HETEROCYCLES FUSED WITH THE 2,3-BOND OF [1]BENZOPYRAN

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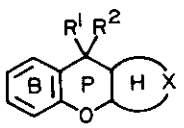
Abstract — This review gives a comprehensive survey on the synthesis of mono- and poly-heterocycles containing one or more than one like or unlike heteroatom fused with the 2,3-bond of [1]benzopyran and covers the literature through volume 103 of Chemical Abstracts.

A. INTRODUCTION

The oxygen heterocycle [1]benzopyran has been extensively studied and several treatises on this system have appeared from time to time[1-6]. None of these treatises has, however, given any comprehensive account, though highly warranted, of the voluminous works done on [1]benzopyran having a heterocyclic moiety fused at its pyran ring. A heterocycle containing a heteroatom X may get fused with the pyran ring of [1]benzopyran through either 2,3- or 3,4-bond of the latter so as to lead to linearly or angularly fused systems as shown by the figures (A) and (B), respectively; the letters B, P, and H inscribed in the assemblage (A) denote respectively the benzene, pyran and heterocyclic moieties. Coumarino fused heterocycles partaining to the latter system (B, R^1R^2 = O) have been reviewed a few years back[7]. The present review gives a comprehensive survey on the synthesis of the heterocycles of type (A) and covers the literature through volume 103 of Chemical Abstracts. The ring size of the heterocycle (H) as well as the bond with respect to the heteroatom (X), through which it gets fused with the pyran, may vary. Again, this heterocycle may be a mono-

cyclic one or a part of a polycyclic system and may even contain more than one heteroatom, like or unlike. The fused heterocycles of type (C) having the 2,3-bond of its pyran moiety in fusion with the carbocyclic part of another heterocycle and various reactions of the preformed system (A) are kept out of the purview of the present survey. The carbon corresponding to C-4 of the [1]benzopyran, which is not in fusion with any ring in the fused system (A), may be optionally functionalised.



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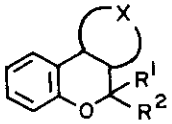

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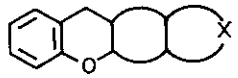

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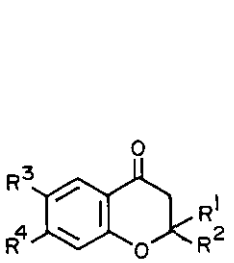
B. GENERAL SYNTHETIC PROCEDURES AND COMPOUNDS USED AS SYNTHONS

The framework of the system (A) can be constructed by (i) forming the heterocyclic (H) ring over the preformed (BP) ring (i.e. BP ⟶ BPH procedure), several suitably functionalised [1]benzopyrans providing the requisite (BP) ring system, (ii) reacting the appropriate benzene derivatives with certain hetero atom containing acyclic compounds (B ⟶ BPH), and (iii) forming the pyran ring starting from the appropriate phenoxy- and benzoyl-heterocycles (B-H ⟶ BPH method); the alternative PH ⟶ BPH procedure is rarely used. As it is very difficult to generalise the wide variety of reactions involved in the enumerated three general procedures adopted for synthesising a vast array of compounds encompassed by the title system, the projected survey is recorded here in the following few sections based on the nature of the key substrate.

I. From 2,3-dihydro-4-oxo-4H-[1]benzopyran (4-chromanone)

The reactivity of the keto-methylene group of 4-chromanone has been taken advantage of for preparing the benzopyrylium salts as 3. Thus, chromanone 1 ($R^1 = R^2 = R^4 = H$; $R^3 = OMe$) undergoes aldol condensation with 2-hydroxy--4,5-dimethoxybenzaldehyde to give the styrene 2 ($R^1 = R^2 = R^4 = R^7 = H$; $R^3 = R^5 = R^6 = OMe$) that on refluxing with ferric chloride in acetic anhydride gives the pyrylium salt 3 ($X = FeCl_4$)[8]. Similarly the condensate 2 of 7-methoxy-2-methylchromanone and 2-hydroxy-3-methoxybenzaldehyde on refluxing

in ethyl acetate saturated with HCl produces the benzopyrylium chloride 3 (R^1 = Me; R^2 = R^3 = R^5 = R^6 = R^8 = H; R^4 = R^7 = OMe; X = Cl)[9]. The correct formulation of peltogynol is established by the total synthesis of tri-O-methyl-peltogynidin chloride 3 (R^1 = R^2 = R^4 = R^7 = R^8 = H; R^3 = R^5 = R^6 = OMe; X = Cl)[10]. A French group[11] reported that o-hydroxyaromatic aldehydes as well as ketones admixed with chromanone on being dissolved in AcOH protonated with perchloric acid produce the pyrylium salts 3 (R^8 = H, Me, Et or Ph; X = ClO_4) in high yields. In the same vein 3-formyl-6,7-dimethoxy-4-hydroxycoumarin has been condensed with resorcinol in AcOH saturated with HCl at room temperature to give the pyrylium salt 3 (R^1R^2 = O; R^5 = R^7 = R^8 = H; R^3 = R^4 = OMe; R^6 = OH; X = Cl)[12].



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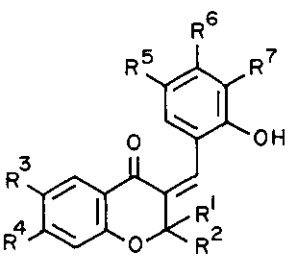

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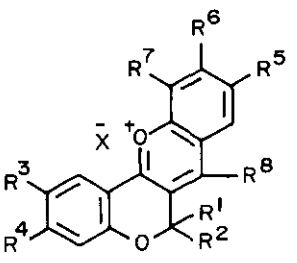

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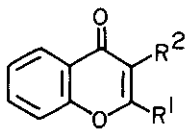
II. From 4-oxo-4H-[1]benzopyran (trivial name : chromone or chromenone), flavone, and chalcone

1,3-Dimethylbarbituric acid in refluxing AcOH containing fused AcONa undergoes 1,4-addition to the chromone (4, R^1 = R^2 = H) with concomitant opening of the pyran ring; the resultant intermediate reacts further with a second molecule of 1,3-dimethylbarbituric acid to give the pyrimidinone 5 as the final product[13]. 2-Methylchromone (4, R^1 = Me; R^2 = H) optionally substituted at the benzene nucleus on aminomethylation with R_2NH,HCl [R = Me or RR = $(CH_2)_5$, $CH_2CH_2OCH_2CH_2$] and paraformaldehyde gives [1]benzopyrano[3,2-c]pyridinium chloride 6[14]. Chromones and isoflavones, but not flavones, are epoxidised by alkaline H_2O_2. The epoxide 7 (R^1 = Me; R^2 = Ph) on treatment with conc. H_2SO_4 in Ac_2O forms the fused heterocycle 8[15].

Irradiation of quercetin pentamethyl ether (9, R^1 = R^3 = R^7 = R^8 = H; R^2 =

$R^4 = R^5 = R^6 = OMe$) in methanol gives four photoproducts, namely α-photomethylquercetin (10, $R^1 = R^3 = R^7 - R^9 = H$; $R^2 = R^4 - R^6 = OMe$), β-photomethylquercetin (10, $R^1 = R^3 = R^5 = R^8 = R^9 = H$; $R^2 = R^4 = R^6 = R^7 = OMe$), methoxy--β-photomethylquercetin (10, $R^1 = R^3 = R^5 = R^8 = H$; $R^2 = R^4 = R^6 = R^7 = R^9 =$



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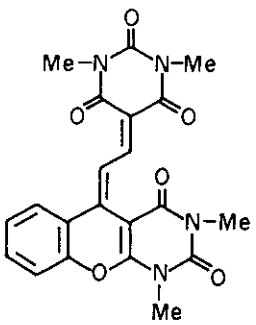

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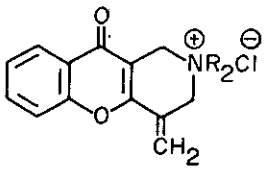

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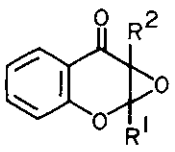

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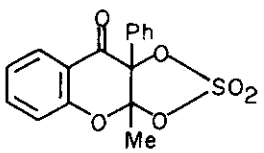

