropyridine **104** (R = khellin-6-yl, R^1 = NH_2, X = Y = CN) through the intermediacy of **105** [93].



100 : Y = Ac, Z = Me
101 : Y = CO_2Et, Z = OH, amide form
102 : Y = CN, Z = OH, amide form



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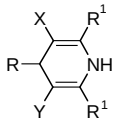


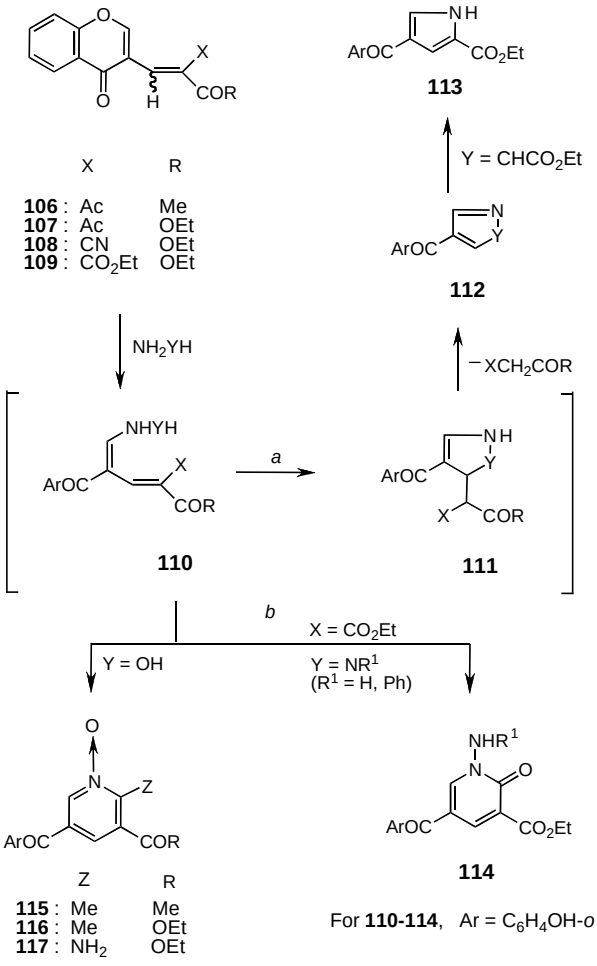
104

$RCH[CH(CN)_2]_2$

105

The Knoevenagel condensates **106-109** have been reacted with the bisnucleophile H_2NYH (Y = NH, NPh, $CHCO_2Et$) [109]. The nucleophile attacks at the pyran 2-position with concomitant opening of the pyran ring (Scheme 4). Depending on the nature of X and Y groups the resultant intermediate **110** undergoes two different types of cyclisations; an intramolecular 1,4-addition reaction (→ **111**) followed by elimination of XCH_2COR gives **112** (path *a*) whereas cyclisation involving intramolecular 1,2-addition of the nucleophilic species in Y leads to the six-membered ring system (path *b*). It has been shown that the chromone **106** gives the pyrazole **112** (Y = NPh) with phenylhydrazine whereas **109** gives, with H_2NNHR^1 (R^1 = H, Ph), the pyridone **114**. Hydroxylamine converts **106-108** into the pyridine-*N*-oxides **115-117**, respectively. The reaction of **108** with ethyl glycinate follows the path *a*, the intermediate **112** (Y = $CHCO_2Et$) giving the pyrrole **113** by a 1,5-hydrogen shift.

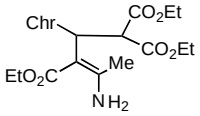
Scheme 4



110 **111** **112** **113** **114**

With ethyl β-aminocrotonate, the chromone **106** gives a mixture of **103** (X = $CHAc_2$, R = OEt) and **104** (R = Chr, R^1 = Me, X = Ac, Y = CO_2Et), **107** gives **104** (R = Chr,

R^1 = Me, X = Y = CO_2Et), and **109** varying amounts of **118** and **119**; pyridine **103** (R = OEt, X = OH), is obtained in small amount (~ 3%) in each case [110]. The aforesaid 1,4-dihydropyridines **104** can be dehydrogenated by



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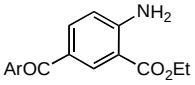

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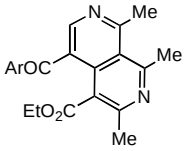


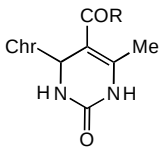
120

For **119** and **120** :

Ar = C_6H_4OH-*o*

palladised charcoal. Ammonia converts **104** (R = Chr, R^1 = Me, X = Ac, Y = CO_2Et) into the diazanaphthalene **120** [110].

