Chemistry of 4-Oxo-4*H*-[1]benzopyran-3-carboxaldehyde

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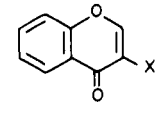
I. Introduction.

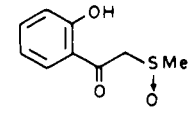
4-Oxo-4*H*-[1]benzopyran (trivial name - chromone) received early attention of chemists because of its natural abundance in the flavonoid family, and the chemistry of this benz-annulated γ-pyrone as well as the parent γ-pyrone itself has been extensively studied in the past over a long period [1-3]. The resurgent interest in the chemistry of chromones is, however, due largely to their pharmaceutical activity [4]. The success of disodium chromoglycate in the treatment of certain types of bronchial asthma [5] and the recognition of the O-C=C-C=O grouping as the structural requirement for activity in this compound [6] have led to a spate of investigations into chromones bearing a reactive functionality on the pyran ring [7-10]. Of the different functionalised chromones, chromone-3-carboxaldehyde occupies a unique position because of a number of heterocycles obtainable thereform and this system is being extensively studied since 1967. The reactions of chromone bearing a formyl group attached to the pyran as well as the benzene ring published up to 1976 have been compiled by Ellis [11] in a review article. Since then many publications on the chemistry of chromone-3-carboxaldehyde alone have appeared, and thus they warrant a current review. The present review will present a comprehensive survey of the synthesis, properties, reactions of chromone-3-carboxaldehyde and the utilisation of its simple condensates for the preparation of different chemical systems, and covers the literature through volume **97** of *Chemical Abstracts*. Alkyl, alkoxy, and halogeno substituents in the benzene ring remain unaffected in most of the reactions described for the unsubstituted chromone-3-carboxaldehyde in this review.

II. Synthesis.

A mixture of *o*-hydroxy-ω-formylacetophenone and ethyl orthoformate on refluxing in acetic acid [12] or by mild treatment with perchloric acid [13] produces 3-formylchromone **1**. *o*-Hydroxy-ω-formylacetophenone also gives rise to **1** by treatment with acetic-formic anhydride and sodium formate under mild conditions [14]. A facile synthesis of **1** involves the treatment of *o*-hydroxyacetophenone with Vilsmier-Haack reagents [15-18]. *o*-Hydroxy-ω-(methylsulfinyl)acetophenone (**6**) obtained by the action of sodium methyl sulfinylmethide on salicylic ester on treatment with two moles of formaldehyde in the presence of a base gives 3-(hydroxymethyl)-3-(methylsulfinyl)-4-chromanone (**7**) that can be converted by thermal elimination of CH_3SOH to 3-hydroxymethylchromone (**2**) [19]. The latter can be oxidised to **1** with either concentrated nitric acid or sodium dichromate-acetic acid [12].



1 : X = CHO
2 : X = CH_2OH
3 : X = Cl
4 : X = Br
5 : X = H



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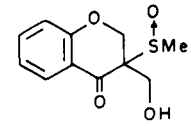

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III. Properties and Spectra.

The properties of the γ-pyrone ring are essentially aliphatic, even though it gives reaction characteristics of an aromatic pyryllium betaine more readily than an α-pyrone and the properties of the heterocyclic ring are not greatly modified as a consequence of benz-annulation [20]. Being non-aromatic, the parent chromone **3** may be regarded as a β-keto-enol ether, this property being manifested in its reaction with a number of nucleophiles. Hence chromone-3-carboxaldehyde (**1**) is likely to behave as an α-benzoyl-β-aryloxy-α,β-unsaturated aldehyde. Strong ir absorbance of **1** at 1695, 1650 and 1620 cm^{-1} has been attributed to its CHO, CO and C=C groupings, respectively [17]. Dipole moment and ir data indicate it to have *S-cis*-configuration stabilised by intramoleclar hydrogen bonding [21]. In its ^{1}H-nmr spectrum the aldehydic proton and the proton at the 2-position appear at approximately δ 10.40 and 8.60 ppm respectively [17]. The ^{13}C nmr spectrum [22,23] and mass spectral fragmentation [17] of 3-formylchromone have also been fully described. The protonation of **1** has been examined by uv, the basicity constant calculated using different equations differing markedly. The Bunnett-

Olsen equation is the most suitable for estimation of its reactivity and for comparison with quantum chemical calculation [24]. The ir frequencies of protonated chromone-3-carboxaldehyde indicate its ketonic oxygen having higher basicity than that of the aldehydic oxygen [25]. Molecular orbital parameters as electron charge, net free charge, frontier electron density, bond order, delocalisation energy and free valency for **1** have been calculated, and a correlation between these parameters and antiasthmatic

activity of the compound has been expressed [26]. Polarogram of **1** contains two waves corresponding to the reduction of the aldehyde group; Swain-Lupton relations are obtained for half-wave potentials (E), the latter also having linear relationship with the proton acceptor ability of the compound [27].