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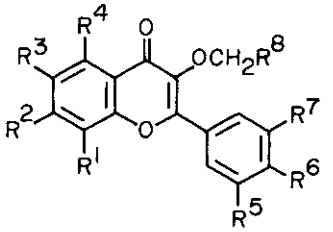

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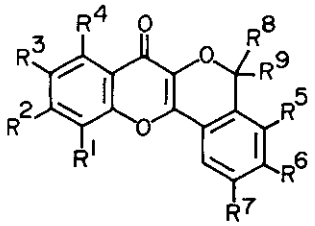

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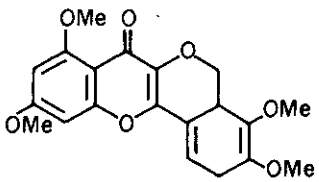

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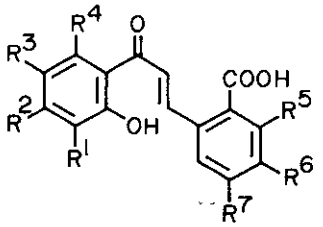

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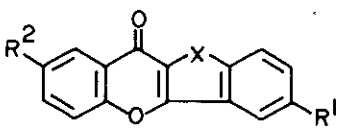

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OMe), and lumimethylquercetin (11)[16]. In the photooxidation of 3-methoxyflavones with oxygen using a high pressure Hg lamp, the compound 9 (R^1 - R^8 = H) gives 10 (R^1 - R^9 = H) whereas 3,7-dimethoxyflavone (9, R^2 = OMe; R^1 = R^3 - R^8 = H) gives a mixture of 10 (R^2 = OMe; R^1 = R^3 - R^9 = H) and 10 (R^2 = OMe; R^1 = R^3 - R^7 = H; R^8R^9 = O), and 3-methoxy-5-hydroxyflavone (9, R^1 - R^3 = R^5 - R^8 = H; R^4 = OH) remains unreactive under these conditions[17]. Photoirradiation of karanjin (9, R^1R^2 = CH=CH-O; R^3 - R^8 = H) alone or with benzil gives photokaranjin (10, R^1R^2 = CH=CH-O; R^3 - R^9 = H); similarly, 3-allylkaranjonol (9, R^1R^2 = CH=CH-O; R^3-R^7 = H; R^8 = CH=CH_2) gives 10 (R^1R^2 = CH=CH-O; R^3-R^8 = H; R^9 = CH=CH_2)[18]. Racemic peltogynol trimethyl ether has been synthesised starting from 3-hydroxy-2'-hydroxymethyl-7,4',5'-trimethoxyflavone by a series of standard reactions[19].

Properly substituted chalcones can also give rise to the heterocycle of the type 10. Thus tetra-O-methyldistemonanthin (10, R^2 - R^6 = OMe; R^1 = R^7 = H; R^8R^9 = O) is prepared by condensation of opianic acid (2,3-dimethoxy-6--formylbenzoic acid) with 2-hydroxy-4,5,6-trimethoxyacetophenone followed by alkaline H_2O_2 oxidation (Algar-Flynn-Oyamada reaction) of the intermediate chalcone 12 (R^2 - R^6 = OMe; R^1 = R^7 = H)[20]. A number of compounds of the type 10 (R^8R^9 = O) has been prepared using various o-hydroxyacetophenones and 2-formylbenzoic acids in the above condensation[20,21]. The chalcone 12 (R^1 = R^3 - R^5 = H; R^2 = R^6 = R^7 = OMe) on sequential treatment with alkaline H_2O_2, $LiAlH_4$, and HCl gives tri-O-methylpeltogynidin chloride[22].

The chalcone prepared from 2-hydroxy-5-methylacetophenone and 2-nitrobenzaldehyde simply on digestion with alkali forms the indole 13 (R^1 = H; R^2 = Me; X = NOH)[23]; its methanolic solution on treatment with SO_2 gives 13 (R^1 = H; R^2 = Me; X = NH) which can also be prepared by heating 6-methyl-2'-nitroflavone with $P(OEt)_3$[23]. Boiling an aqueous solution of the diazonium salt of 2'-amino-5'-nitroflavone results the pyranocinnoline 13 (R^1 = NO_2; R^2 = H; X = N=N) whereas 2'-aminoflavone gives simply 2'-hydroxyflavone in complete exclusion of 13 (R^1 = R^2 = H; X = N=N) under similar conditions[24].

III. From isoflavone and ω-aryl- and ω-hetaryl-o-hydroxyacetophenones

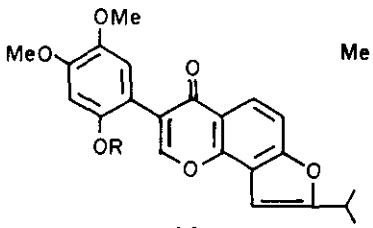
Properly functionalised isoflavones are good synthons for rotenoids. Certain

ω-aryl-o-hydroxyacetophenones also give rise to rotenoids and that too most often through isoflavone intermediates. Again, reactions of ω-hetaryl-o--hydroxyacetophenones resemble those of the aryl analogs. Hence application of all these three systems for the synthesis of the title heterocycles is described together in this section.

Synthesis of rotenoids has been accomplished by one carbon insertion to 2'-hydroxyisoflavone using dimethylsulfoxonium methylide. As for example, isoderritol isoflavone (14, R = H) is treated with dimethylsulfoxonium methylide to give 15 that on heating in pyridine at 100°C affords isorotenone [16, R^1 = R^4 = R^5 = H; R^2 = R^3 = OMe; R^6R^7 = $OC(CHMe_2)$=CH; R^8 = R^9 = β-H][25]. Several other rotenoids have been synthesised by using this procedure[26].

The ω-aryl-o-hydroxyacetophenones as 17 having various substituents at the two phenyl rings have been prepared. These compounds on refluxing in AcOH containing fused AcONa give rise to the rotenoid structure 16 (R^8R^9 = bond)[27]. The compound 16 (R^1 - R^5 = R^7 = H; R^6 = OH; R^8R^9 = bond) has been prepared by sequential treatment of ω-(2-hydroxyphenyl)resacetophenone with ethoxyacetyl chloride in pyridine, HBr in glacial acetic acid, and K_2CO_3 in acetone[28]. ω-(2,4-Dimethoxyphenyl)resacetophenone has been converted by a series of reactions to 7,2',4'-trihydroxy-2-hydroxymethylisoflavone which on refluxing in acetone in the presence of dry K_2CO_3 affords 16 (R^1 = R^3 = R^4 = R^5 = R^7 = H; R^2 = R^6 = OH; R^8R^9 = bond)[29]. Synthesis of 16 (R^1 = R^3 - R^7 = H; R^2 = OH; R^8R^9 = bond) has been similarly achieved from ω-(2-methoxyphenyl)resaceto-phenone[30]. 7-Hydroxy-2-ethoxymethyl-2'-methoxyisoflavone, prepared by two different routes, has also been converted to 16 (R^1 = R^3 = R^5 = R^7 = H; R^2 = R^6 = OH; R^8R^9 = bond)[31]. Dehydromundeserone 16 (R^1 = R^4 = R^5 = R^7 = H; R^2 = R^3 = R^6 = OMe; R^8R^9 = bond) has been synthesised from tephrosic acid or tephrosic acid monomethyl ether (17, R^1 = R^4 = R^5 = R^7 = H; R^2 = R^3 = R^6 = OMe) or the corresponding esters by a number of groups[32]. The Hoesch reaction product from methyl 2-cyanomethylphenoxyacetate and 6-hydroxycoumarin has also been converted to the corresponding chromenochromone of the type 16[33]. (2,3-Dihydro-2-ethyl-4-hydroxybenzofuran-5-yl) (2-carbomethoxymethoxy-4,5--dimethoxybenzyl) ketone has been cyclised to nordihydrodehydrorotenone[34].

