

BENZOPYRAN-4-ONES CONTAINING A 2,3-FUSED HETEROCYCLIC RING

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Abstract — The chemistry and biological properties of
4-oxo-[1]benzopyrano-2,3-fused heterocycles are reviewed.

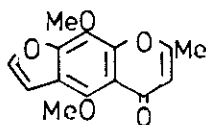
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References

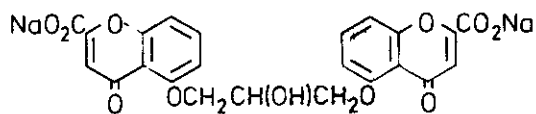
1. Introduction

Since khellin [a 5H-furo[1]benzopyran, (1)¹] was shown over 50 years ago to have bronchodilator activity², several benzopyran-4-ones have been shown to be biologically active³⁻¹⁰.



(1)

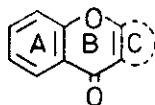
The best known benzopyran-4-one, namely, disodium cromoglycate [Intal, Cromolyn, (2)¹¹] is a valuable drug in the treatment of bronchial asthma¹².



(2)

The literature on benzopyran-4-ones is well documented¹³ but more recently the work has been extended to benzopyran-4-ones which contain a heterocyclic ring. These compounds have also exhibited biological activity¹⁴ and are, therefore, of interest.

This review will concentrate on benzopyran-4-ones containing a 2,3-fused heterocyclic ring (3). Although there are benzopyran-4-ones in which the heterocyclic ring is attached to the 3,4-position or to the benzene ring, fusion at the 2,3-position may enhance biological activity. This may be supported by the fact that the more biologically active benzopyran-4-ones are those in which there is a C-2 substituent, usually a carboxylic acid or derivative^{3, 4}.



(3) C=Heterocyclic ring

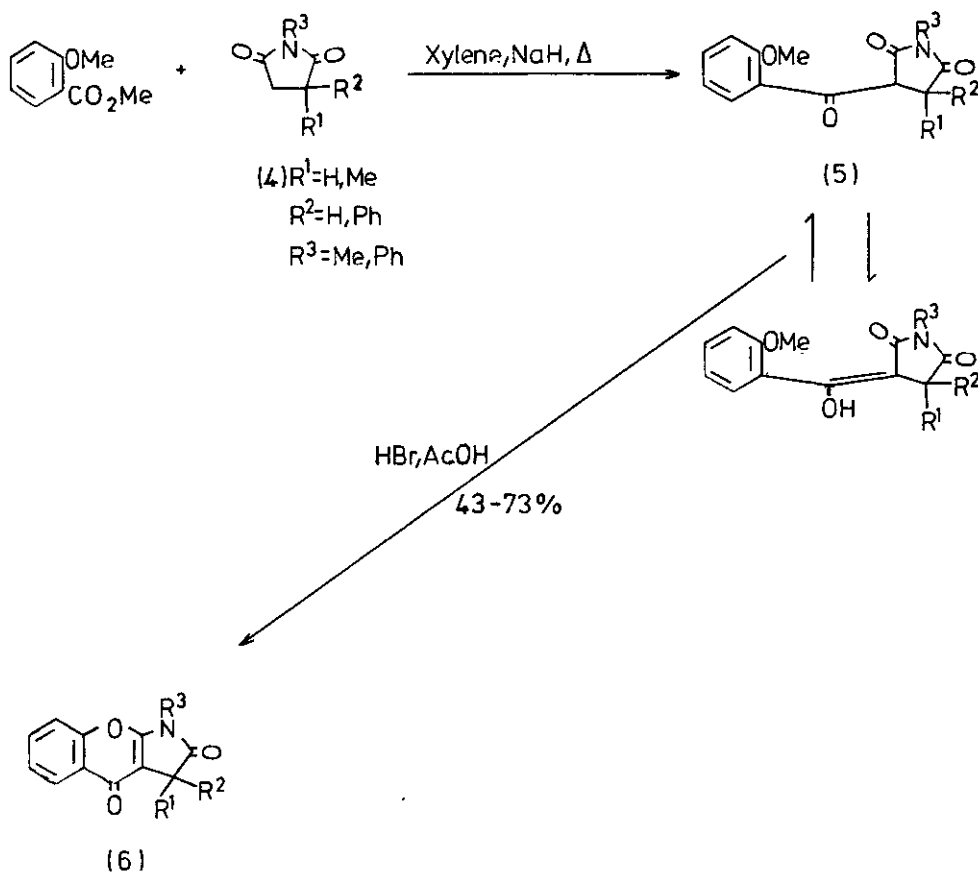
Although a considerable amount of work has been published on this subject¹⁵, no review has been published until now. Compounds both naturally occurring and synthetic are considered and their biological activity described.

2. Compounds containing a 5-membered heterocyclic ring

Several benzopyran-4-ones bearing a 2,3-fused 5-membered heterocyclic ring are known. The ring may contain 1, 2 or 3 heteroatoms, similar or different, and may itself be fused to a benzene or hetero-ring. The precedence of nitrogen over oxygen and sulphur shall be used here.

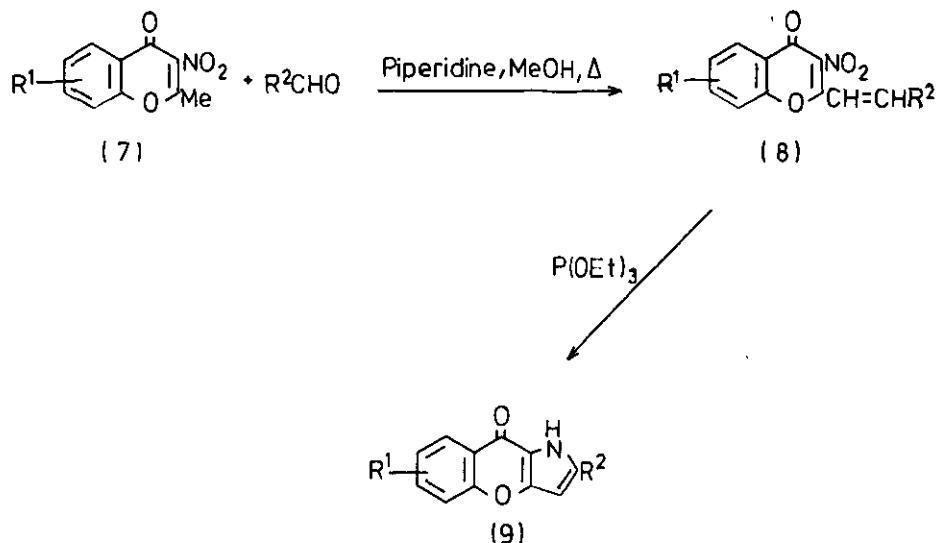
2.1 One heteroatom

Eiden and Hirschmueller¹⁶ synthesized [1]benzopyrano[2,3-b]pyrrole (6) in moderate to good yield by condensation of the succinimide derivatives (4) with 2-methoxybenzoate to yield the methoxybenzoylsuccinimides (5) which were converted to the pyrroles (6) with pyridine hydrochloride or hydrogen bromide and acetic acid (Scheme 1).