Biginelli reaction of **1** with $MeCOCH_2COR$ (R = Me, OEt) and urea in refluxing acetic acid forms the 2-oxo-1,2,3,4-tetrahydropyrimidine **121** [111]. When urea is replaced by thiourea in the above reaction, the product is 6*H*-1,3-thiazine **122** [111]. Here also the active methylene compounds condense with ChrCHO. A 1,4-nucleophilic addition of urea or thiourea to the exocyclic α,β-unsaturated carbonyl group of the condensate ChrCH=C(COMe)COR followed by cyclization gives the Biginelli product [111]. 3-Formyl-6-methylchromone [112] and 6-formylkhellin [113] have been condensed with ethyl acetoacetate and urea in the presence of piperidine to give the appropriate 6-substituted tetrahydropyrimidine. A dry slurry of **1**, ethyl acetoacetate, urea and $In(OTf)_3$ with sodium sulfate as the solid support has been heated under microwave irradiation to give **121** (R = OEt) [114]. The condensate, derived from 6-formylkhellin and XCH_2CN (X = CN, CO_2Et) on treatment with urea and thiourea



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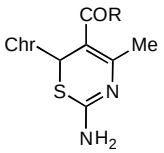

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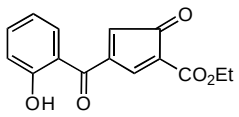

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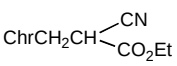
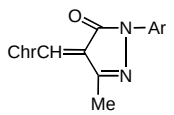


124

gives respectively the appropriate pyrimidine and 1,3-thiazine of the types **121** and **122** [93].

Reduction of **108** with Zn in THF containing aqueous NH_4Cl produces **123** whereas that with Zn in AcOH gives **124** [115].

VII.3 Reactions with Heterocycles Having an Active Methylene Group. Active methylene group present in many heterocycles condenses with the formyl group of **1**, the stereochemistry around the exocyclic olefinic bond of the resultant condensate remaining undetermined in most cases. Condensation of ChrCHO with active methylene group (*cf.* ref. 85) of 3-methyl-1-phenyl (or *p*-nitrophenyl)-pyrazolin-5-one yielding **125** is catalysed by triethylamine [59], MCM41-SO_3H [116], and lithium chloride [117]. The above condensation has also been executed under microwave irradiation [118,119], at room temperature in an ionic liquid like triethylammonium nitrate [120], and under ultrasonic irradiation in acetic acid [83] or in distilled water containing borate zirconia solid acid catalyst [121]. The compound **125** can even be obtained by just grinding a mixture of the reactants in solid state without any solvent at room temperature [122]. The chromone **1** has also been condensed with several other pyrazolinones [99,123,124], barbituric acid [125], thiobarbituric acid [99,123,126], hydantoin, thiohydantoin [127,128], chromanone [129], azlactone [123,130,131], 2-methylthiazolo[3,2-*b*]-*s*-triazol-inone **126** [132] *etc*. Condensations of several 6-substituted 3-formylchromones with creatinine, thiohydantoin, 3-ethylrhodanine, 2-oxo-1,4-benzo-thiazine *etc*. under thermal as well as microwave



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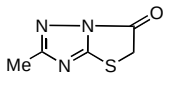

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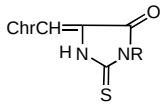

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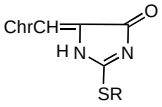

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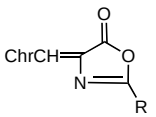

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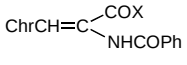
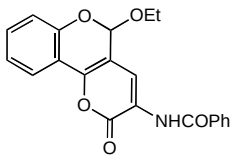


130 : X = NR^1R^2
131 : X = OEt

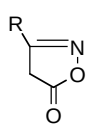


132

conditions [101,133] are known. Isopropylidene malonate and 2,4-thiazolidinedione have also been condensed with **1** under microwave irradiation [119].

Condensation of **125** with thiourea in alcoholic KOH gives **67** (X = SH, Y = OH, thioamide form) [59]. The compound **127** (R = H), derived from **1** and thiohydantoin, gives **127** (R = 4-morpholinomethyl) on Mannich reaction with HCHO and morpholine, and the *S*-alkyl derivative **128** on treatment with R-halide (R = Me, $PhCOCH_2$, CH_2COOH) [128]. The oxazolone **129** (R = Me, Ph), derived from **1** and the appropriate azlactone, has been subjected to hydrolysis and aminolysis [130,131]. The nitrogen nucleophile NHR^1R^2 [$R^1 = R^2$ = Et; R^2R^2 = -$(CH_2)_5$-, $(CH_2)_2$-O-$(CH_2)_2$; R^1 = H, R^2 = Ar, NMe_2, NHPh) brings about transamidation of the lactone function of **129** (R = Ph) to give **130** that may undergo further transformation depending on the reaction conditions and the nature of the R^1 and R^2 groups. The oxazolone **129** (R = Ph) when refluxed with an equimolar or catalytic amount of an aromatic secondary or tertiary amine in ethanol produces the pyranopyran **132** sometimes contaminated with **131** [130].