IV. Oxidation and Reduction.

Nohara *et al.* [28] studied the oxidation of 3-formylchromone (**1**) with several reagents. Aqueous solution of 30% hydrogen peroxide in acetic acid brings about oxidative degradation of 3-formylchromone to salicylic acid; the same reagent in acetone gave a mixture of products. Other oxidation with silver oxide, arsenic oxide, dilute nitric acid, chromic anhydride-dimethylformamide, or electrolytic oxidation failed to give satisfactory results. Oxidation with chromic anhydride in acetic acid did produce chromone-3-carboxylic acid but in a very poor yield. However, oxidation by Jone's reagent (chromic anhydride-acetone) at 15-20° improved the yield of chromone-3-carboxylic acid. A higher yield (~75%) of the acid is obtained by oxidation of the aldehyde with sodium hypochlorite at 10-20° in the presence of sulfamic acid, resorcinol or pyroglutamic acid as chlorine scavengers [29]. Under the conditions of the latter two oxidation processes, an alkyl, alkoxy, acetoxy group attached to benzene ring remain unaffected. Platinum catalysed oxidation of **1** has not been properly investigated [*cf.* 30]. Treatment of a solution of **1** in carbon tetrachloride with 1.2 equivalents of *N*-bromosuccinimide under reflux in the presence of azobisisobutyronitrile or under illumination and subsequent quenching with water also affords chromone-3-carboxylic acid in excellent yield, any ethyl, isopropyl, benzyloxy group attached to the benzene ring, however, undergoing concomitant benzylic oxidation [31,32]. Baeyer-Villiger oxidation of **1** gives 3-hydroxychromone [33].

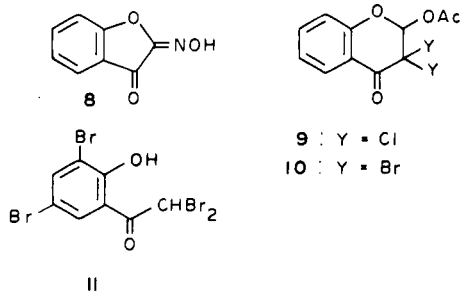
Though the attempts to hydrogenate 3-formylchromone with palladium black in methanol or platinum oxide in acetic acid were unsuccessful, the reduction of **1** with sodium borohydride in the presence of anhydrous aluminium chloride in tetrahydrofuran to 3-hyroxymethylchromone **2** in 10-12% yield had been achieved [17,28]. Borane in tetrahydrofuran brings about smooth and quantitative reduction of **1** to **2** [34].

V. Electrophilic Substitution.

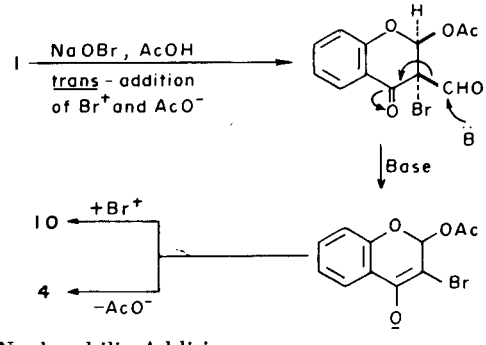
Electrophilic substitution of **1** is not well studied. The nitration reaction is worth special mention. The usual mixture of concentrated nitric acid and concentrated sulfuric acid nitrates **1** at its 6-position [17,28], whereas Curran *et al.* [35] reported with the proper mechanism the conversion of **1** by treatment with red fuming nitric acid to 5-nitro-2,3-benzofurandione 2-oxime **8**.

VI. Electrophilic Addition.

Electrophilic addition to the 2,3-double bond of **1** is manifested in its reaction with sodium hypohalite in acetic acid medium [36]. An acetic acid solution of **1** when reacted with aqueous sodium hypochlorite gives mainly 3-chlorochromone **3** together with a small amount of 2-acetoxy-3,3-dichlorochromanone **9**, similar reaction with hypobromite in the dark resulting in the corresponding bromo compounds **4** and **10**. The latter reaction when conducted under normal lighting conditions produces the tetrabromoacetophenone **11** in addition to the normal products **4** and **10**. The formation of **11** has been explained by assuming a radical reaction and that of the normal products by an ionic mechanism [36] as depicted in Scheme 1.



Scheme I

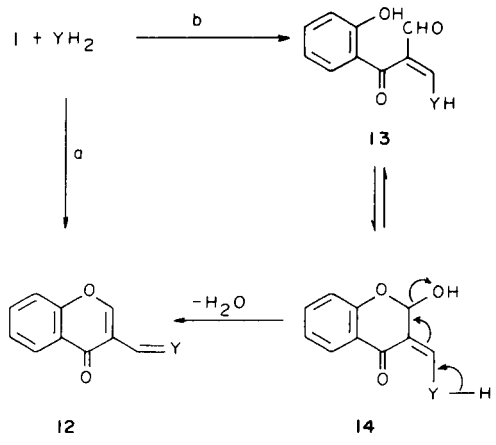


VII. Nucleophilic Addition.

In 3-formylchromone there are three electron deficient sites *viz.* C-2, aldehydic carbon and the benzylic carbonyl carbon, the last one having obviously the least electrophilicity compared to that at the other two centres. The reaction of **1** with any nucleophile YH_2 such as an amine, hydrazine, monosubstituted hydrozine, hydroxylamine or a reactive methylene compound in conjunction with an appropriate base gives initially the condensation product **12** that appears to arise by a straight forward 1,2-addition of the nucleophile to the aldehyde function (Scheme 2-Path a). An alternative route involving the 1,4-addition of the nucleophile with concomitant opening of the pyrone ring and subsequent recyclisation of the intermediate **13** *via* **14** (Scheme 2-Path b) may also be evisaged for the formation