Deoxybenzoin based rotenoid synthesis producing the rotenoid at the desired oxidation level has been described by Carson et al[35]. Thus, treatment of the deoxybenzoin 17 [$R^1 = R^4 = R^5 = H$; $R^2 = R^3 = OMe$; $R^6R^7 = OC(CHMe_2)=CH$; OH in place of OCH_2COOH] with ethyl orthoformate in the presence of molecularised sodium gives the isoflavone 14 (R = H) which on allylation ($CH_2=CHCH_2Br$, NaH, DMF) followed by alkaline hydrolysis affords 17 (R^1 - R^7 as before, OCH_2--$CH=CH_2$ in place of OCH_2COOH); the latter on sequential oxidation (OsO_4-HIO_4) and heating in pyridine forms isorotenone (16, $R^1 = R^4 = R^5 = H$; $R^2 = R^3 = OMe$; $R^6R^7 = OC(CHMe_2)=CH$; $R^8 = R^9 = \beta$-H). The ω-arylacetophenone 17 ($R^1 = R^2 = R^3 = R^5 = R^7 = H$; $R^4 = R^6 = OH$; OMe in place of OCH_2COOH) has been converted via 2-ethoxycarbonyl-5,7-dihydroxy-2'-methoxyisoflavone to the pyran derivative 18 ($R^1 = R^3 = OH$; $R^2 = R^4 = H$; P = Y = CO; Q = Z = O)[36].



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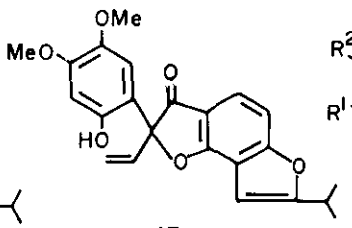

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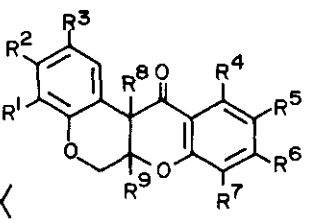

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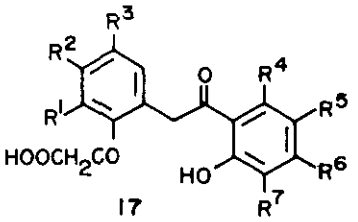

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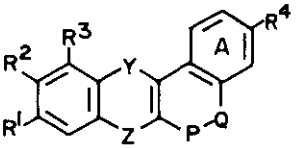

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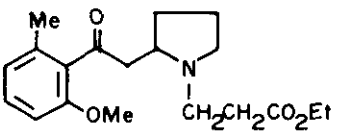

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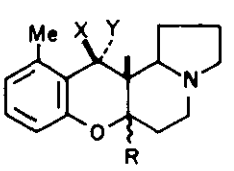

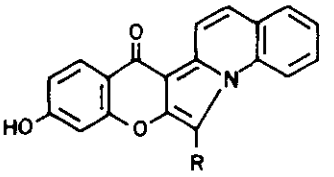

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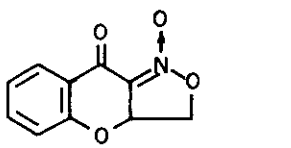
20, X = OH; Y = H; R = α-H
21, X = OH; Y = H; R = β-H
22, XY = O; R = α-H
23, XY = O; R = β-H

The acetophenone 19, prepared from 2-methoxy-6-methylphenyl diazomethyl ketone by a series of standard reactions, on sequential Dieckmann cyclisation, treatment with BBr_3, methanolic HCl, and $NaBH_4$ furnishes a mixture of 20 and 21; these are separated and subjected to chromic acid oxidation to yield elaeocarpine (22) and isoelaeocarpine (23), respectively[37]. ω-(1-Quinolinyl)-resacetophenone reacts with RCHXCOCl (R = H or Me; X = halogen) yielding 24[38].

IV. From 2- or 3-nitro- and -amino-chromone

3-Nitrochromone gives with diazomethane mainly a cyclopropa[1]benzopyran derivative together with a little of the isoxazoline oxide 25[39], but no pyrazole or pyrazoline is formed as reported by Russian workers in a related reaction[40]. 2-Aminochromone undergoes Michael addition to diethyl ethoxymethylenemalonate (DEMM) and the resultant adduct on refluxing in Ph_2O yields the pyridone 26[41,42]. 3-Aminochromone also gives Michael adducts with DEMM and dimethyl acetylenedicarboxylate (DMAD), and the adducts on similar treatment give the pyridones 27 and 28, respectively[41,43]. 2-Amino-6-bromo-3',4'--dimethoxyisoflavone on treatment with $NaNO_2$ in AcOH affords the [1]benzopyrano-[3,2-c]cinnoline 29 (X = N) whereas the N-acetyl derivative of the same



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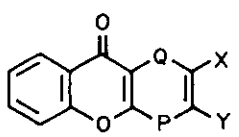
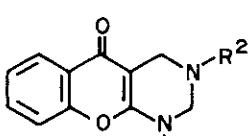


	P	Q	X	Y
26:	NH	CO	CO_2Et	H
27:	CO	NH	H	CO_2Et
28:	CO	NH	CO_2Me	H



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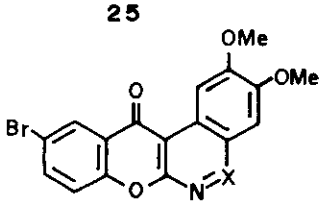

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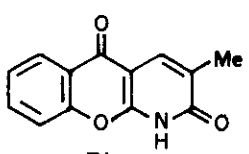

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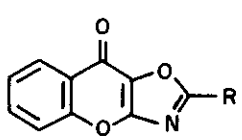

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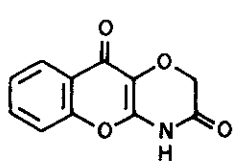

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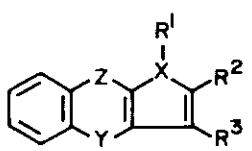


34

isoflavone on refluxing with P_2O_5 in $CHCl_3$ gives 29 (X = CMe)[44]; naphthaleno analogs of 29 (X = N) have also been similarly prepared[44].

The Mannich reaction of 2-acylaminochromone produces the tetrahydropyrimidine derivative 30[45]. Chromone-2-isocyanate, the precursor of 2-aminochromone, reacts with 1-piperidinopropylene to afford the pyridone 31[46]. 2-Amino-3--hydroxychromone gives the oxazole 32 (R = Me or Ph) on heating with acetic or benzoic anhydride at 150-160°C and the oxazine 33 on refluxing with chloroacetyl chloride in dioxane[47]. The reductive cyclisation with $P(OEt)_3$ at 180°C of the aldol condensate from 2-methyl-3-nitrochromone and an aromatic aldehyde ArCHO gives the indole 34 ($R^1 = R^3 = H$; R^2 = Ar; X = N; Y = O, Z = CO)[48].

V. From 3-acylchromones

A recent review[49] on the chemistry of 3-formylchromone includes the synthesis from this substrate a number of heterocycles fused at the 2,3- as well as 3,4-bond of [1]benzopyran. The various types of reagents allowed to react with 3-acylchromone in order to achieve the stated goal and the types of reactions involved therein are described in the following subsections.

V. 1. By [4π + 2π] cycloaddition reaction

3-Acylchromone possesses a conjugated enone system further activated by the presence of an electron withdrawing carbonyl group at the α-position, hence it functions as a reactive diene in the inverse electron demand Diels-Alder reaction towards electron rich olefins. Ghosh et al[50] reported the formation of the cis-adduct 36a by reacting 35a with ethoxyethylene. Wallace[51] could isolate small amount of the trans-isomer 37 in addition to the major cis-adduct 36 by treating 35 (R^2 = H) with excess ethoxyethylene in CH_2Cl_2. On the other hand, Dean et al[52] reported the formation of the single isomer 38a (R^2 = Me) by adding 3-formyl-6-methylchromone 35a (R^2 = Me) with 2-methoxypropene at 18°C. The other diastereoisomer 39a (R^2 = Me) could be produced by removing the hydride ion from 38a with triphenylcarbenium perchlorate and reducing the resultant oxonium ion selectively with sodium borohydride in methanol[52]. 3-Formylchromone produces with ethoxyethylene 36a and/or 37a at room temperature

whereas its 3-acetyl- and -benzoyl analogs require heating with ethoxyethylene at 115°C in a sealed tube[51], indicating some adverse electronic effect in the latter two substrates.