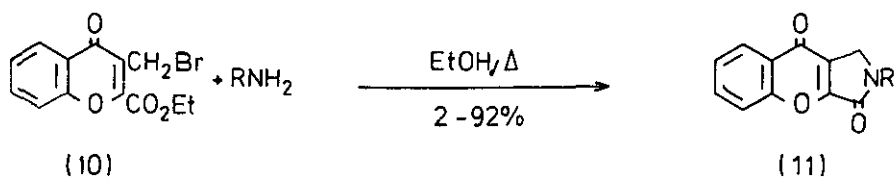
Scheme 1

The benzopyrano[3,2-b]pyrrole (9) isomer is also known, having been reported by Paparao and co-workers¹⁷. A 2,3-disubstituted-4H-1-benzopyran-4-one, namely, 2-methyl-3-nitro-4H-1-benzopyran-4-one (7) was condensed with an aromatic or heterocyclic aldehyde in the presence of piperidine. The condensation between the 2-methyl substituent of benzopyran-4-ones and aromatic aldehydes in the presence of a base is well known¹⁸⁻²⁰ and indicates the high acidity of the 2-methyl hydrogen. Reductive cyclization of the 3-nitro compound (8) resulted in the [1]benzopyrano[3,2-b]pyrrole (9) in moderate yields (Scheme 2).



Scheme 2

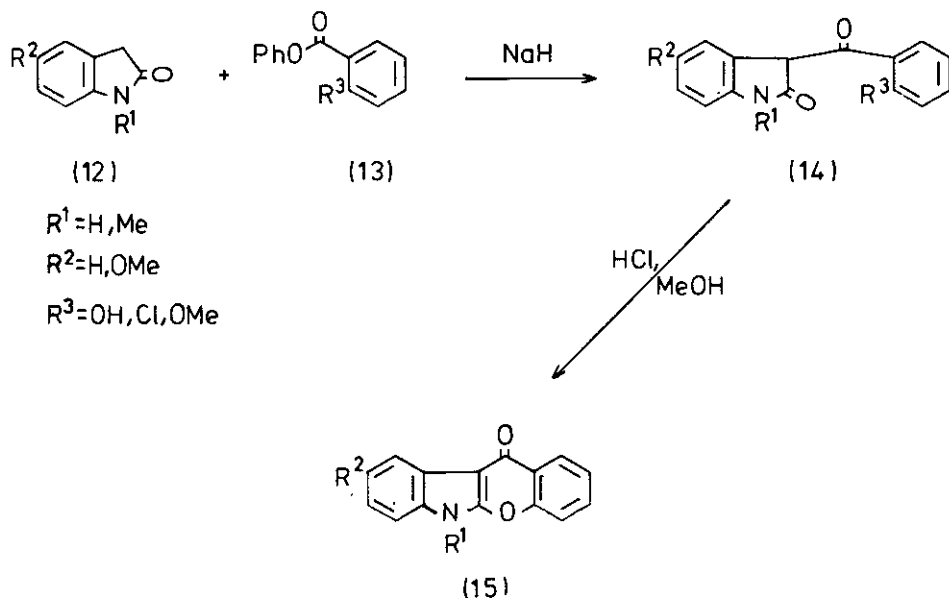
The use of a 2,3-disubstituted-4H-1-benzopyran-4-one in the synthesis of the [1]benzopyrano[2,3-c]pyrrole has recently been described by Ellis and Romney-Alexander¹⁵. Thus, the reaction of ethyl 3-bromomethyl-4-oxo-4H-1-benzopyran-2-carboxylate (10) with a variety of primary amines (arylamines, heterylamines and aralkylamines) resulted in the formation of N-substituted 1,2-dihydrobenzopyrano[2,3-c]pyrrole-3,9-dione (11) in low to high yields.



R = aryl, heteryl or aralkyl

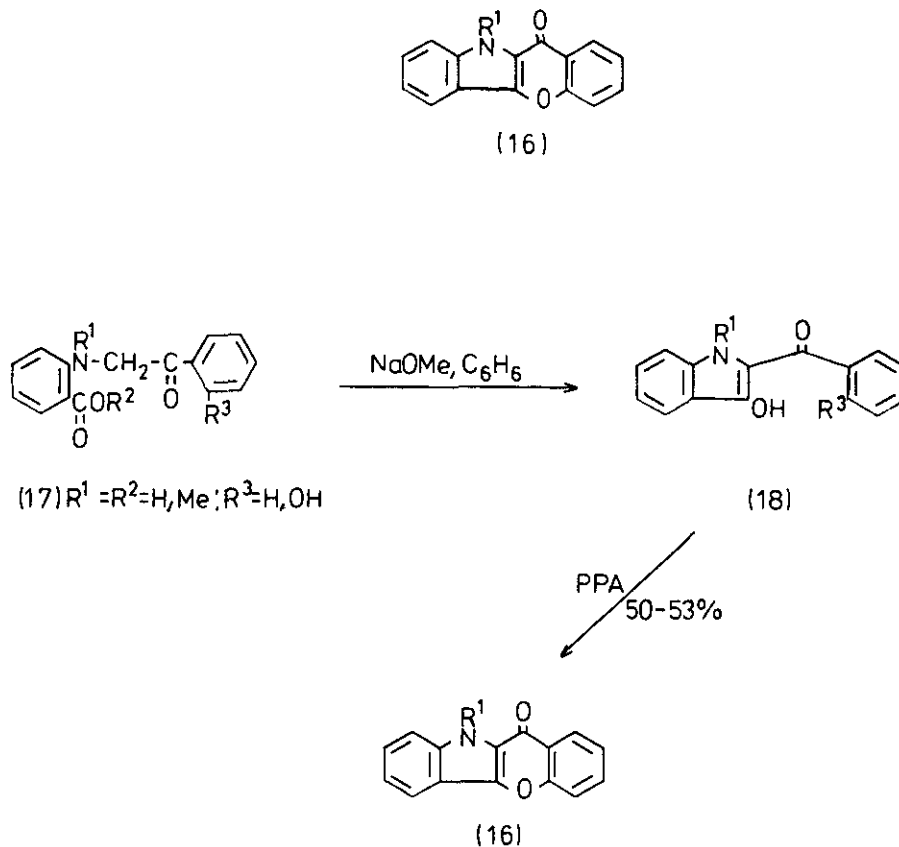
The synthesis of a benzopyran-4-one bearing a cyclic imide at the 2,3-position has been reported^{20a} from the corresponding anhydride.