The isoxazolin-5-one **133** (R = Me or Ph), prepared by treating $RCOCH_2CO_2Et$ with NH_2OH, condenses with **1** giving **134** that on sequential reduction with $NaBH_4$ in methanol and treatment with $NaNO_2$ in AcOH containing $FeSO_4$ gives the acetylene **135** [134].



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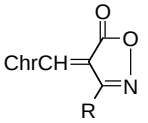

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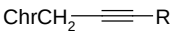
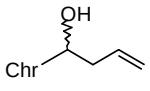


135

VII.4 Addition of Alkyl- and Alkynyl-metal. The homoallylic alcohol **136** is formed by treating **1** with allyltributylstanane in the presence of catalytic amount of CAN in MeCN at room temperature [135] as well with allyl bromide and indium metal in THF-H_2O (1:1) at 30 ºC [136]. The racemic alcohol has been subjected to kinetic resolution with lipase using vinyl acetate as an acyl donor when *R*-alcohol is acylated [136]. Lithium dialkynylcuprate $(RC{\equiv}C)_2CuLi$ (R = TMS, Ph, *n*-Pr, *t*-Bu) undergoes conjugate addition to the unsaturated aldehyde **1** giving **137** which partially isomerises to **138** in the presence of acid. Prolonged contact with silica gel effects total conversion of **137** to **138** having *E*-stereochemistry [137].



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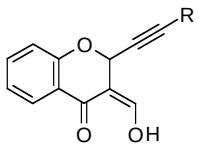

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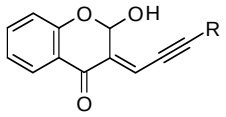
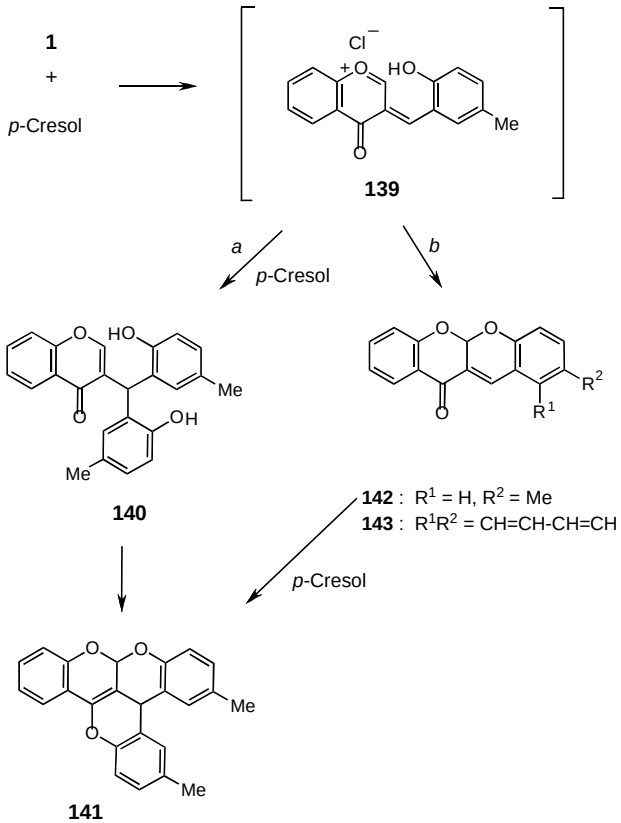


138

VII.5 Addition of Aromatic Compounds. The reaction of **1** with aromatic tertiary amines like *N,N*-diethylaniline and 3-*N,N*-diethylaminophenol in the presence of sulfuric acid has been mentioned in an earlier review [1]. *p*-Cresol reacts with **1** in AcOH - HCl giving the tribenzo[*b,e,i*][1,6,7]trioxophenalene **141** sometimes admixed with the benzopyrano[2,3-*b*]-benzopyran **142** [138]. The aldehyde **1** with *p*-cresol under acidic conditions gives the pyrrilium salt **139**; a second molecule of *p*-cresol undergoes 1,4-addition to **139** giving **140** that cyclises to **141** (Scheme 5 – path *a*)