[4+2]Cycloaddition of the chromones 35a and 35c (R^2 = H) with diphenylketene yields the fused pyran derivative 40 that on heating or base treatment results 42[53]. The compound 40 (R^5 = H) has been reacted with R^6NH_2 (R^6 = H or alkyl) to give the pyridine 41. Mild alkali hydrolysis of 40 (R^5 = H) gives 2-chromanonyldiphenylacetic acid 43, the latter producing 44 by reacting with ArCHO[53]. 3-Formylchromone (35a, R^2 = H) also undergoes [4+2]cycloaddition with dichloroketene, generated in situ from dichloroacetyl chloride and triethylamine; the initially formed cycloadduct 45 being a reactive heterodiene captures a second molecule of dichloroketene yielding the tetrachlorocompound 46 (R^1 = Cl; R^2 = H) that eliminates two molecules of HCl under base catalysis to form 46 (vicinal R^1R^2 = bond)[54].

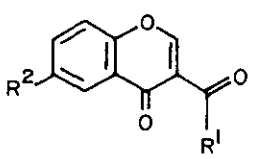
V. 2. By 1,3-dipolar cycloaddition

3-Formylchromone gives with diazomethane a mixture of 3-acetyl-2-methylchromone, pyrazole 47 (X = CH; R = H) and dihydrofuran 48 (R = H); 3-acetylchromone also behaves similarly to yield 3-acetyl-2-methylchromone, 47 (X = CH; R = H) and 48 (R = Me). The formation of the above products can be rationalised by initial 1,3-dipolar cycloaddition of diazomethane to the 2,3-double bond of 3-acyl-chromone and subsequent transformation of the resultant 1-pyrazoline intermediate[55]. 3-Benzoylchromone forms with diazomethane 3-benzoyl-2-methyl-chromone, pyrazole 47 (R = H; X = CH), but no dihydrofuran as 48 (R = Ph); two additional products, namely the furan 49 and 1-pyrazoline 50 result in[55].

V. 3. By reaction with the reagents having a heteroatom as the key nucleophilic centre and a nucleofugal element or group

Treatment of 3-formylchromone with halogenoalkanol $X(CH_2)_nOH$ (X = I or Br; n = 2 or 3) under standard alkylation reaction conditions gives a furan or pyran 51 fused with [1]benzopyran in cis fashion as the major product[56]. An anil derived from chromone-3-carboxaldehyde functions as a better Michael acceptor than the aldehyde itself. So it was reported that thioglycolic acid (or its

ethyl ester) underwent 1,4-addition to the anil and the adduct 52 cyclised to the fused thiazepinone 53 provided the amine moiety contained an electron



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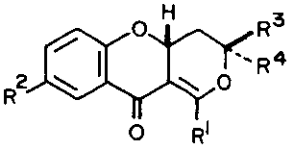
For 35 - 39

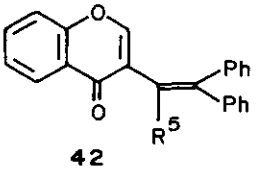
a , R^1 = H

b , R^1 = Me

c , R^1 = Ph



	R^3	R^4
36 :	H	OEt
37 :	OEt	H
38 :	Me	OMe
39 :	OMe	Me



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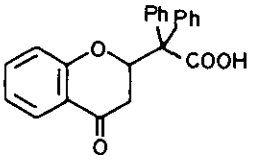

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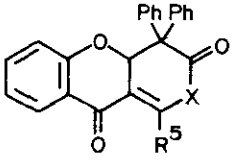
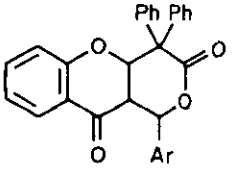


40 : X = O ; R^5 = H or Ph

41 : X = NR^6 ; R^5 = H



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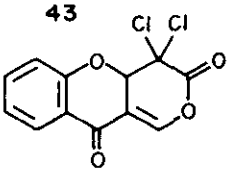

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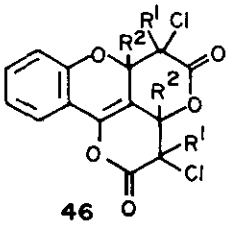

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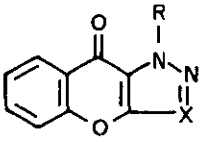

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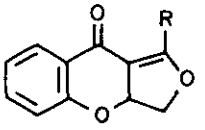

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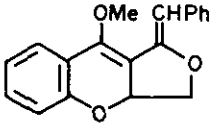

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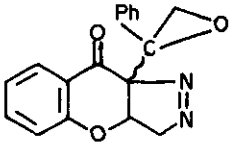

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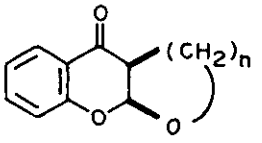

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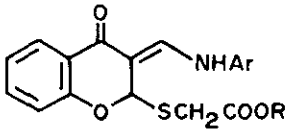
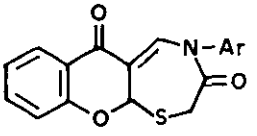


52 , R = H or Et



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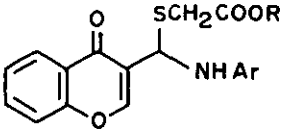

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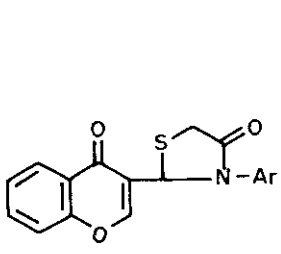
donating substituent[57]. Later on, it has been convincingly proved[58] that the 1,4-adduct 52 instead of cyclising to 53 undergoes sigmatropic rearrangement to 54 that ultimately cyclises to thiazolidinone 55.

V. 4. By reaction with aminophenol

Two molecules of 3-N,N-diethylaminophenol add to one molecule of 3-formylchromone to give the chromenochromone 56[59].

V. 5. By reaction with a bisnucleophile having two heteroatoms, identical or different, as the key nucleophilic centres

The reaction of excess hydroxylamine with 3-formylchromone under acidic conditions gives the pyrazolinone 57 together with 3-hydroxy-4-(2-hydroxybenzoyl)-pyrazole[60], the plausibe mechanism of the reaction being discussed by one of the present authors elsewhere[49].



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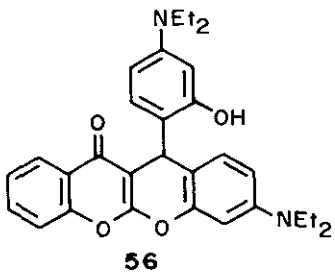

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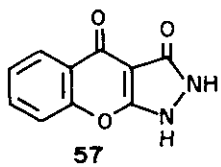

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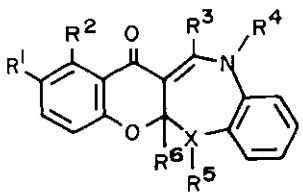

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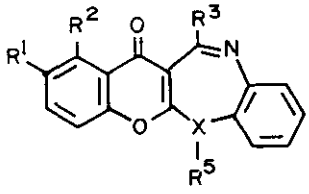

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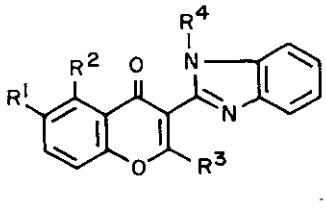

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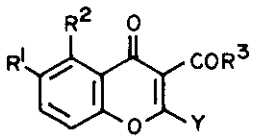
Aniline having a nucleophilic functionality XR^5H (XR^5 = O, S, NH, NMe etc.) at its ortho position is reported to condense with 3-formylchromone giving the fused seven membered heterocycle 58 (R^1 - R^4 = R^6 = H) that dehydrogenates to 59 (R^1 - R^3 = H) either by spontaneous air oxidation or on treatment with

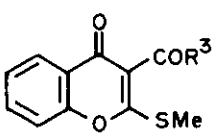
chloranil[61] or nitrobenzene[62]. Later on, a Swiss group[63] has shown that the condensation product of 3-formylchromone and o-phenylenediamine has, instead of the dihydrodiazepine 58 (R^1 - R^6 = H; XR^5 = NH), a complicated tetraaza[14]-annulene structure which on digestion in HOAc[62,64] gives the benzimidazole 60 (R^1 - R^4 = H)[65], not the isomeric benzdiazepine 59 (R^1 - R^3 = H; XR^5 = NH) as proposed earlier[61,62,64].