Eiden and Dobinsky first reported the synthesis of the [1]benzopyrano[2,3-b]indole ring system (15)^{21, 22}. The synthetic route, reported in a later paper²³, has features common to that of the synthesis of [1]benzopyrano[2,3-b]pyrrole¹⁶ (see Scheme 1). Here, the reaction between the oxindoles (12) and ortho substituted phenyl benzoate (13) resulted in the 3-(o-substituted benzoyl) oxindole derivatives (14), which were then cyclized to the [1]benzopyrano[2,3-b]indoles (15) in methanol saturated with hydrogen chloride (Scheme 3). The yields were moderate to high.



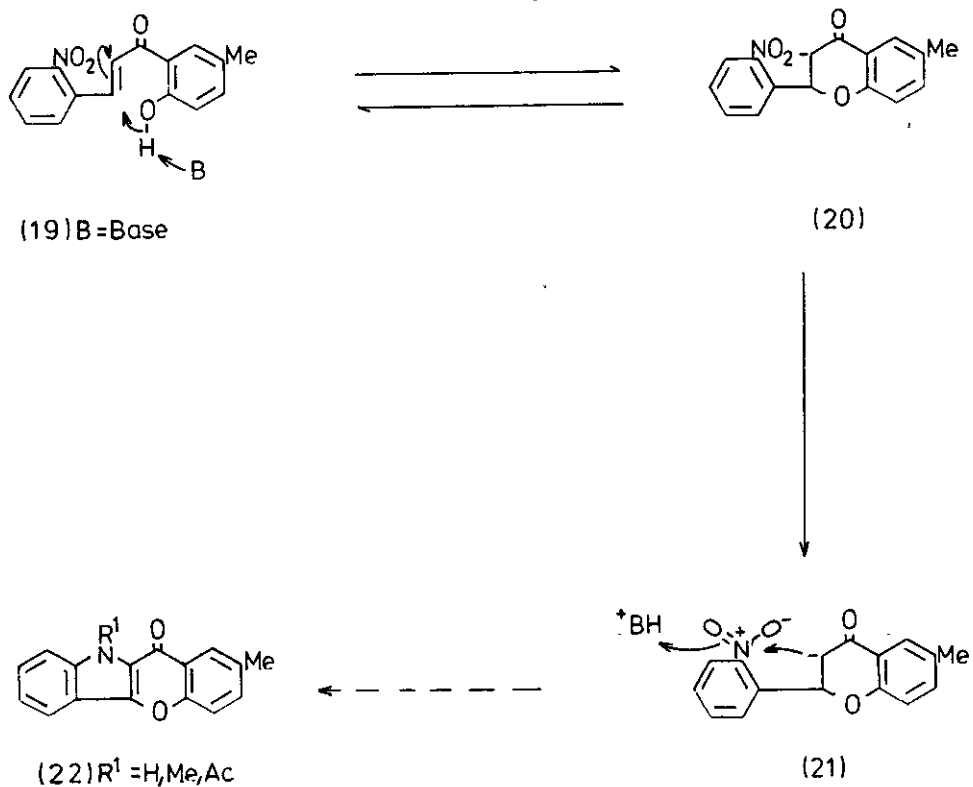
Scheme 3

Both Goerlitzer²⁴ and Dean and co-workers^{25, 26} have described the successful synthesis of the [1]benzopyrano[3,2-b]indole isomer (16). The synthetic route used by Goerlitzer involved the condensation between methyl anthranilate and 2-hydroxy-2-bromoacetophenone, resulting in a product of the type (17). In the presence of sodium methoxide, an intramolecular Dieckmann condensation occurred to give the heterocyclic 1,3-dicarbonyl compounds (18). Subsequent cyclization, using polyphosphoric acid (PPA), gave the [1]benzopyrano[3,2-b]indoles (16) (Scheme 4).



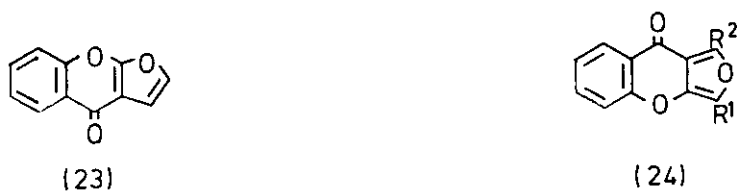
Scheme 4

Dean and co-workers²⁵ utilized alkaline hydrogen peroxide to oxidize 2'-hydroxy-chalcone to 3-hydroxyflavanone (Algar-Flynn-Oyamada reaction). The method was successfully used with chalcones carrying nitro-groups in the 3- or 4-positions. When the nitro-group was in the 2-position (19) it was found that the alkali induced a series of reactions which terminated in the 10-substituted-2-methyl-11H-[1]benzopyrano[3,2-b]indol-11-one (22) in good yield. They postulated that instead of the carbanion (20) effecting nucleophilic substitution at the peroxide oxygen, the nitro-group at the 2-position was uniquely placed to react by nucleophilic addition, as shown in (21) (Scheme 5). Reactions between carbanionic centres and nitro-groups had earlier been reported²⁷. The [1]benzopyrano[3,2-b]-indole ring system has also been synthesized by heating a 6-substituted-2'-nitro-flavone with triethyl phosphite²⁵. Claims have been made that some benzopyrano-indoles exhibit biological activity²².

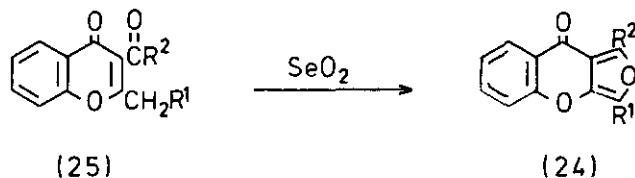


Scheme 5

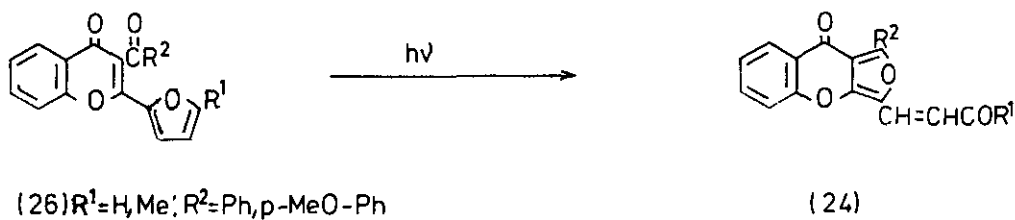
Several papers have been published in which benzopyran-4-ones contain a furan ring fused to the 2,3-position. Yamamoto and co-workers²⁸ have reported the furo[2,3-b][1]benzopyran-4-one (23) whilst the isomeric furo[3,4-b][1]benzopyran-9-one (24) has been reported by several others²⁹⁻³².