of **12**. Because of the "chemical symmetry" of the formyl group and C-2 of the chromone, it is very difficult to pinpoint whether a nucleophile is undergoing 1,2- or 1,4-addition to 3-formylchromone. The best way to sort out this problem is to label **1** specifically at either the 2-position or the aldehyde function, subject the labelled compound to an appropriate nucleophilic addition reaction and subsequently analyse the resultant condensation product or any degradation product thereof. Unfortunately, none of the published methods [12-19] for the preparation of 3-formylchromone is suitable for incorporation of the desired specific labelling. The question of 1,2- or 1,4-addition that has been partially answered by studying the reaction of **1** with amidines and enamines is discussed in later sections.

Scheme 2

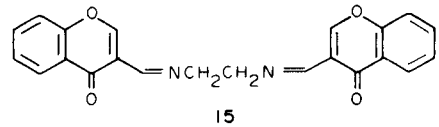


VII. 1. Nucleophilic Addition of Nitrogenous Nucleophiles.

A. Addition of Amines.

No reaction of **1** with any simple aliphatic monoamine is reported as yet. Very recently, interaction of **1** with ethyl aminoethanoate in refluxing toluene containing *p*-toluenesulfonic acid has been reported to give a mixture of ethyl 4-(2-hydroxybenzoyl)-6-(4-oxo-4*H*-1-benzopyran-3-yl)pyridine-2-carboxylate and ethyl 4-(2-hydroxybenzoyl)pyrrole-2-carboxylate [37]. Refluxing an equimolar mixture of **1** and ethylenediamine in benzene gives 1,2-bis[4-oxo-4*H*-1-benzopyran-3-ylmethyleneamino]ethane (**15**) [38], a two fold excess of the amine resulting in the formation of the *E*-isomeric aldimine **16** in a very poor yield. The formation of the acetophenone derivative **17** by reacting **1** with aniline has been cursorily mentioned [39]. Fitton *et al.* [40,41] made a thorough investigation into the above reaction. 3-formylchromone reacts with an aromatic primary amine (1:1 molar ratio) to give a mixture of 3-(aryliminomethyl)chromone **18** and 2-arylamino-3-(aryliminomethylene)chroman-4-one **19**, excess of the amine producing only the 1,4-adduct **19** [40]. The latter is formed by Michael addition of a second molecule of the amine to **18**. The 3-aryliminomethyl group not only stabilises the pyrone ring of **18** towards the usual ring cleavage by amines, but also facilitates the addition of other external nucleophiles which would not otherwise react with the pyrone ring as evident by Michael addition of alcohols and thiols to the anil **18** [41]. The aldehyde **1** condenses with 2-aminofurans [42] and 4-aminothiomorpholine 1,1-dioxide [43] to give simply the azomethine derivatives.

Aniline (**20**) having a nucleophilic functionality XH (X = O, S, NH, NCH_3 *etc.*) at its *ortho* position condenses with **1** giving the fused seven-membered heterocycle as **21** that dehydrogenates to **22** either by spontaneous air oxidation or on treatment with chloranil [44] or nitrobenzene [45]. Recently, a Swiss group [46] has shown that the condensation product of **1** and *o*-phenylenediamine **20** (X = NH), tentatively assigned as the anil **27** by Ghosh and Khan [38] or the dihydrodiazepin **21** (X = NH) by Fitton *et al.* [44] has a complicated tetraaza[14]annulene structure, and it on oxidation by chloranil [44] or on digestion in acetic acid [38,45] gives the benzimidazole **24**, not the isomeric benzdiazepin **22** (X = NH) as proposed earlier [38,44,45]. However, the structure **24** assumed merely on the basis of its ^{13}C-nmr spectrum is not convincing to the present reviewer.



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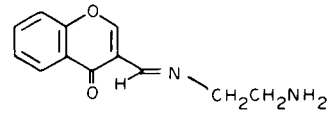

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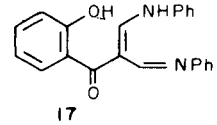

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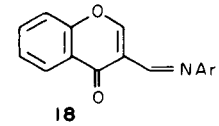

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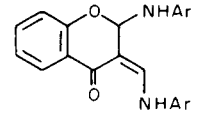

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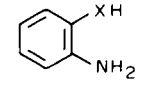

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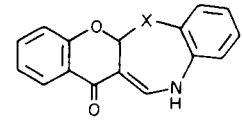

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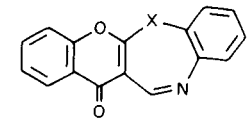

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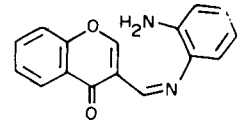

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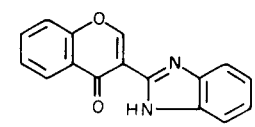