VI. From 3-acylchromones having a nucleofugal substituent at their 2-position

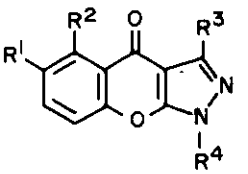
The acylchromone 61 and 62 and the furoderivative of the latter have been extensively used to synthesise a number of heterocycles belonging to the title system. Heteroannulation of the dialkylamino compound 61 with NH_2NHR^4 (R^4 = H, Me, Et or Ph) to 63 (R^1R^2 = CH=CH-CH=CH; R^3 = H) is believed to occur by initial 1,2-addition of hydrazine to the aldehyde function of 61 followed by



61, Y = Dialkylamino; R^1R^2 = CH=CH-CH=CH; R^3 = H



62, R^3 = Me or Ph



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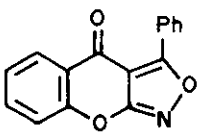

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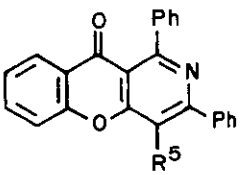

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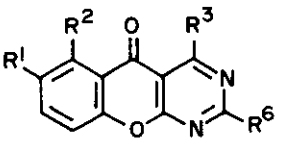

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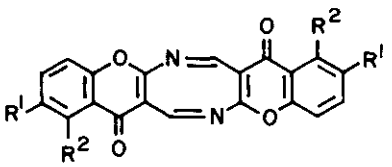

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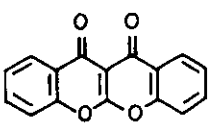

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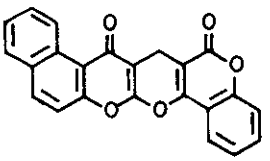

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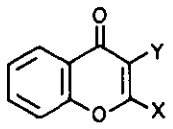
cyclisation through 1,4-addition - elimination sequence[66]. The reverse reaction sequence is found to be true for the condensation of hydrazine with the thiomethyl compound 62 yielding 63 ($R^1 = R^2 = R^4 = H$)[67]. The compound 62 (R^3 = Ph) produces 64 with hydroxylamine, and 59 ($R^1 = R^2 = H$; R^3 = Ph; XR^5 = NH) with o-phenylenediamine[67]. Treatment of 62 (R^3 = Ph) with $PhCOCH_2R^5$ (R^5 = H or COPh) followed by refluxing with NH_4OAc in HOAc yields the pyridine 65[68]. 2-Aminopyrone 61 and 2-thiomethylpyrone of the type 62 give with amidine $H_2NC(R^6)=NH$ (R^6 = H, Me, Ph, NH_2, OMe, SMe etc.) the fused pyrimidine 66[67,69,70]. In the course of condensing methoxyamidine with 61, the diazocine derivative 67 is also formed[69]. Roma et al[71] have studied thoroughly the condensation of 61 with different 2-arylaminoanilines and found that depending on the reaction conditions and the nature of the aryl group any of the isomers 58 (R^1R^2 = CH=CH-CH=CH; R^3 = H; R^4 = Ar; R^5R^6 = bond; X = N), 59 (R^1R^2 = CH=CH-CH=CH; R^3 = H; XR^5 = NAr), and 60 (R^1R^2 = CH=CH-CH=CH; R^3 = NMe_2; R^4 = Ar) may be formed. Disalicyloylmethane on heating with CS_2, alkali, and Me_2SO_4 gives 68 evidently via 62 (R^3 = 2-hydroxyphenyl), 68 rearranging to 13 ($R^1 = R^2 = H$; X = COO) on heating in aqueous HOAc[72]. It should be pointed out that reaction of 61 (H in place of COR^3) with a mixture of 4-hydroxycoumarin and formaldehyde gives 61 [(4-hydroxycoumarin-3-yl)methyl in place of COR^3] that on refluxing in HOAc cyclises to 69[73].

VII. From 3-cyanochromone, 2-amino-3-formylchromone, and chromone-3-carboxaldehyde-oxime

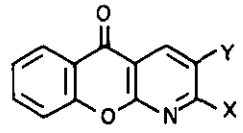
3-Cyanochromone 70, prepared by dehydration of chromone-3-carboxaldehyde-oxime 72, is prone to form 2-amino-3-formylchromone 71 under base catalysis and all these chromone derivatives most often behave similarly towards several reagents to form the identical products; hence the application of the chromones 70-72 for the synthesis of the title system is described together in this section.

The nitrile 70 on refluxing with NH_4OAc in AcOH undergoes self-condensation to the pyrimidine 66 ($R^1 - R^3$ = H; R^6 = 4-oxo-4H-1-benzopyran-3-yl)[74] that also results from heating 71 with p-toluenesulfonic acid in toluene[75]. The amine 71 gives a mixture of 4-hydroxycoumarin and bis(benzopyrano)pyridine 73 on treatment with acid catalyst in isopropanol[75]. An aliphatic amine as

ethylenediamine induces self-condensation of 70 as well as 72 to the diazocine 67 (R^1 = R^2 = H)[76]. The nitrile 70 condenses under base catalysis with acetylacetone, ethyl acetoacetate, diethyl malonate, ethyl cyanoacetate[77,78], and dimethyl β-ketoglutarate[79] to afford the pyridine derivatives 74a, b, c, d, and e, respectively. The chromones 71 and 72 give the same pyridine 74 on similar treatment[78,80]. Malononitrile condenses with 71 to give 74f. A Japanese group[81] has utilised 2-amino-3-formylchromone to prepare several 2-substituted or unsubstituted pyridine derivatives 74. Thus, the adduct obtained from 71 and ethyl propiolate in the presence of NEt_3 in DMF produces



	X	Y
70 :	H	CN
71 :	NH_2	CHO
72 :	H	CH=NOH



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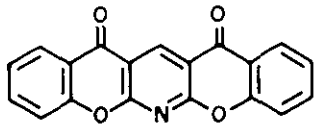
	X	Y
a :	Me	Ac
b :	Me	CO_2Et
c :	OH	CO_2Et
d :	NH_2	CO_2Et
e :	CO_2Me	CH_2CO_2Me
f :	NH_2	CN
g :	H	CO_2Et
h :	H	CN
i :	OH	CN
j :	H	CO_2Me
k :	H	CHO
l :	OAc	NHCOPh



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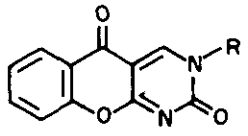

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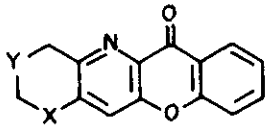

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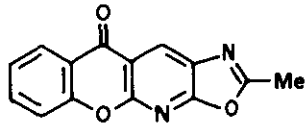

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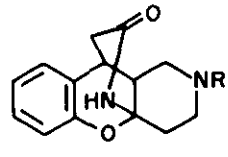

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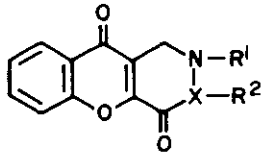

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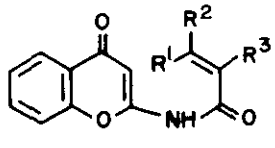

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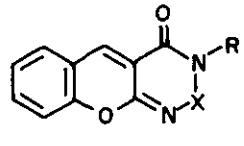

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74g. Treatment of 71 with either cyanoacetylene or α-chloroacrylonitrile or cyanoacetyl chloride in DMF affords 74h. $NCCH_2COCl$ in CH_2Cl_2, instead of DMF, gives with 71 an amide that on heating in pyridine produces 74i. The aldehyde 71 produces 74j with methyl malonyl chloride in DMF, and 74k with malondialdehyde bis(dimethylacetal) in HCOOH in the presence of BF_3 etherate. 2-Amino-3-formylchromone also condenses with RNCO (R = Me or Ph) to give the pyrimidine 75[80]. 3,4,5,6-Tetrahydro-3-oxo-2H-pyran or the enamine, silyl enol ether and lithium enolate derivative thereof condenses with 2-amino-3-formylchromone in ethanol containing DBN yielding a mixture of 76 (X = O; Y = CH_2) and 76 (X = CH_2; Y = O)[82]. When refluxed with benzoyl- and acetyl-glycine in CH_3COOH containing fused NaOAc, the nitrile 70 gives the pyridine 74l and pyridino-oxazole 77, respectively[74,83]. o-Phenylenediamine is reported to condense with 70 giving the diazepine 59 (R^1 = R^2 = H; R^3 = NH_2; XR^5 = NH)[74]; Rihs et al[65] contended that this condensate might have the imidazole structure 60 (R^1 = R^2 = R^4 = H; R^3 = NH_2).