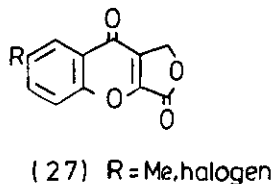
Henderson and Ullman²⁹ obtained a trace amount (<1%) of compound (24, R¹=R²=Ph) when 2-benzyl-3-benzoyl-4H-1-benzopyran-4-one (25) was exposed to both ultraviolet and visible light in the presence of oxygen. Oxidation of the 2,3-disubstituted-4H-1-benzopyran-4-one (25) using selenium dioxide also gave (24, R¹=R²=Ph) in low yield.



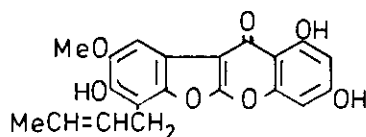
Huftman and co-workers³¹ were also able to synthesize the furo[3,4-b][1]benzopyran-9-ones (24) by the photolysis of the isomeric 3-aroyle-2-(2-furyl)-4H-1-benzopyran-4-ones (26).



Furo[3,4-b][1]benzopyran-3,9-diones (27) were found not to exhibit any appreciable antibacterial activity³⁰.

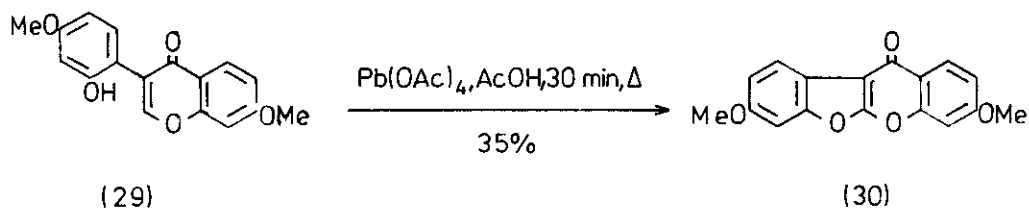


Several benzofuro[2,3-b][1]benzopyran-11-ones have been reported³³⁻³⁶ and these are mainly naturally occurring compounds. Of these, the best known is lisetin (28)^{33, 34, 36}, first isolated from the root-bark of the Jamaican Dogwood, Piscidia erythrina L. The analgesic and insecticidal properties of the root-bark, as well as its pharmacodynamic properties, have been the subject of numerous investigations^{37, 38}.

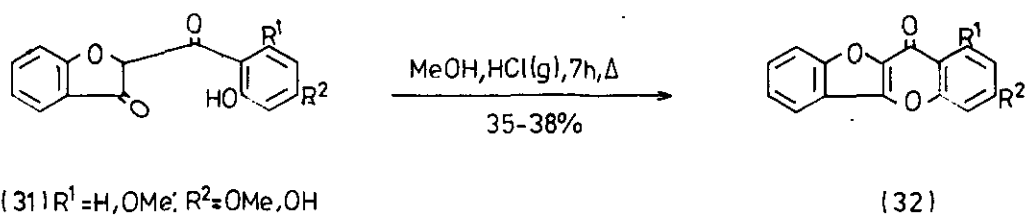


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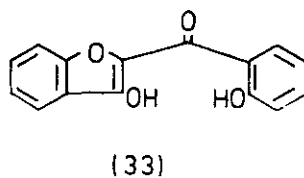
Kurosawa and Araki³⁵ observed that the lead(IV) acetate oxidation of 2'-hydroxyisoflavone (29), when conducted at reflux temperature, gave the benzofuro[2,3-b][1]benzopyran-11-one (30) as the major product and this could therefore be utilized as a synthetic method.



The synthesis of benzofuro[3,2-b][1]benzopyran-11-ones (32) has been described³⁹⁻⁴¹ and this includes the demethylation of 2'-methoxyflavanols under harsh conditions³⁹ and the acid-catalysed dehydration of 2-(2'-hydroxybenzoyl)coumaran-3-ones (31)⁴⁰.

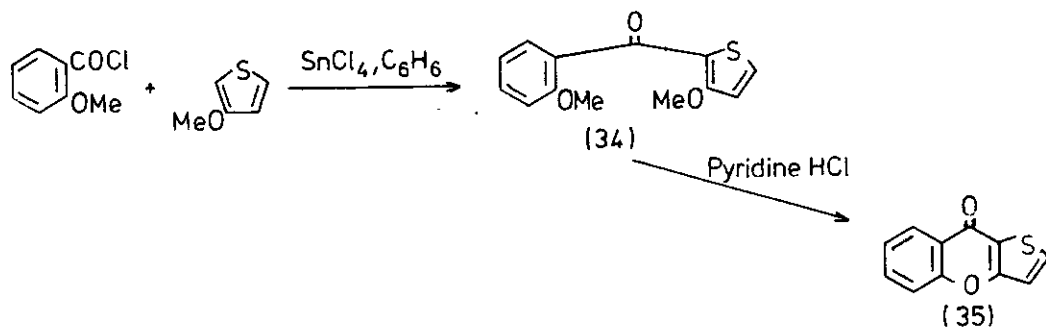


Goerlitzer²⁴ effected the cyclization of 2-(2'-hydroxybenzoyl)-3-hydroxybenzo[b]-furan (33), using PPA, to give (32) in 54% yield.

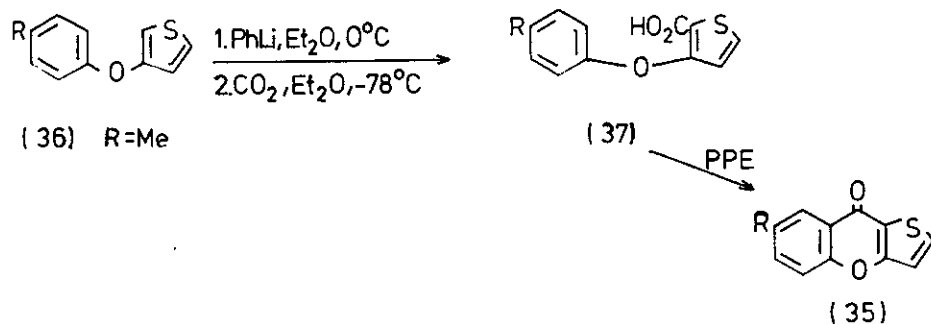


There are very few examples in which the heteroatom of the 2,3-fused heterocyclic ring is sulphur. Henrio and co-workers⁴² condensed 3-methoxythiophene and *o*-anisoyl chloride in the presence of stannic chloride (Friedel-Crafts acylation), and cyclization of the resulting dimethoxy ketone (34) afforded the thieno[3,2-*b*]-[1]benzopyran-9-one (35) in 80% yield (Scheme. 6).