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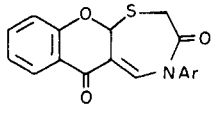
Thioglycollic acid (or its ethyl ester) gives a 1,4-adduct with the anil **18** that cyclises to the fused thiazepinone **25** provided there is an electron-donating substituent in the amine moiety of the anil [41]. Activated manganese dioxide transforms **18** to 3-(arylaminomethylene)chroman-2,4-dione **26**, presumably *via* oxidation of 2-hydroxy-3-arylaminomethylene)chroman-4-one intermediate [41]. Compound **18** reacts with dichloroketene or chloro(phenyl)ketene to afford the fused pyridine derivative **28**, the latter presumably arising from the [4 + 2] adduct **27** by spontaneous dehydrohalogenation [47].



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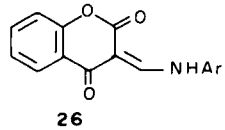

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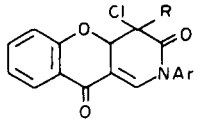

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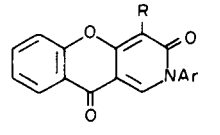
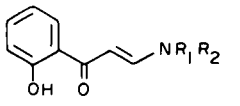
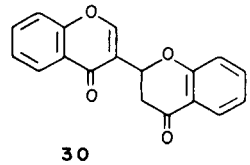


28 : R = Cl, Ph

A secondary aliphatic amine undergoes 1,4-addition to **1**, the resultant adduct undergoing in presence of the base spontaneous Grob fragmentation to yield the *trans*-enaminoketone **29** [48]. Triethylamine gives with **1** a complicated mixture from which the dihydrobischromone **30** has been isolated in a poor yield (~5%) though pyridine fails to bring about any change in 3-formylchromone [49]. The reaction of **1** with an aromatic tertiary amine as *N,N*-diethylaniline in sulfuric acid is known to produce a leuco base which on dehydrogenation with lead tetraacetate gives a green dye **31** [15] analogous to Malachite Green. A similar reaction of the aldehyde **1** with 3-*N,N*-diethylaminophenol forms the bischromone **32** [15]. Unlike aromatic aldehydes, chromone-3-carboxaldehyde does not condense with ethyl 2-methyl- and 2,4-dimethylpyrrole-3-carboxylate to give any trihetarylmethane derivative, but it condenses with strongly basic kryptopyrrole (2,4-dimethyl-3-ethylpyrole) in presence of boron trifluoride etherate to give 2,4-dimethyl-3-ethyl-4-(4-oxo-4*H*-1-benzopyran-3-ylmethylene)-pyrrilium fluoborate, the addition of a second molecule of kryptopyrrole to this pyrrilium salt not taking place at all [50].



29 : $R_1 = R_2 = CH_3$,
$R_1 R_2 = -(CH_2)_5-$



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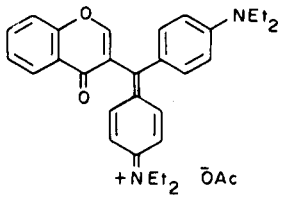

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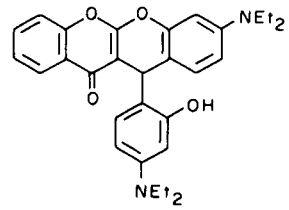

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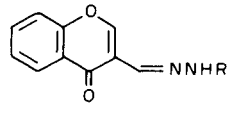
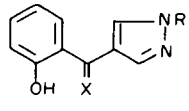
B. Addition of Hydrazines.

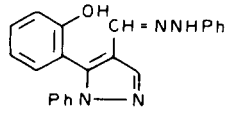
The reaction of **1** with hydrazine and monosubstituted hydrazines has been studied in some details by Ghosh and Mukhopadhyay [51]. On being treated with hydrazine and phenylhydrazine, **1** produces the hydrazones **33** and **34** which on prolonged boiling in ethanol furnish by intramolecular addition - elimination sequence the pyrazoles **38** and **39** respectively. On the other hand, the hydrazones **35-37** do not give any pyrazole even on prolonged refluxing in either ethanol or acetic acid. As the thermal energy is increased by refluxing these hydrazones in ethylene glycol, the semicarbazone **35** and the hydrazone **36** afford the same pyrazole **38** as obtained from **1** and hydrazine, and the hydrazone **37** isomerises to **40**. Eiden and Haverland [52] reported by refluxing in ethanol a mixture of **1** and phenylhydrazine in a 1:2 molar ratio the formation of the phenylhydrazone **42** of 1-phenyl-5-(2-hydroxyphenyl)pyrazole-4-carboxaldehyde. A later publication [53] describes the reaction of **1** with excess phenylhydrazine leading to the formation of **39, 41** and **42**. Here the initially formed hydrazone **34** takes up two different reaction courses as shown in Scheme 3. It undergoes intramolecular 1,4-addition with concomitant opening of the pyrone ring to **39** that gets derivatised by phenylhydrazine present in excess to form **41** (Path a). In the other course of reaction, nucleophilic attack by phenylhydrazine at C-2 of