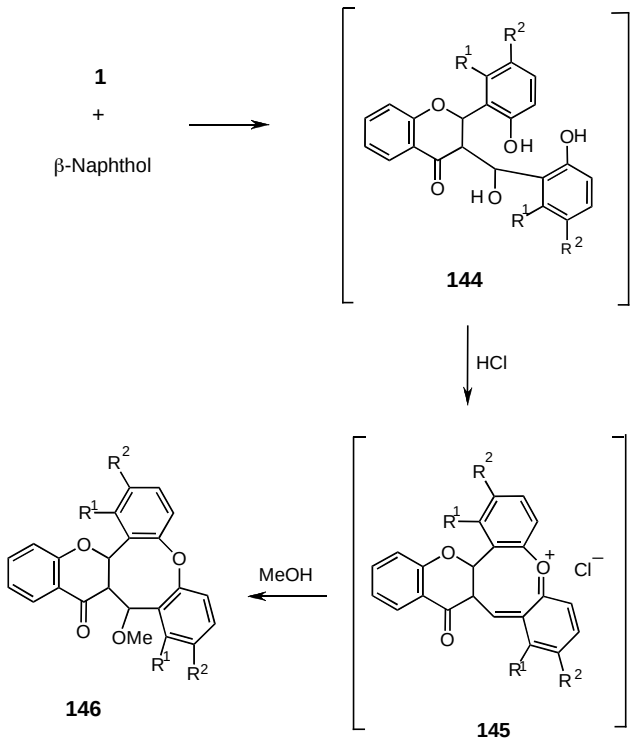
Scheme 5



and an acid catalysed cyclisation of **139** forms **142** (path *b*). That the formation of **141** involves the intermediacy of **140** is proved by the fact that the latter, obtained by treating **1** with *p*-cresol in the presence of anhydrous $AlCl_3$, is indeed cyclised by AcOH - HCl to **141**. The present authors, however, contend that **141** may also arise by Michael addition of *p*-cresol to the α,β-unsaturated carbonyl functionality of **142** and subsequent cyclisation of the resultant adduct.

β-Naphthol and **1** dissolved together in AcOH-HCl form a little bit of **143** and a red mass which on digestion in methanol forms the oxocine **146** as the major product. The formation of **143** involves the cyclisation of the pyrrilium salt analogous to **139** whereas that of **146** involves addition of two molecules of β-naphthol to **1** to give *via* **144** the oxonium salt **145** followed by reaction with methanol (Scheme 6) [138].

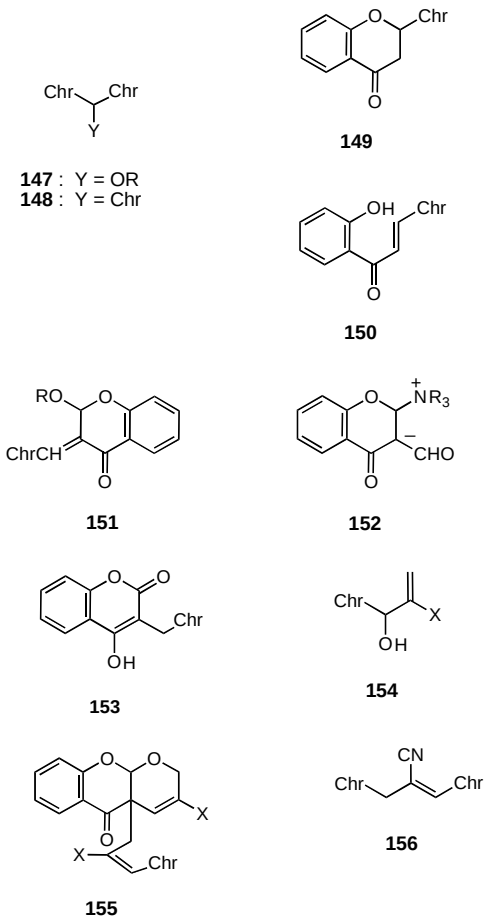
Scheme 6



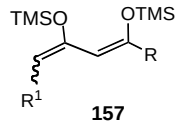
For **144**-**146** : R^1R^2 = CH=CH-CH=CH

VII.6 Baylis-Hillman Reaction. ChrCHO on refluxing with catalytic amount of NEt_3 in a protic solvent ROH (R = Me, Et) gives in addition to Chr-H and **84** its self-condensation products **147-149** and **151** *albeit* in low yields [30]. Here the zwitterionic intermediate **152** (R = Et), derived from **1** and NEt_3, undergoes 1,2- as well as 1,4-addition to the α,β-unsaturated aldehyde functionality of **1**, the resultant Baylis-Hillman adducts undergoing further transformation giving the aforesaid condensation products [30].

Alumina not only brings about disproportionation of **1** to the alcohol **6** and acid **7** but also catalyses the Baylis-Hillman type reaction of **1** and **7** with **1** as well as **7** giving the chromones **9**, **149**, **150** and **153** [12]. Anhydrous $AlCl_3$ catalysed self-condensation of **1** to **9**, **150** and **153** also involves an initial Baylis-Hillman reaction of the aldehyde **1** with itself [13]. 1,4-Diazabicyclo[2,2,2]octane (DABCO] catalysed Baylis-Hillman reaction of **1** with CH_2=CH-X (X = CO_2Me [139] and COMe [140]) gives the adduct **154** accompanied by the adduct's self-condensation product **155** whereas that with acrylonitrile produces a mixture of **154** (X = CN) and **156** [140].