Since a number of antiallergy agents possess xanthone-like structures, Watthey and Desai⁴³ synthesized thieno[3,2-*b*]benzopyran-9-ones (35), through the regioselective lithiation-carbonation of 3-(aryloxy)thiophenes, and subsequent cyclization using polyphosphate ester (PPE) in refluxing chloroform. Therefore, the treatment of 3-(*p*-tolylloxy)thiophene (36), from the condensation of 3-bromothiophene and *p*-cresol, with 1 equivalent of phenyllithium followed by carbonation with solid carbon dioxide in ether at -78°C gave 3-(*p*-tolylloxy)thiophene-2-carboxylic acid (37). Cyclization was effected using PPE (Scheme 7). The yields varied from low to high.

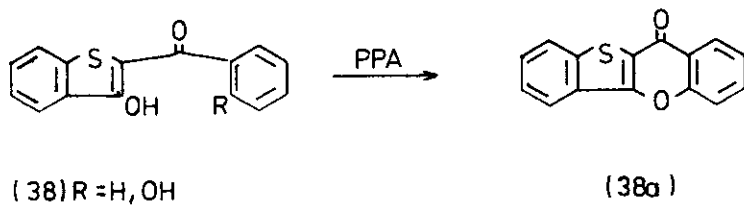


Scheme 6



Scheme 7

The synthesis of benzothieno[3,2-*b*][1]benzopyran-11-one (38a) has been described by Goerlitzer²⁴ and involved the cyclization of the heterocyclic 1,3-dicarbonyl compound (38) using PPA.

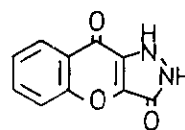


2.2 Two heteroatoms

Benzopyran-4-ones, in which the ring attached to the 2,3-position is a pyrazole, have been described. These are mainly [1]benzopyrano[2,3-c]pyrazoles (39)⁴⁴⁻⁴⁹ although the [1]benzopyrano[3,2-c]pyrazole isomer (40)^{50,51} has also been reported.

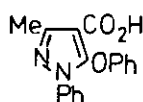


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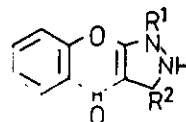
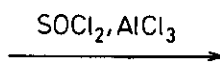


(40)

Sarenko and his co-workers⁴⁴ synthesized [1]benzopyrano[2,3-c]pyrazole (39, R¹=Ph, R²=Me) from the 3-phenoxypyrazole-4-carboxylic acid (41) via an intramolecular Friedel-Crafts acylation.

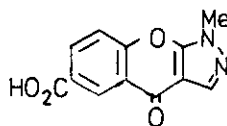


(41)



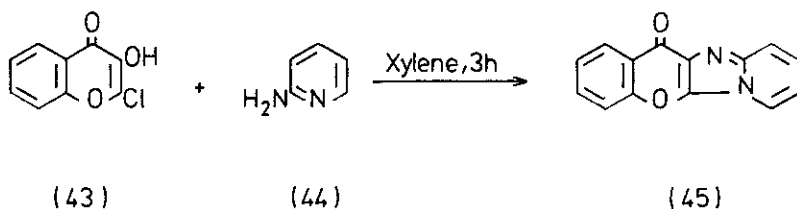
(39)

Compound (42) exhibited antiallergic activity when administered interperitonally or orally in rats⁴⁵.

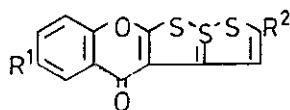


(42)

The reaction between 2-chloro-3-hydroxy-4H-1-benzopyran-4-one (43) and 2-aminopyridine (44) gave [1]benzopyrano[3',2':4,5]imidazo[1,2-a]pyridin-12-one (45)⁵² in 46% yield.

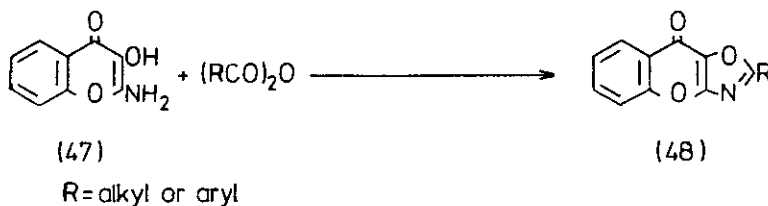


Dean, Goodchild and Hill⁵³ reported the synthesis of [1,2]dithiolo-[1⁴,5⁴:1,5][1,2]dithiolo[3,4-b]benzopyran-11-S^{IV} (46) in low yield, by the condensation of a dithiolium salt with 4-hydroxy-2H-1-benzopyran-2-thione.

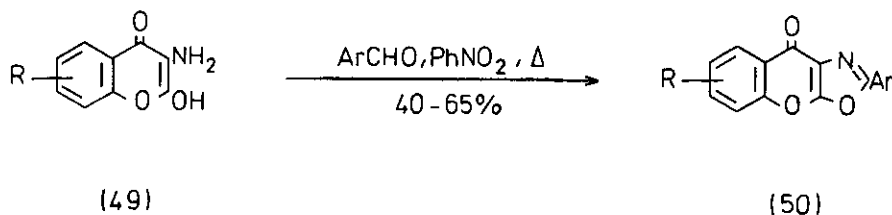


(46) R¹=Me; R²=Ph

Substituted [1]benzopyrano[2,3-d]oxazol-9-ones⁵⁴ (48) have been synthesized in moderate to high yields by reacting 2-amino-3-hydroxy-4H-1-benzopyran-4-one (47) with acid anhydrides.



The isomeric [1]benzopyrano[3,2-d]oxazol-9-ones (50)⁵⁵ have been obtained from the reaction of 3-amino-2-hydroxy-4H-1-benzopyran-4-one (49) with aromatic aldehydes and these compounds are effective antibacterial and antifungal agents.