33 : R = H
34 : R = Ph
35 : R = $CONH_2$
36 : R = COPh
37 : R = $C_6H_4NO_2(p)$



38 : R = H ; X = O
39 : R = Ph ; X = O
40 : R = $C_6H_4NO_2(p)$; X = O
41 : R = Ph ; X = NNHPh



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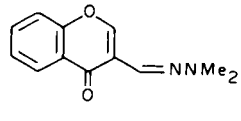

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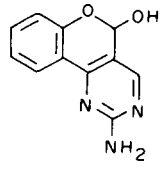

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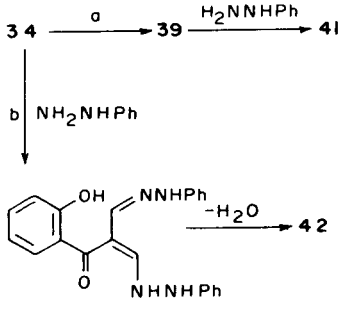
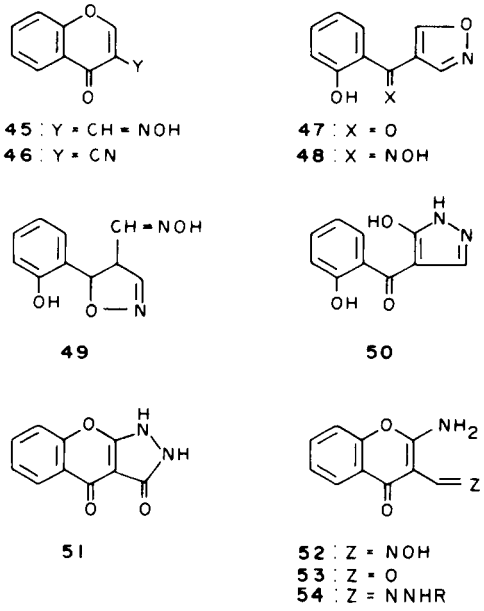
the pyrone moiety of **34** opens up the pyrone ring, (Path b), the resultant intermediate further cyclising to **42**. Dimethylhydrazone **43** of 3-formylchromone on refluxing with phenylhydrazine and guanidine in ethanol gives respectively the same pyrazole **39** and pyrimidine **44** [54] as are obtained from the parent aldehyde **1** under similar conditions.

Scheme 3

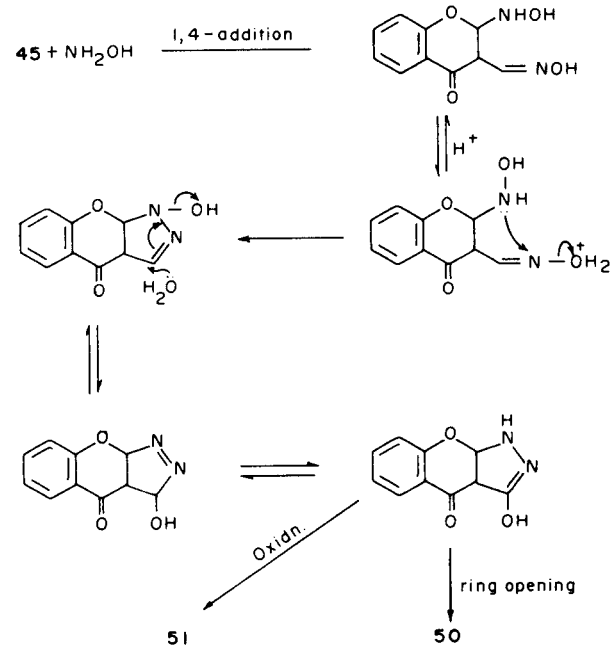


C. Addition of Hydroxylamine.

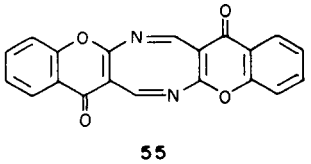
When 3-formylchromone is treated with hydroxylamine hydrochloride in a 1:1 molar ratio, 3-hydroxyiminomethylchromone **45** results. The facile dehydration of the oxime **45** by refluxing it either in formic acid in presence of sodium formate or in ethanol containing hydrochloric acid to 3-cyanochromone **46** [55] suggests that the oxime has *Z*-isomeric structure. While refluxing **1** with hydroxylamine hydrochloride in presence of hydrochloric acid, 4-(2-hydroxybenzoyl)isoxazole **47** is also obtained in nearly 8% yield as against 75% yield of **46**, the former can be converted to the latter in quantitative yield by heating in dimethylsulfoxide [55]. Recently, the reaction of **1** with hydroxylamine has been reinvestigated by a Polish group [56]; depending on the reaction conditions and the proportion of the reagents used, the compounds **48-52** are formed. The formation of **48** and **49** from **1** with excess hydroxylamine under alkaline condition is analogous to the formation of **41** and **42** by reacting **1** with excess phenylhydrazine and can be rationalised by the same type of mechanism as shown in Scheme 3. The mechanism for the formation of **50** and **51** under acidic condition is depicted in Scheme 4. Alkali converts **45** to **53** [15] that is further derivatised by hydroxylamine to **52**.