VII.7 Addition of Enol Ethers. The 1,3-bis-silyl ether **157** (R = OMe, OEt, Et, Ph; R^1 = H, Me, Et, CH_2=CH-CH_2, *n*-Bu, Bn *etc*.) undergoes domino Michael-retro-Michael-aldol condensation with **1** dissolved in CH_2Cl_2 containing trimethylsilyl triflate giving the substituted benzophenone **94** [141]. [3+3]Cyclisation of 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-diene **158** with 6-chloro-3-formyl-7-methylchromone followed by an intramolecular Williamson reaction gives the 6-(salicyloyl)chroman **159** [142].



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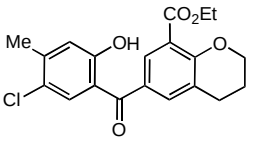

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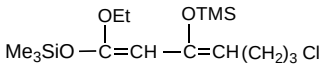

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VII.8 Addition of Enamines. The reactions of a variety of acylic, alicyclic and heterocyclic enamines with **1** leading to either 5*H*-1-benzopyrano[4,3-*d*]pyridines or 3(5)-salicycloylpyridines or a mixture of both have been comprehended in earlier two reviews [1,2]. There are, however, conflicting reports on the reaction of **1** with β-aminocrotonic acid derivatives **160** (R = OMe, OEt). A mixture of **1** and enamine **160** (R = OEt) in refluxing ethanol gives the fused pyridine **103** (X = OH); a cursory report on the formation of the dihydropyridine **104** (R = Chr, R^1 = Me, X = Y = CO_2Et) by reacting **1** with two molar proportion of **160** (R = OEt) in AcOH has been made [143]. Later on, the same reaction in AcOH at 60 ºC is reported to give a mixture of the dihydropyridines **104** (R = Chr, R^1 = Me, X = Y = CO_2Et) and **161** (E = CO_2Et), both of which can be dehydrogenated by manganese dioxide [144]. $MeCOCH_2CO_2Et$ with **1** under reflux in ethanol containing liquor ammonia gives exclusively the pyranopyridine **103** (X = OH, R = OEt) identical with that obtained by treating **1** with **160** (R = OEt) indicating that the formation of **160** (R = OEt) from $MeCOCH_2CO_2Et$ and ammonia predominates over the base catalysed condensation of the acetoacetic ester with the aldehyde **1**; the enamine **160** (R = OEt) thus formed reacts with **1** giving **103** (X = OH, R = OEt) [108]. Similar condensation of $MeCOCH_2CO_2Me$ with **1** in refluxing methanol-ammonia gives the fused pyridine **103** (X = OH, R = OMe) [108] in contrast to the previously reported exclusive formation of **104** (R = Chr, R^1 = Me, X = Y = CO_2Me) [145].

Both 2-aminochromone **162** [146] and 4-amino-2*H*-1-benzopyran [39] behave as enamines to undergo initial Michael addition to the α,β-unsaturated aldehyde **1** to give ultimately the fused pyridines **164** and **165**, respectively. 5-Aminopyrazole **166** (R = alkyl, aryl), however, behaves differently from the aforesaid two aminobenzopyrans; it undergoes through its exocyclic and endocyclic nucleophilic nitrogens a [3+3]cyclization with **1** with concomitant opening of the pyran ring to afford the pyrazolo[1,5-*a*]pyrimidine **167** [147]. The initially formed Michael adduct of the chromone based dienamine **163** with **1** reorganizes to the xanthone **90** (R = CHO) [148]. The formation of the pyridopyrimidine **169** by reacting **1** with the pyrimidine **168** (R = H, Me; R^1 = MeO, MeS, NH_2, OH, SH) has been explained by the authors [149] as 'termic rearrangements' of the intermediate arising from the condensation of C-5 and 6-amino group of **168** respectively with the aldehyde and ketogroups of **1**. The present authors, however, contend that the heterocyclic enamine **168** like other enamines undergoes Michael addition to ChrCHO with concomitant opening of the pyran ring; the resultant intermediate undergoes double cyclisation, the first one involving phenolic OH and CHO groups and the other NH_2 and keto functionalities, to give **169**. Pyrrole functions as a dienamine in condensing with the aldehyde **1** to give the *meso*-tetrakis (chromen-3-yl)-porphyrin **170** [156].