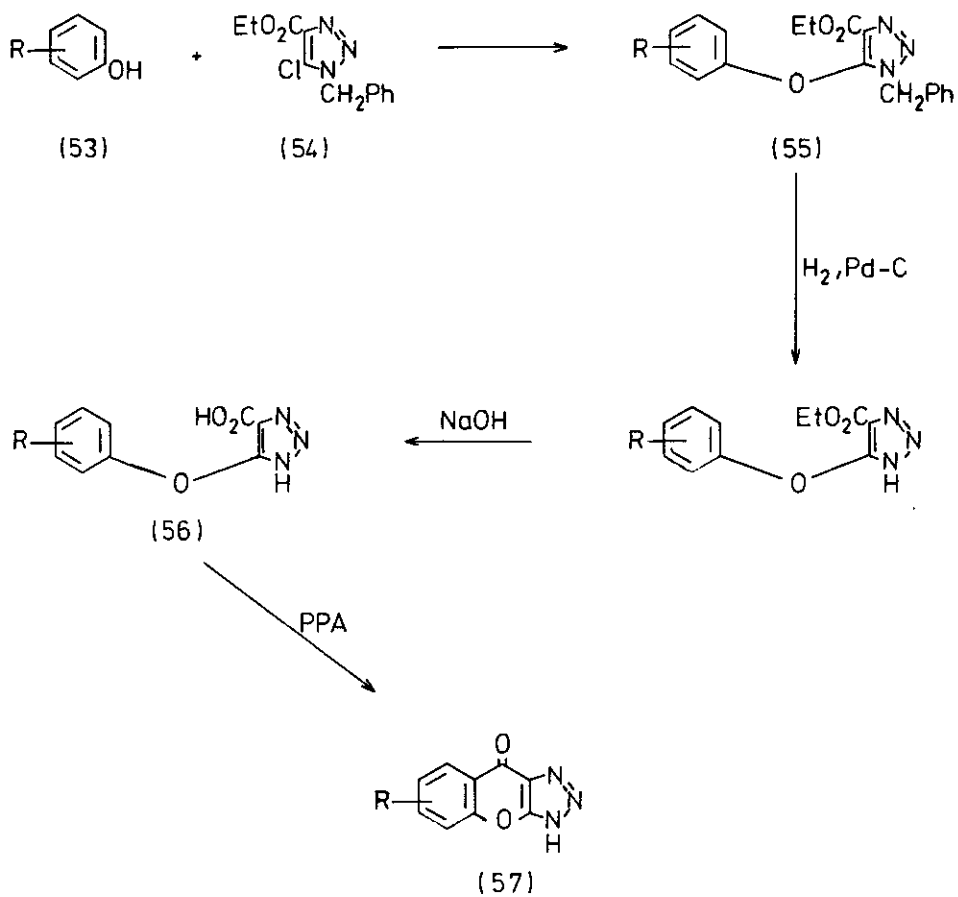
Examples of [1]benzopyrano[2,3-c]isoxazol-4-ones (51)⁴⁷ and [1]benzopyrano[3,2-c]-isoxazol-9-ones (52)⁵⁶ are also known.



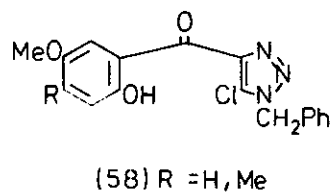
2.3 Three heteroatoms

[1]Benzopyrano[2,3-d]-1,2,3-triazoles (57) are the only known compounds containing three heteroatoms and work on their synthesis has been carried out by Buckle and his co-workers⁵⁷⁻⁶⁴. This involved the formation of (aryloxy)triazoles (55), by reacting phenols (53) with ethyl 1-benzyl-5-chloro-1,2,3-triazole-4-carboxylate (54), followed by debenzoylation by high-pressure catalytic hydrogenolysis and alkaline hydrolysis of the ester to the acid (56). The acids were cyclized using either PPA or phosphoric oxide in methanesulphonic acid.

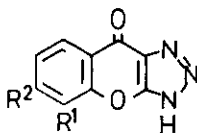
The yields were moderate to high. A recent paper⁶⁴ described the formation of substituted triazoles (58) via direct acylation of an appropriate arene. Compounds of the type (58) were readily cyclized using sodium hydride.



Scheme 8



Compounds (57a) and (57b) were claimed to be ten times more potent than disodium cromoglycate when evaluated for antiallergic activity by the rat passive cutaneous anaphylaxis (PCA) screen⁶².



(57) a) $R^1 = H, R^2 = MeSO_2O$

b) $R^1 = Me, R^2 = MeSO_2O$

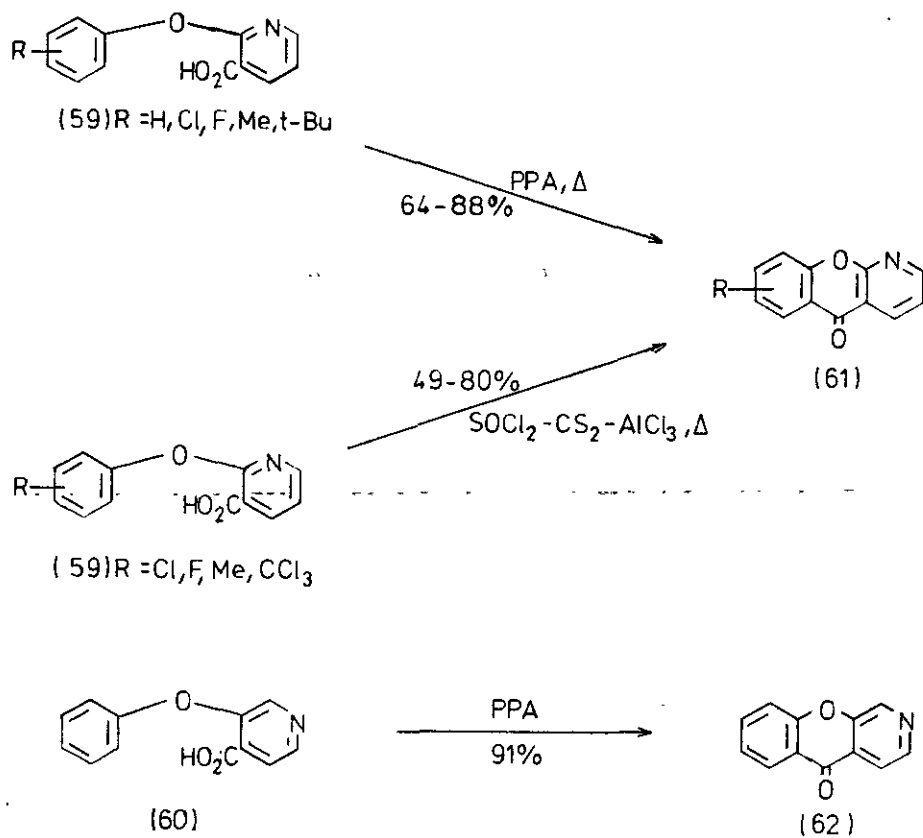
Other compounds of type (57), which contained dialkyl groups at C-5 and C-6 or C-6 and C-7, showed considerable potency. The 6-methoxy compounds also exhibited activity and 6,7-dimethyl-9-oxo-1H,9H-benzopyrano[2,3-d]-1,2,3-triazole was shown to be a potent inhibitor of rat PCA when given orally.

3. Compounds containing a 6-membered heterocyclic ring

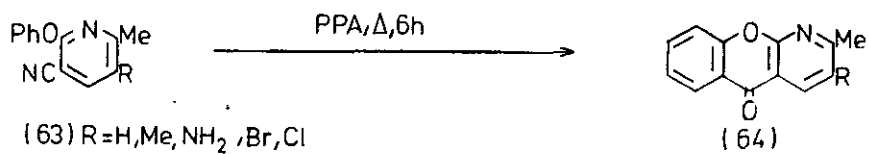
Of the benzopyran-4-ones which bear a heterocyclic ring at the 2,3-position, those with a 6-membered ring comprise the largest group. This ring may contain one heteroatom or two similar or different heteroatoms and may itself be fused to a benzene or hetero-ring.