Scheme 4



The pyrazoles **38** and **39** arise from the reaction of the oxime **45** with the hydrochlorides of hydrazine and phenylhydrazine respectively; with free hydrazine base, an ethanolic solution of **45** as well as a benzene solution of **46** affords the hydrazone **54** (R = H, Ph) corresponding to 2-amino-3-formylchromone **53** [54]. An aliphatic amine induces self-condensation of **45** as well as **46** to the 1,5-diazocine derivative **55** susceptible to hydrolysis to **53** [54]. With guanidine the oxime **45** and the nitrile **46** give the fused pyrimidines **56** and **57** [53,54] respectively. The oxime **45**, like 2-amino-3-formylchromone (**53**) and 3-cyanochromone (**46**), condenses with active methylene compounds as acetylacetone, ethyl acetoacetate, diethyl malonate and ethyl cyanoacetate to give the fused pyridine derivatives **58-61** respectively [57,58].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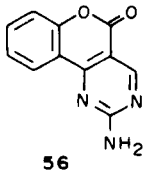
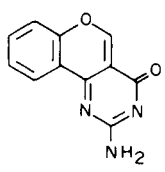

56



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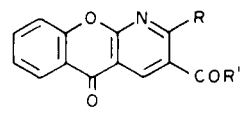
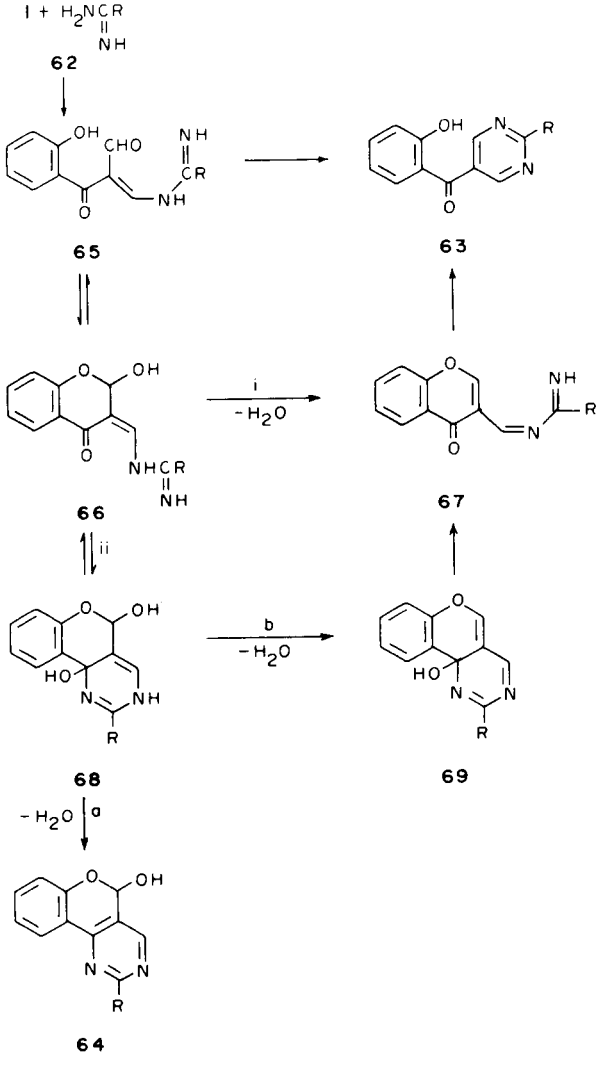


58 : R = R' = Me
59 : R = Me ; R' = OEt
60 : R = OH ; R' = OEt
61 : R = NH_2 ; R' = OEt

D. Addition of Amidines.

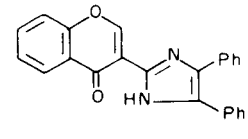
Several conflicting reports regarding the action of amidines on 3-formylchromone have appeared in literature. By subjecting **1** to react with formamidine (**62**, R = H) Loewe [59] obtained 5-(2-hydroxybenzoyl)pyrimidine (**63**, R = H) and 5-hydroxy-5*H*-[1]benzopyrano[4,3-*d*]pyrimidine (**64**, R = H) in 13 and 31% yield respectively. This result is in agreement with the formation of a mixture of **63** (R = NH_2) and **64** (R = NH_2) by the action of guanidine (**62**, R = NH_2) on **1** [53]. Petersen and Heitzer [60] and also Loewe [61] were, however, able to isolate only the benzopyranopyrimidine **64** by reacting 3-formylchromone with C-substituted formamidines (**62**, R = alkyl, aryl, hetaryl, NH_2, SCH_3, OCH_3). An initial 1,2-addition of **62** to the aldehyde function of **1** can account for the formation of **63** but not the benzopyranopyrimidine system **64**. Formation of both these products can, however, be rationalised in terms of an initial 1,4-addition of the nucleophile to the γ-pyrone system with concomitant opening of the pyrone ring (Scheme 5); the intermediate **65** thus formed may cyclise directly to **63** by involving its aldehyde and guanidino imine functions, and to **66** by involving the aldehyde and phenolic OH groups. The latter (**66**) analogous to the general formulation **14** in Scheme 2 through dehydration to **67** (step i) will ultimately lead to **63**. The other reaction course of **66** is its cyclisation to **68** [62] (step ii). Two modes (a) and (b) of water elimination from **68** can be envisaged. The one (a) that relieves steric crowding at the benzylic centre and creates a double bond in conjugation with the benzene ring is energetically more favoured than the other (b) that leads to opening of the dihydropyrimidine ring *via* **69**, the resulting intermediate **67** finally rearranging to **63**. The preponderant, if not exclusive, formation of **64** from **1** and **62** entails that the intermediate **65** preferentially undergoes double cyclisation to **68**, the latter by water elimination collapsing to **64**.