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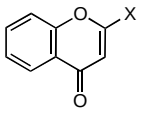
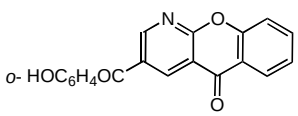


162 : X = NH_2

163 : X = CH=NMe_2 -*E*



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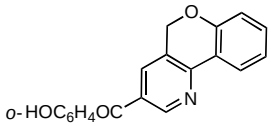

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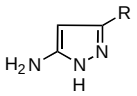

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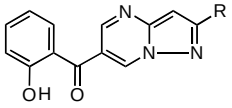

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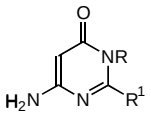

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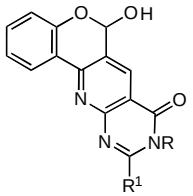

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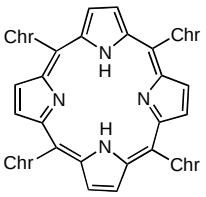

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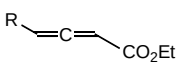
VIII. Cycloaddition Reactions.

The cycloaddition reactions of all chromone based compounds reported till July, 1996 have been

comprehended in a review article [151]. So the present write-up on the cycloaddition reactions of ChrCHO and some simple derivatives thereof gives emphasis only on later publications with passing references to the earlier ones. Neither [2+1]- nor [2+2]-cycloaddition reaction of ChrCHO or any of its derivatives is known. The other types of cycloaddition reactions are written in the following few subsections.

VIII.1 [3+2]Cycloaddition. The [3+2]cycloaddition reactions of **1** [152,153], the acetal **83** (Y = bond) [154], the condensates **106-109** [155,156] and the oxazolone **129** (R = Ph) [155] with diazomethane and those of 3-formyl-6-methylchromone with diazomethane, diazoethane and diazopropane [157], and of **1** [158] and **106** [159] with phenyldiazomethane have been elaborately discussed in the aforesaid review article [151]. The pyridinium phenacylide, generated by treatment of phenacyl-pyridinium bromide with a base, also undergoes [3+2]cycloaddition to the olefinic bond of **1**, the resultant adduct undergoing further transformation [151,160]. The dipole **172**, obtained by interaction of triphenylphosphine with the allenic ester **171** (R = H), undergoes [3+2]cycloaddition to the pyran 2,3-bond of **1** in refluxing benzene, the resultant adduct being deformylated under the reaction conditions to give the cyclopentenochromone **173** [161].



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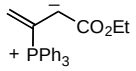

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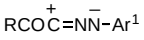

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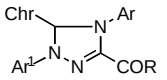

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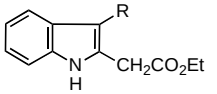

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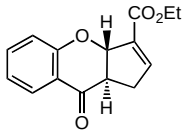

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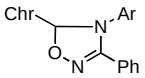

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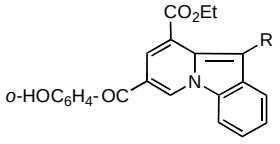

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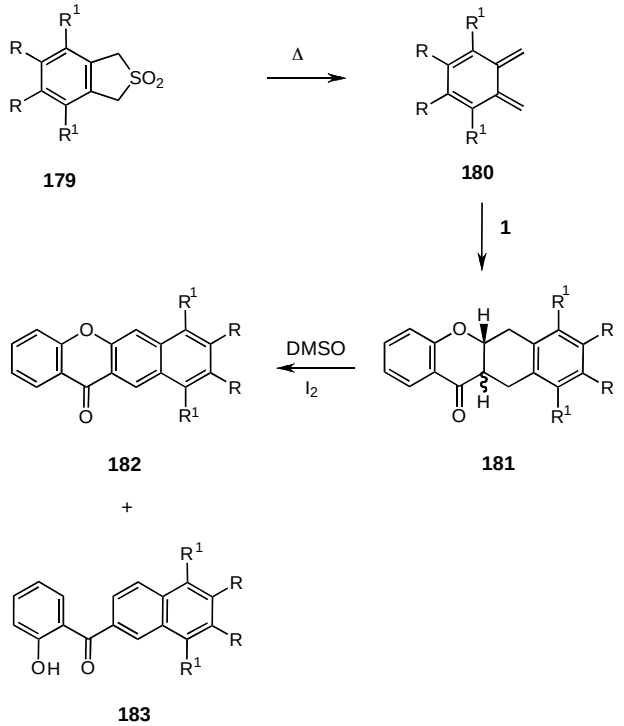
1,3-Dipoles like benzonitrile oxide [162] and the nitrilimine **174** (R = Me, OEt; Ar^1 = *p*-tolyl, *p*-bromophenyl) [163] add across the azomethine double bond of the Schiff base **19** to give respectively the 1,2,4-oxadiazoline **175** and 1,2,4-triazoline **176**. [3+2]Cyclo–addition of the nitrone **43** (R = Ph) with several electron rich as well as electron deficient olefins [163- 165] has been comprehended elsewhere [21] by one of the present authors. The said nitrone undergoes regiospecific 1,3-dipolar cycloaddition to C_2-C_3 π-bond of the allenic ester **171** (R = H, Me, Et) and the resultant cycloadduct reorganizes to form the benzo[*b*]indolizine **177** admixed with a small amount of the indole **178** [166].