3.1 One heteroatom

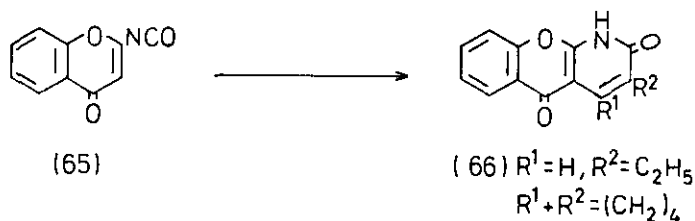
The simplest and most common ring is that which contains nitrogen, that is, a pyridine ring. Villani and his co-workers⁶⁵ described the synthesis of [1]benzopyrano[2,3-b]pyridin-5-ones (61) and [1]benzopyrano[2,3-c]pyridin-5-ones (62) from the corresponding phenoxy pyridinecarboxylic acids (59) and (60), respectively. Cyclization was by use of either PPA or thionyl chloride-carbon disulphide-aluminium chloride. Compound (61, R=H) had previously been prepared, in poor yield, by the cyclization of (59) using phosphorus oxychloride⁶⁶. 3-Substituted-2-methyl[1]benzopyrano[2,3-b]pyridin-5-ones (64) have been obtained in moderate to good yields by heating 5-substituted-6-methyl-2-phoxynicotinonitriles (63) in PPA⁶⁷.



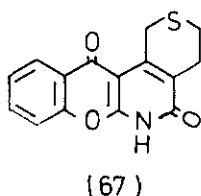
Scheme 9



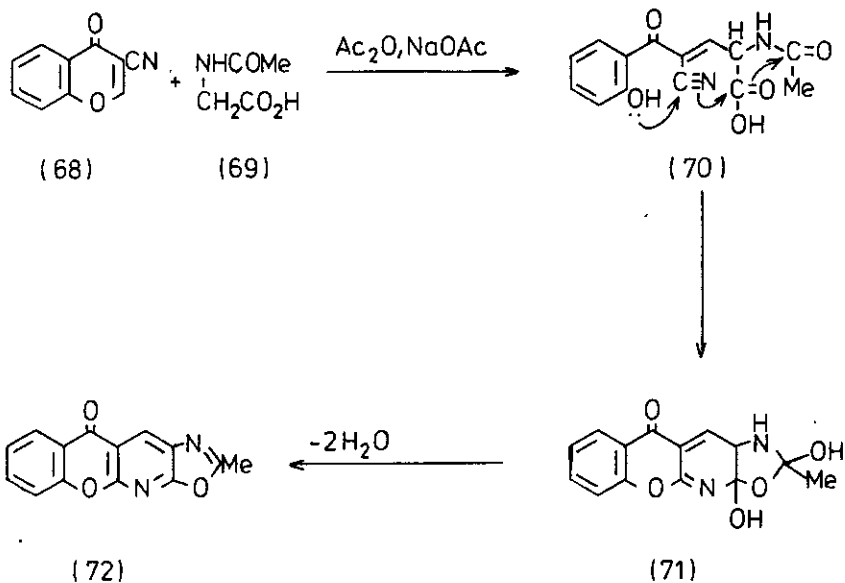
These are examples in which the heterocyclic ring is present in the precursor and the pyran-4-one ring is formed by cyclization. The majority of pyridine rings at the 2,3-position are formed via intramolecular condensation to the 2- or 3-position. Glozman, Zagorevskii and Zhmurenko⁶⁸ have, by the reaction of 2-isocyanato-4H-1-benzopyran-4-one (65) with enamines, for example 1-piperidino-1-cyclohexene, synthesized [1]benzopyrano[2,3-b]pyridine-2,5(1H)diones (66) in 22-78% yields.



The synthesis of [1]benzopyrano[2,3-b]thiopyrano[3,4-d]pyridine-5,12-dione (67) has also been reported⁶⁹ and involves the reaction between 2-acylamino-4H-1-benzopyran-4-one and 5-piperidino-5,6-dihydro-2H-thiopyran.

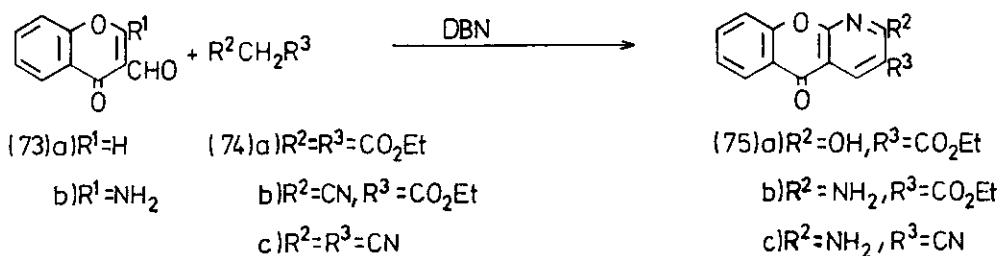


When 4-oxo-4H-1-benzopyran-3-carbonitrile (68) was reacted with acetylglycine (69) in acetic anhydride containing fused sodium acetate, [1]benzopyrano[2,3-b]oxazolo[4,5-e]pyridin-10-one (72) was obtained⁷⁰. The carbanion formed, by the action of sodium acetate on acetylglycine, attacked the benzopyran-4-one at the C-2 position. This opened the pyrone ring to give the intermediate hydroxynitrile (70) which then underwent triple cyclization to (72) via the dihydroxy compound (71) (Scheme 10).