Scheme 5



E. Reaction With 1,2-Diketone in Presence of Ammonia.

4,5-Diphenyl-2-(4-oxo-4*H*-1-benzopyran-3-yl)imidazole **70** is obtained by relfuxing **1** with benzil and ammonium acetate in glacial acetic acid [63]. Here the benzil is first converted to the corresponding diimine with which chromone-3-carboxaldehyde reacts as a typical aromatic aldehyde to form the imidazole **70**.



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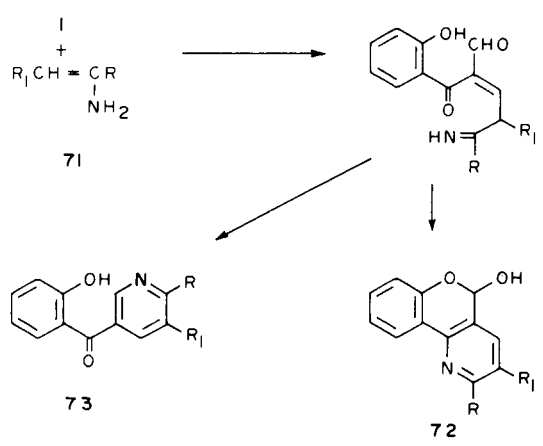
VII. 2. Nucleophilic Addition of Carbanions.

A. Addition of Enamines.

That a carbanion undergoes 1,4-addition to 3-formylchromone is revealed from the formation of [1]benzopyrano[4,3-*d*]pyridines **72** or the benzoylpyrimidine **73** by reacting **1** with enamines **71** (Scheme 6). An acyclic [64] as well as a carbocyclic enamine [65] gives the fused pyridine **72** whereas a heterocyclic enamine [65] gives **73** with **1**.

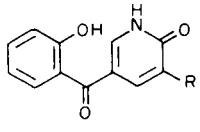
Scheme 6



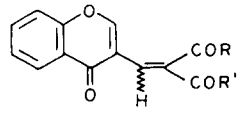
B. Addition of Active Methylene Compounds.

Chromone-3-carboxaldehyde condenses readily in presence of a base with active methylene compounds. Condensation of **1** with aryl methyl ketones gives chromone analogs of chalcone [66] which have been further condensed with *o*-aminothiophenol to give dihydrothiazepine derivatives [67]. Compound **1** gives *E*-β-(4-oxo-4*H*-1-benzopyran-3-yl)acrylic acid [68] and -acrylonitrile [69] with malonic acid and cyanoacetic acid respectively in the presence of pyridine. When condensed with cyanoacetamide in presence of pyridine containing traces of water, **1** gives some amount of **75** in addition to the expected 3-cyano-5-(2-hydroxybenzoyl)pyridin-2(1*H*)-one (**74**), the former being the normal condensation product of **1** and malondiamide [70]. Condensation of **1** with an equivalent amount of ethyl acetoacetate, acetylacetone and ethyl benzoylacetate in sodium acetate-acetic anhydride or pyridine-ethanol yields the condensates **76-78** respectively [71]. 1,3-Indandione, thiohydantoin [72], oxindole [65], 5-nitrofurfuryltrichloromethylsulfone [63], 3-methyl (or monosubstituted methyl)-4-phenyl-3-cyclobutene-1,2-dione [74] and several pyrimidine derivatives as barbituric acid [65], 1,3-dimethyl-4-aminouracil and dipyrimidinopyran [75] have also been condensed with **1**. Dimidone gives with **1** in aqueous ethanol under pyridine catalysis the 2:1-adduct **79** [12] that on recrystallisation in ethanol containing hydrochloric acid is dehydrated to **80** [65]. Azalactone **81** and the rhodanine condensate **82** of chromone-3-carboxaldehyde have also been prepared [76].