A fullerene-chromone dyad has been prepared by 1,3-dipolar cycloaddition of the azomethine ylide, generated *in situ* by refluxing a mixture of **1** and *N*-methylglycine in toluene, to C_{60} [167].

VIII.2 [4+2]Cycloaddition.

VIII.2.1 ChrCHO as a 2π-Component. The first proof for the dienophilicity of ChrCHO came from its cycloaddition with 2,3-dimethyl-1,3-diene and Danishefsky's diene, the reaction with the former diene necessitating the use of a catalytic amount of $TiCl_4$ [168]. The dienamine **163** undergoes Diels-Alder (D-A) reaction with the aldehyde **1** in refluxing DMF; the adduct ultimately gives the xanthone **90** (R = H) by base catalysed elimination of $NHMe_2$ and deformylative pyran ring opening, the amine **163** or the adduct itself functioning as the base [148].

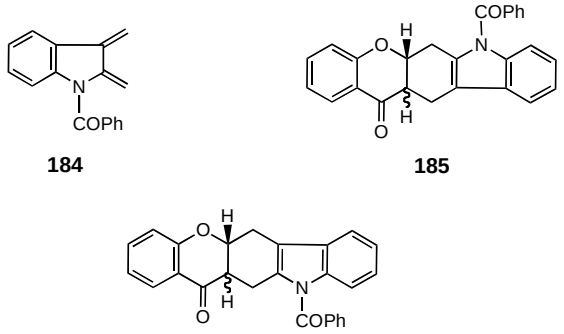
Scheme 7



179 **180** **181** **182** **183**

D-A reaction of **1** with *ortho*-benzoquinodimethane **180**, generated *in situ* by thermal decomposition of 1,3-dihydrobenzo[*c*]thiophane-2,2-dioxide **179** (R = H, Br; R^1 = H, OMe), gives a stereoisomeric mixture of the adduct **181** which on refluxing with DMSO-I_2 is dehydrogenated to the xanthone **182**, a small amount of the naphthyl phenyl ketone **183** arising during oxidation (Scheme 7) [169].

[4+2]Cycloaddition of **1** with indole-*o*-quinodimethane **184**, generated from 1-benzoyl-2,3-di(bromomethyl)-indole, gives diastereoisomeric mixtures of **185** and **186** after *in situ* defoπrmylation [170].



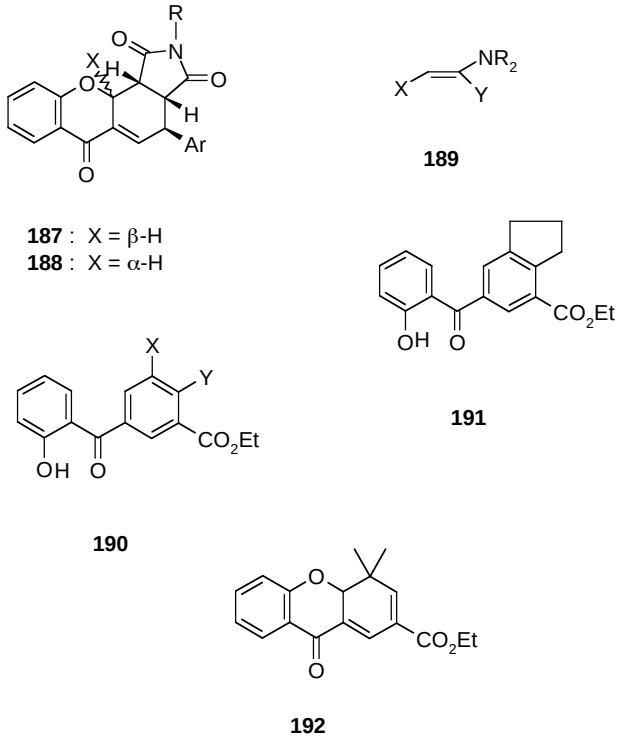
184 **185**

186

VIII.2.2 ChrCHO as a 4π-Component. 3-Formylchromone **1** behaves as a heterodiene in Inverse Electron Demand Diels-Alder (IEDDA) reaction with various olefins. Its reactions with diphenylketen, dichloroketen and several enol ethers, and some important transformations of the resultant cycloadducts have been well comprehended [2, 151].