VIII. From chromene-, chromone- and coumarin-carboxylic acids and their derivatives

Several chromene-carboxylic acids and their derivatives have been condensed with resorcinol in order to form rotenoids[84]. As for example, 4-ethoxycarbonyl-8-methoxy-2H-chromene together with 2-isoamylresorcinol when treated with anhydrous HF, the initially formed benzoyl derivative undergoes spontaneous cyclisation to afford the isomeric mixture of 16 (R^1 = OMe; R^2 - R^5 = R^8 = R^9 = H; R^6 = OH; R^7 = $CH_2CH_2CHMe_2$). Similarly, resorcinol on Friedel Craft acylation with coumarin-3-acid chloride followed by dehydrogenation with $Pb(OAc)_4$ gives the coumarinochromone 18 (R^1 = R^3 = R^4 = H; R^2 = OH; Y = Q = O; P = Z = CO)[85]. Acylation of resorcinol with the chloride corresponding to 3,7-dimethoxycoumarin-4-carboxylic acid followed by treatment with HBr in AcOH affords 18 (R^1 = R^4 = OH; R^2 = R^3 = H; Y = P = CO; Q = Z = O)[85]. Benzopyranopyridine 78 (R = H, alkyl, aralkyl etc.) has been prepared by reaction of coumarin-3-carboxylic ester with the appropriate 4-piperidone and cleavage of the product by NH_4OAc followed by dehydrative cyclisation by conc. HCl[86]. Ethyl 3-bromomethylchromone-2-carboxylate on treatment with a primary arylamine, o-phenylenediamine, and phenylhydrazine gives respectively 79 (R^1 = Ar; X

absent), 5,6,13,14-tetrahydro-6,12-dioxo-12H[1]benzopyrano[2,3-c][1,6]benzdiazocine, and 79 (R^1 = Ph; XR^2 = NH), amide formation preceding substitution in all these reactions[87]. Other bisnucleophiles as 2-amino-pyridine, -pyrimidine, and -thiazole give with the above ester the fused heterocycles that arise by amidification with amino group of the nucleophilic reagent followed by displacement of bromine by the ring nitrogen[87]. 1,3-Dipolar cycloaddition of $N_2CHCH(OMe)_2$ to chromone-3-carboxylic ester giving diastereoisomeric mixture of 1-pyrazoline together with cyclopropane derivatives has been reported[88].

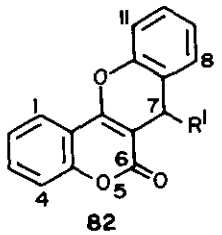
2-Isocyanatochromone, prepared by Curtius rearrangement of chromone-2-acid azide, when kept at room temperature with 1-piperidino-1-cyclohexene or 1-morpholino-1-cyclopentene gives 80 [R^1 = piperidino, R^2R^3 = $(CH_2)_4$; R^1 = morpholino, R^2R^3 = $(CH_2)_3$]; this on heating with 10% HCl gives chromenopyridone 18 (R^1 - R^4 = H, Q = Y = CO; P = NH, Z = O; ring A; tetrahydro)[89]. The anilide corresponding to chromone-2-carboxylic acid on irradiation in benzene in the presence of iodine gives benzopyranoquinolinedione 18 (R^1 - R^4 = H; Q = NH; P = Y = CO; Z = O)[90]. 3-Carbamoyl-2-iminochromene gives 81 (R = H; X = SO) with $SOCl_2$[91] and 81 (R = H; X = CHAr) with ArCHO in the presence of a base[92]. 2-Iminochromene-3-carbohydrazide reacts with $NH_2OH.HCl$ to give the azolone 81 (R = H; X absent)[92]. Like the oxygen analog, 2-imino-3-thiocarbamoylchromene reacts with an aromatic aldehyde in the presence of piperidine yielding 81 (R = H; X = CHAr: C=S in place of C=O)[93].

IX. From 4-hydroxycoumarins

Michael addition of 4-hydroxycoumarin to o-HOC_6H_4CH=CHCOR (R = alkyl or aryl), the aldol condensate of salicylaldehyde and an alkyl (or aryl) methyl ketone, is accompanied by spontaneous cyclisation resulting [1]benzopyrano[4,3-b][1]-benzopyran derivative 82 (R^1 = CH_2COR)[94]. Even the aldol condensate of 4-hydroxycoumarin and substituted or unsubstituted salicylaldehyde, 2,6-dichloro- or iodo- and 2-chloro-6-nitro-benzaldehyde has been subjected to react with 4-hydroxycoumarin under pyridine catalysis when the compound of the type 82 (R^1 = 4-hydroxycoumarin-3-yl) is produced, this product being better synthesised in one step by reacting two molecules of 4-hydroxycoumarin with one molecule of

the said aldehyde[95]. An aflatoxin analog having 4-hydroxycoumarin moiety has been similarly subjected to react with salicylaldehyde[96].

Condensation of even equimolar amount of 4-hydroxycoumarin and salicylaldehyde gives a minor amount of 83 in addition to the major product 82 (R^1 = 4-hydroxycoumarin-3-yl). Hydrogenation over Pd-C reduces the exocyclic double bond of 83, the reduced product on treatment with $POCl_3$ cyclising to 82 (R^1 = H)[97]. It is interesting to note that even 83 on boiling with 30% ethanolic HCl can produce 82 (R^1 = H), here ethanol transfering the hydride and itself being oxidised to acetaldehyde[97]. Passing HCl gas through an equimolar mixture of 4-hydroxycoumarin and 2-hydroxy-3,5-dimethylbenzyl alcohol in $CHCl_3$ gives 3-(2-hydroxy-3,5-dimethylbenzyl)-4-hydroxycoumarin which on treatment with $POCl_3$ cyclises to 82 (R^1 = H; Me in place of H at 9- and 11-positions)[98]. 3-(2-Hydroxybenzyl)-4-hydroxycoumarin, prepared from 4-hydroxycoumarin and o-hydroxyphenolic Mannich bases, has been similarly cyclised to 82 (R^1 = H)[99]. The compound 82 (R^1 = H) can also be prepared by heating the Mannich base obtained from 4-hydroxycoumarin, formaldehyde, and benzylamine with phenol[99]. A new synthesis of 18 (R^1 - R^4 = H; P = Z = CO; Q = Y = O) consists of condensation of 4-hydroxycoumarin with 2-bromobenzoic acid in the presence of anhydrous $CuCl_2$ and dry pyridine[100]. 4-Hydroxycoumarin on treatment with betaine followed by chromic acid oxidation furnishes 18 (R^1 - R^4 = H; P = Z = O; Q = Y = CO)[101] and it condenses with 2-methylbut-3-en-2-ol in the presence of H_3PO_4 giving the



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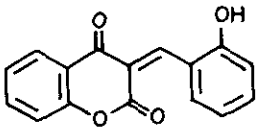

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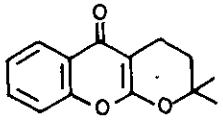

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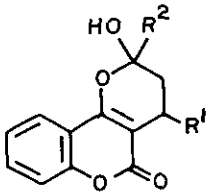

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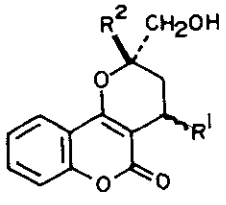

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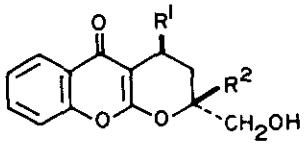

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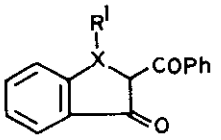
pyranone 84 together with 3,4-dihydro-2,2-dimethyl-5-oxo-2H, 5H-pyrano[3,2-c][1]-benzopyran[102]. The Michael adduct 85 (R^1, R^2 = Me, Ph) of 4-hydroxycoumarin and α,β-unsaturated ketone $R^1CH=CH-COR^2$ reacts with 2-3 moles excess of $Me_2S(O)=CH_2$ in Me_2SO or THF to give a diastereoisomeric mixture of coumarin derivative 86 together with a minor amount of pyranobenzopyran 87[103].