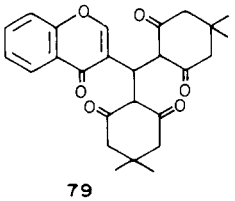
The condensates **76** and **77** have been utilised for the preparation of benzophenone and pyridine derivatives. Thus, **76** on treatment with ethyl acetoacetate in ethanol under piperidine catalysis affords the benzophenone **83**, the latter being also formed in one step by reacting **1** with excess ethyl acetoacetate in piperidine-ethanol medium [71]. Refluxing **77** or a mixture of **1** and acetylacetone in ethanol containing ammonium acetate furnished 3-acetyl-5-(2-hydroxybenzoyl)-2-methylpyridine (**84**) [77]. Compound **76** on similar treatment gives the pyridine **85** [65]. When treated with methanolic or ethanolic sodium carbonate, the azalactone **81** gives either the pyrrole-2-carboxylic ester **90** or the intermediate acrylic ester **88** [76]. Aminolysis of **81** to the amide **89** by diethylamine has been carried out at low temperature, excess amine at elevated temperature converting **81** to the pyrrole **91** [78]. On treatment with aqueous sodium hydroxide, the rhodanine condensate **82** givs the thiophene-2-carboxylic acid **92** [76]. An elegant synthesis of 3-chromonylacetylene has been accomplished by condensing **1** with 3-methyl-5(4*H*)-



74 : R = CN
75 : R = $CONH_2$



76 : R = OEt ; R' = Me
77 : R = R' = Me
78 : R = OEt ; R' = Ph



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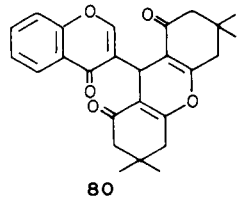

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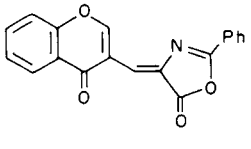
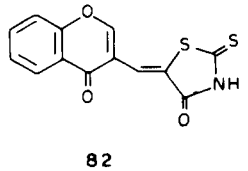
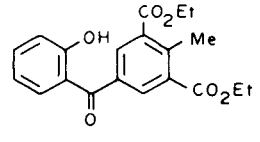


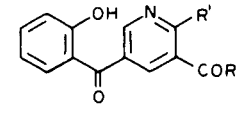
81



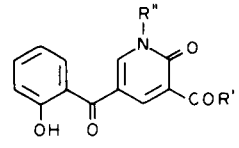
82



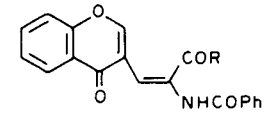
83



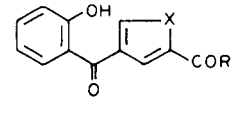
84 : R = R' = Me
85 : R = OEt ; R' = Me



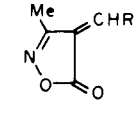
86 : R' = Me ; R" = H
87 : R' = R" = Me



88 : R = O-Alkyl
89 : R = NEt_2



90 : X = NH ; R = O-Alkyl
91 : X = NH ; R = NEt_2
92 : X = S ; R = OH

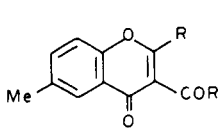


93 : R = 3 - Chromonyl

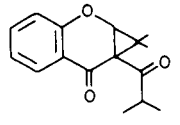
isooxazolone and subjecting the resultant methylene-oxazolone **93** to flash pyrolysis [79].

C. Addition of Diazoalkanes.

The reaction of 3-formylchromone with diazomethane was cursorily reported to yield 3-formyl-2-methylchromone in a very poor yield [17]. Later, it has been found [80] that the formyl group at 3-position not only activates the chromone ring towards attack by a diazoalkane, but also the formyl group itself is attacked. The formyl group is found to survive only when diazoethane is used. At −70° both diazomethane and diazopropane affect dual alkylation of 6-methyl-3-formylchromone (**94**). The former gives **95** and the latter mainly **96** along with a little of the cyclopropane derivative **97** which undergoes on keeping or on heating a sigmatropic shift leading to the enol derivative **98**.



94 : R = H
95 : R = CH_3
96 : R = $CH(CH_3)_2$



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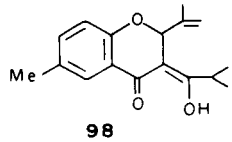
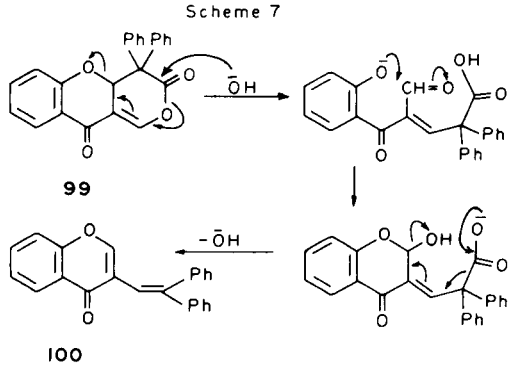


98

VIII. 3-Formylchromone as a Heterodiene.

3-Formylchromone being an α,β-unsaturated aldehyde activated by an electron-withdrawing group is a sufficiently active diene to participate particularly in inverse electron demand Diels-Alder reaction. Thus, with ethyl vinyl ether it gives a [4 + 2] cyloadduct [81], and with diphenylketene a mixture of [1]benzopyrano[3,2-*c*]pyran derivative **99** and 3-(diphenylvinyl)chromone (**100**), the latter being formed exclusively at elevated temperature [39]. In the latter reaction the initial adduct **99** undergoes thermal rearrangement with extrusion of carbon dioxide to give **100**. Apart from the anticipated thermal rearrangement, treatment with a base also brings about the conversion of the pyran **99** to **100**. The mechanism of this conversion reaction may be as depicted in Scheme 7.

Scheme 7



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