VIII.3 [4+2]Cycloaddition of 3-(2-Substituted vinyl)-chromone. D-A reaction of 3-styrylchromone **86** (R = Ar = phenyl, *m*-chloro- and *m*-ethoxy-phenyl) with *N*-methyl- and *N*-phenyl-maleimide has been executed under microwave irradiation. D-A reactions of both *Z*- and *E*-isomers of the aforesaid 3-styrylchromone with *N*-methylmaleimide gives the cycloadducts in a stereoselective manner, *Z*-isomer giving the *endo*-adduct **187** (R = Me) and *E*-isomer the exo-adduct **188** (R = Me). Predominant formation of the exo-adduct **188** (R = Ph) from the *Z*-isomer of **86** (R = Ar) and less reactive *N*-phenylmaleimide involves conversion of *Z*-isomer to the *E*-isomer followed by normal D-A reaction [171]. D-A reactions of several 3-(2-hetarylvinyl)chromones with maleic anhydride in toluene have been described [133b].

The formation of 2-hydroxybenzophenone **190** from the electron deficient diene **91** (R = OEt) and several acyclic as well as cyclic enamines **189** [X = H, Y = Ph; X = Ph, Y = H; XY = -$CH_2(CH_2)_{1-4}CH_2$-, *o*-$C_6H_4(CH_2)_{1-2}$, -$(CH_2)_{1-2}C_6H_4$-*o*] involves a domino IEDDA reaction, elimination and intramolecular elimination (*i.e.* pyran ring opening) [106,172]; for example, the reaction between **91** (R = OEt) and 1-(1-pyrrolidinyl)cyclopentene gives **191**. When a 2,2-disubstituted 1-aminoalkene like Me_2C=$CHNR_2$ (NR_2 = pyrrolidinyl) is used, no intramolecular elimination is possible, the final product being a 4,4a-dihydroxanthone derivative **192** [106].



187 : X = β-H
188 : X = α-H

189

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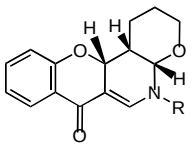
192

VIII.4 [4+2]Cycloaddition of Anils and Hydrazones of 4-Oxo-4*H*-1-benzopyran-3-carbox-aldehyde. The anil **19** and hydrazone ChrCH=$NNMe_2$ participate as heterodienes in [4+2]cycloaddition reactions. D-A reaction of the former with highly active dienophiles like dichloroketene and chloro–(phenyl)–ketene [173] and that of the latter with *N*-phenylmaleimide [174] are known. 3,4-Dihydro-2*H*-pyran reacts with ChrCH=NR (R = C_6H_4X-*p*; X = H, Me, OMe, Cl, Br) in the presence of indium or scandium triflate at ambient temperature to give the *endo*-adduct **193** regiospecifically in high yields; ChrCH=NCH_2Ph, however, gives **193** (R = CH_2Ph) in 55% yield with $In(OTf)_3$ but 100% with $Sc(OTf)_3$ [175]. Stirring a mixture of **1**, $ArNH_2$ (Ar = phenyl, *p*-tolyl) and 1-vinylpyrrolidin-2-one in water or H_2O-MeCN containing 5 mol% CAN at room temperature produces the tetrahydroquinoline **194** (R = H, Me) in 80-82% yield. Here the azomethine π-bond in conjugation with the phenyl π bond of the initially formed anil ChrCH=NAr undergoes [4+2] cycloaddition with the said vinyl-pyrrolidine. Treatment of the adduct **194** with 2.5 equivalent of CAN in MeCN at 0 ºC brings about its aromatisation to **195** [176].



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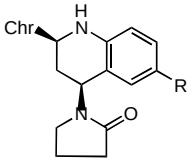

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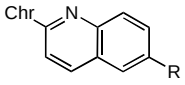

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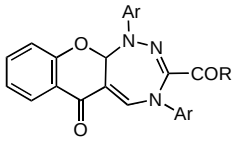
VIII.5 [4+3]Annulation of 3-(*N*-Aryliminomethyl)-chromone with a 1,3-Dipole. The nitrilimine **174** (R = Me, OEt; Ar^1 = *p*-bromophenyl) undergoes [4+3] annulation with the 4π component of the title aryliminomethylchromone **19**, apart from [3+2]cyclo-addition with its azomethine function, to give the fused triazepin **196** [163]. Similar annulation of the dipole **172** with **19** gives **197** that reorganises to 1-benzopyrano[2,3-*b*]azepin **198** [161].



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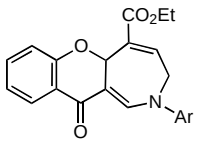

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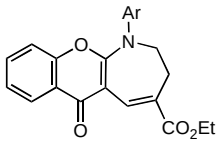

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