3-Acetyl-4-hydroxycoumarin on refluxing with guanidine in ethanol in the presence of sodium ethoxide yields 5% of the pyrimidine 66 (R^1 = R^2 = H; R^3 = Me; R^6 = NH_2)[104]. 3-Acyl-4-hydroxycoumarin can be converted to the pyrazoles 63 (R^1 = R^2 = H; R^3 = H, Me or Et; R^4 = Ph) by reacting with phenylhydrazine under certain particular conditions[105].

X. From α-unsubstituted lactam and heterocyclic ketone other than 4-chromanone, and heterocyclic β-keto-ester

The enamine corresponding to 3,4,5,6-tetrahydro-3-oxo-2H-pyran condenses with o-acetoxybenzoyl chloride in methanolic HCl giving 3,4-dihydro-10-oxo-2H, 10H--pyrano[3,2-b][1]benzopyran[82]. Dehydrorotenone has been synthesised by condensing the enamine corresponding to 6,7-dimethoxychroman-3-one with acetyl-1-tubaic acid chloride followed by refluxing in water containing pyridine and piperidine[106]. PPA cyclises the heterocyclic ketone 88 (XR^1 = NH, NOH, O,S) to 34 (R^2R^3 = CH=CH-CH=CH; Y = O; Z = CO)[107]. Oxindole or N-methyloxindole on acylation with ethyl salicylate followed by treatment with methanolic HCl gives 34 (R^1 = H or Me; R^2R^3 = CH=CH-CH=CH; X = N; Y = CO; Z = O)[108]. The condensate of 7-methylindolinone with 2-aminobenzaldehyde on diazotisation yields 89[109]. The benzylidene derivative prepared from 2,4,6-triacetoxybenzaldehyde and indoxyl gives with CF_3COOH the trifluoroacetate salt of the cation 90[110]. The pyrrolidine enamine of N-benzoyl-4-piperidone on condensation with the Mannich base from β-naphthol followed by mild hydrolysis gives 91 (R^1 = COPh; R^3 = OH; R^4R^5 = CH=CH-CH=CH; R^2 = R^6 = R^7 = H)[111]. The compound 91 (R^1 = Me; R^2R^3 = R^6R^7 = bond; R^4 = R^5 = H) has also been synthesised by reacting the pyrrolidine enamine of 1-methylpiperidin-4-one with salicylaldehyde[112]. A Japanese group[113] has claimed to isolate 91 (R^1 = H, allyl or arallyl; R^2 = R^4 = R^5 = R^7 = H; R^3 = 1-morpholino; R^6 = OH) by reacting the morpholine enamine of the appropriate 4-piperidone with salicylaldehyde. 2-Azaxanthone has been prepared

by condensation of morpholine enamine of 1-benzyl-4-piperidone with salicylaldehyde followed by CrO_3 oxidation and subsequent aromatisation[114]. Pyrrolidinedione 92 (R^1 = Me, Ph; R^2 = H, Me; R^3 = H, Ph) on acylation with 2-hydroxy- or 2-methoxy-benzoic ester followed by heating in pyridine yields 93[115]. Heating N-phenylmaleimide together with phenol and paraformaldehyde in a high boiling aromatic hydrocarbon results 94[116]. Thiochromanone on sequential condensation with salicylaldehyde (H_3PO_4, 85°C), reduction ($NaBH_4$) and cyclisation (50% HOAc, reflux) gives 95[117]. The pyrazole 96 (R^1, R^2 = H, alkyl, Ph; R^3, R^4 = H, halogen, alkyl, alkoxy, hydroxycarbonyl) has been synthesised by condensing the appropriate pyrazolinone with the appropriately substituted 2-hydroxy- or -chloro- or -bromobenzoic ester or the corresponding acid chloride[118]. 3-Acetyl-3,4-dihydro-2-oxo-2H-[1]benzopyran with guanidine forms



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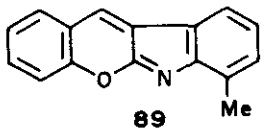

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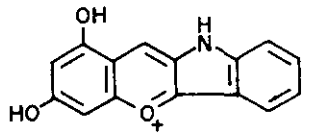

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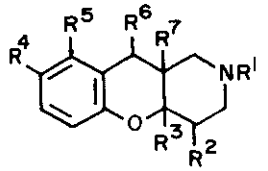

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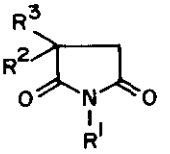

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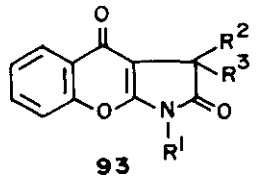

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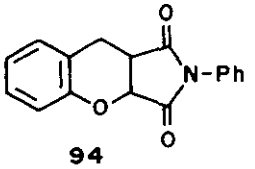

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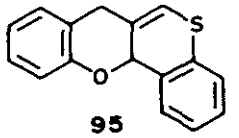

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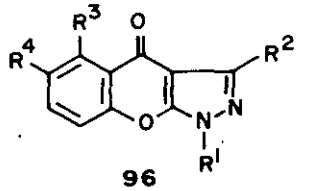

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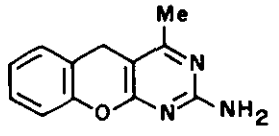

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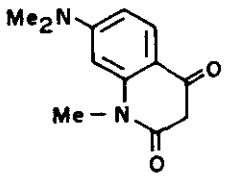

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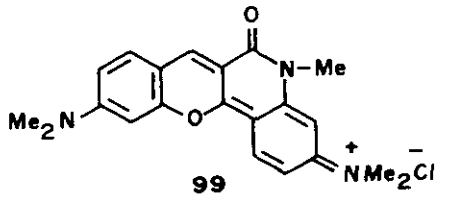

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97 on treatment with $POCl_3$[119].

3-Methyl-1-phenyl-2-pyrazolin-5-one on treatment with $POCl_3$-DMF gives 5-chloro--4-formyl-3-methyl-1-phenylpyrazole that on reacting with β-naphthol followed by oxidation and cyclisation affords 96 (R^1 = Ph; R^2 = Me; R^3R^4 = CH=CH--CH=CH)[120]. The chlorovinylaldehyde, obtained by treating the ketone 98 with $POCl_3$-DMF, reacts with 3-dimethylaminophenol in boiling AcOH containing HCl to give the blue-violet dye 99[121].

Heating 4-ethoxycarbonylchroman-3-one with resorcinol monomethyl ether at 150-160°C under nitrogen results the rotenoid 16 (R^1 - R^5 = R^7 = H; R^6 = OMe; R^8R^9 = bond)[122]. 6,7-Dimethoxy-4-ethoxycarbonylchroman-3-one has been similarly condensed with tubanol to dehydrorotenone[123]. Dehydromunduserone, dehydrosermundone and dehydroapotoxicarol and other dehydrorotenoids have also been prepared by thermal condensation of appropriately substituted 3-oxo--chroman-4-carboxylic ester and phenol derivatives[123,124]. Reaction of phenol with ethyl 1-benzyl-5-chloro-1,2,3-triazole-4-carboxylate, prepared from the corresponding triazolinone-4-carboxylic ester, gives 1-benzyl-5-phenoxy-ν-triazole-4-carboxylic ester that on sequential debenzylation, saponification, and cyclisation gives the fused triazole 47 (R = H; X = N)[125].

XI. From aryl hetaryl ethers and ketones

4-Azaxanthone appropriately substituted at benzene and/or pyridine ring possesses antibacterial properties and it is synthesised by cyclisation of appropriately substituted 2-phenoxynicotinic acid or nitrile[126-133]. 5-Phenoxy--ν-triazole-4-carboxylic acid has been cyclised to 47 (R = H; X = N)[134]. 3-Carbamoyl-4-phenoxyquinoline on PPA cyclisation gives 59 (R^1 = R^2 = H; R^3 = Ph; XR^5 absent)[135]. Similar treatment of 5-formyl-3-methyl-6-phenoxyuracil obtained by formylation of 3-methyl-6-phenoxyuracil with Vilsmeier reagent furnishes 3-methyl-5-deaza-10-oxaflavin (81, R = Me; X = CO)[136]. 12H-[1]-Benzopyrano[2,3-b]quinoxaline has been synthesised from ethyl 2-phenoxyquinoxaline-3-carboxylate[139]. 10-Aryl-10-hydroxy- and 10,10-diaryl-4-azaxanthenes have been prepared by reacting 3-cyano- and 3-methoxycarbonyl-2-phenoxypyridines respectively with ArMgBr followed by cyclisation with H_2SO_4-HOAc[138]. 4-Azaxanthone has also been prepared by heating 2-hydroxy-3-salicyloylpyridine in

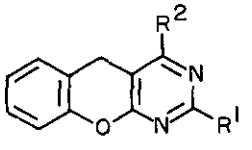
HOAc-HCl[139]. 1-Benzyl-5-chloro-4-salicyloyl-1,2,3-triazole cyclises to 3-benzyl-9-oxo-9H-[1]benzopyrano[2,3-d][1,2,3]triazole under base catalysis[140].

XII. From 2-hydroxybenzaldehydes

Some utilities of 2-hydroxybenzaldehyde to synthesise the heterocycles of the general formula (A) have been described in the previous sections. Few other reactions of the said aldehyde with certain other compounds leading to the same goal are enumerated in this section.

Salicylaldehyde on condensation with benzoylacetonitrile in the presence of NH_4OAc gives the pyrimidine 100 (R^1 = 2-hydroxyphenyl; R^2 = Ph)[141]. Treatment of salicylaldehyde with $H_2NC(R^2)=CHCN$ produces 100 (R^1 = 2-hydroxyphenyl; R^2 = Me, MeC_6H_4, Ph)[142]. The compound 100 (R^1 = Ar; R^2 = OH) has been synthesised by condensing an aromatic aldehyde with 3-carbamoyl-2-iminochromone, prepared by reacting salicylaldehyde with malononitrile[143]. Two molecules of salicylaldehyde on condensing with one molecule of $CH_2(H_2N-C=NR^7)_2$ [R^7 = H, Me, Et] produces 66 (R^1 = R^2 = H; R^3 = NHR^7; R^6 = 2-hydroxyphenyl)[144]. Salicylaldehyde on condensation with $NCCH_2CONHCO_2Et$ gives 81 (R = H; X = CO) that on borohydride reduction furnishes 101 (R^1 - R^3 = H; X = O)[145]. Compound 101 (R^1, R^2, R^3 = H, alkyl; X = O or S) has been prepared by heating a mixture of salicylaldehyde, appropriate barbituric or thiobarbituric acid and methanesulphonic acid[146]. Heating a mixture of 4-diethylamino-2-hydroxybenzaldehyde and 2-cyanomethyl-5-benzyl-1,3,4-triazole in ethanol in the presence of pyrrolidine gives a coumarinimine which reacts with $(PhO)_2CO$ to form 102 (X = N; Y = O; ZR^1 = N; R^2 = CH_2Ph)[147]. 4-Diethylamino-2-hydroxybenzaldehyde on sequential treatment with benzimidazole-2-acetonitrile and -malononitrile forms 102 [X = C(CN); Y = NH; Z = C; R^1R^2 = CH=CH-CH=CH][148]. The aldol condensate of salicylaldehyde and $NCC(NH_2)=C(CN)_2$ cyclises to 103[149]. Fluorescent dyes 104 (R = H, alkyl, alkenyl, aryl, hetaryl; X = O, S, NR^1; X^1 = O, S, SO_2, NR^1, CR^1R^2; R^1, R^2 = H, alkylaryl; Y = anion) have been patented[150]; the representative member 104 (R = Me, X = O, X^1 = CMe_2, Y = ClO_4) is synthesised by treating 2-methyldimedone in HMPA successively with NaH, BuLi, and sodium salt of salicylaldehyde followed by acidification of the resultant

product with $HClO_4$[150]. 1-Methylpyridinium iodide on reduction to the dihydro stage with an equivalent of $LiAlH_4$ followed by addition of an equivalent of salicylaldehyde gives 105 (R^1 = Me; R^2 = R^3 = H) which on Jones oxidation gives trans-2-methyl-1,2,3,4,4a,10a-hexahydro-10-oxo-10H-[1]benzopyrano[2,3-d] pyridine. Analogously the corresponding condensation product 105 [R^1R^2 = $(CH_2)_3$; R^3 = Me] of 2,3-dihydro-1H-indolizinium bromide with 6-methylsalicylaldehyde is prepared and subsequently oxidised to give elaeocarpine (22) and isoelaeocarpine (23) which can be separated by chromatography on alumina[151].



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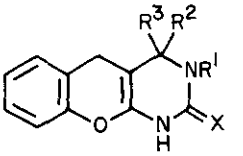

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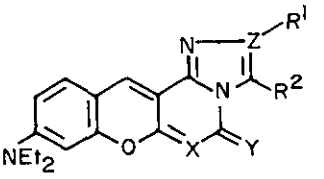

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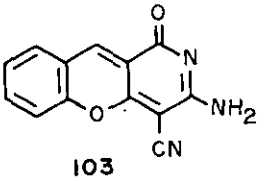

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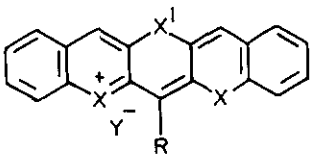

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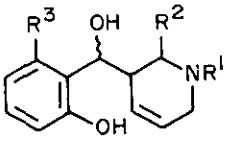

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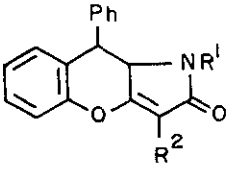

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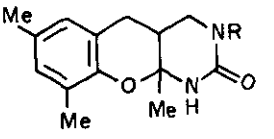

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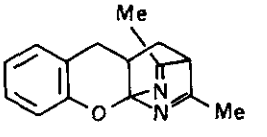

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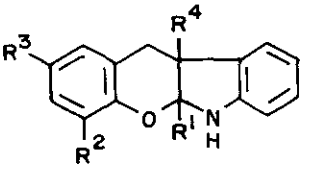

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XIII. From miscellaneous substrates

Phthaloyl chloride on heating with two molar amount of ω-benzoyloxy-2-hydroxy-4--methoxyacetophenone in pyridine gives 2-benzoyloxy-2'-hydroxycarbonylflavone that on acid hydrolysis furnishes 4-methoxy-10,12-dioxo-10H,12H-[1]benzopyrano-[3,2-c][2]benzopyran[152]. The carbanion of 2-$FC_6H_4COCH_2CO_2Et$ reacts with N-alkylisatic anhydride giving 18 (R^1 - R^4 = H; Y = O; Z = P = CO; Q = NR; R = alkyl)[153]. Treatment of $Ph_2C=C=NR^1$ (R^1 = C_6H_4OMe-p, C_6H_4Me-p or t-Bu) with $R^2CH(COCl)_2$ [R^2 = CH_2Ph, Et, Ph, i-C_3H_7 or Me] gives the pyrrole 106[154]. Treatment of vinyl methyl ketone with NH_2CONHR (R = H, Me) gives a pyrimido-[4,5-d]pyrimidinedione derivative that in acid medium reacts with 2,4-dimethyl-phenol to give 107[155]. 2-Chloro-4,5-dimethylpyrimidine with 2-allylphenol gives the normally expected 2-phenoxypyrimidine derivative together with the adduct 108[156]. [1]Benzopyrano[2,3-b]indole 109 (R^1 = R^2 = H, R^3 = NO_2; R^4 = Me) results from dissolution of a mixture of skatole and 2-bromomethyl-4-nitro-phenol[157]. The indole 109 (R^1 - R^4 = Me) is similarly prepared from 2,3-di-methylindole and 2-bromomethyl-4,6-dimethylphenol[158].

ACKNOWLEDGEMENT

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