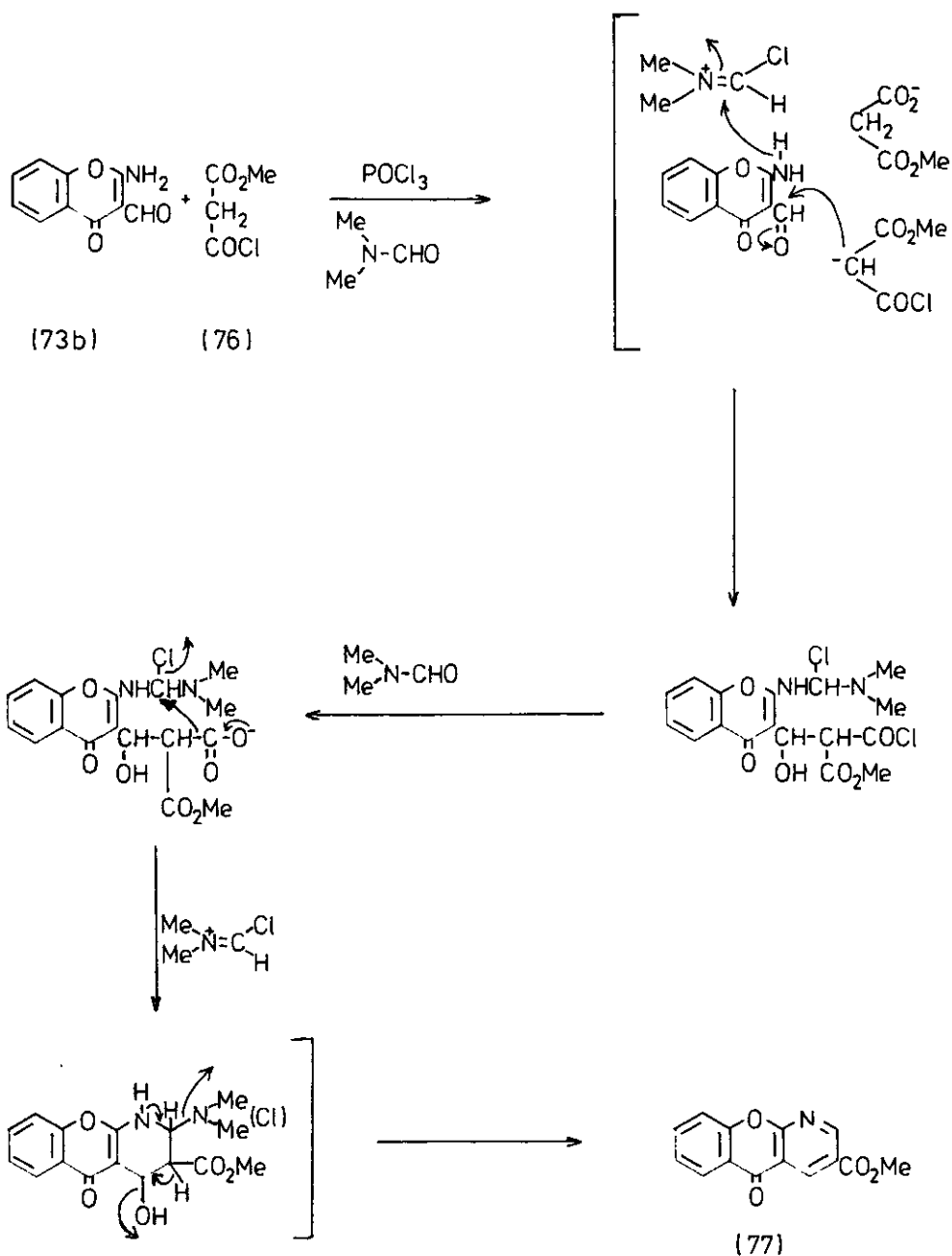


Scheme 10

Petersen and Heitzer⁷¹ first reported the synthesis of 2-amino-4-oxo-4H-1-benzopyran-3-carboxaldehyde (73b) from the 3-aldehyde (73a). The reaction of this aminoaldehyde with various compounds (74), all of which contained an activated methylene group, in the presence of 1,5-diazabicyclo[3.4.0]non-5-ene (DBN) gave 2,3-disubstituted-5-oxo-5H-[1]benzopyrano[2,3-b]pyridines (75). The yields were low to moderate.

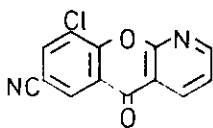


This work has been extended by Ishiguro and co-workers⁷², who synthesized 3-substituted-5-oxo-5H-[1]benzopyrano[2,3-b]pyridines (77). The reaction between the amino-aldehyde (73b) and the ester acyl chloride (76) in dimethylformamide, at 65°C, may follow the proposed mechanism⁷² (Scheme 11).

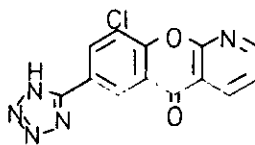


Scheme 11

9-Chloro-5-oxo-5H-[1]benzopyrano[2,3-b]pyridine-7-carbonitrile (78), prepared by dehydration of the 7-amide, has been claimed to exhibit anti-inflammatory and antiallergic activity in both rats and mice⁷³. The corresponding 9-chloro-7-(1H-tetrazol-5-yl)-5-oxo-5H-[1]benzopyrano[2,3-b]pyridine (79)⁷⁴ has been used in antihyperuricemia formulations and administration of 100 mg/kg of (79) to rats increased the urinary level of uric acid from 0.24 to 0.41 mg/100 g urine in 6 h.

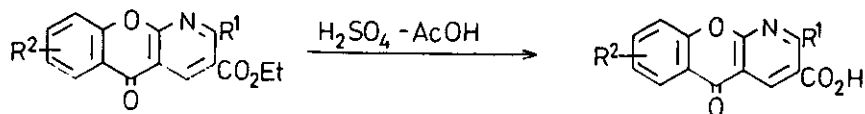


(78)



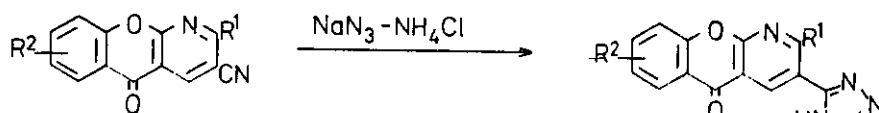
(79)

Compound (79) was also claimed to be most active when orally administered for PCA⁷⁵. In a recent paper, Nohara and co-workers⁷⁶ have described several 5-oxo-5H-[1]benzopyrano[2,3-b]pyridine-3-carboxylic acids (81) and the 3-tetrazole derivatives (83) from the 3-ester (80) and 3-nitrile (82), respectively. When administered intravenously, the compounds (81) and (83) exhibited antiallergic activity in a reaginic PCA test in rats. Compounds (81, R¹=H, R²=7-Et; R¹=NH₂, R²=7-*i*-Pr; and R¹=NHOMe, R²=7-*i*-Pr) and (83, R¹=H, R²=7-*i*-Pr) were claimed to be 41-184 times as potent as disodium cromoglycate, and showed considerable activity when administered orally. 2-Amino-4-oxo-4H-1-benzopyran-3-carboxaldehyde reacted with 4-hydroxy-2H-1-benzopyran-2-one in the presence of piperidine to give a [1]benzopyrano[2,3-b]pyridine ring system (83a)¹⁵.



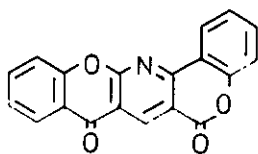
(80) $R^1 = \text{H, Me, OH, OMe, CO}_2\text{Et, NHOR}^3, \text{NH}_2$
 $R^2 = \text{H, Et, i-Pr, OMe, n-Bu}$

(81) $R^1 = \text{H, Me, OH, OMe, NH}_2, \text{NHMe, CO}_2\text{H, NHCOR}^3$



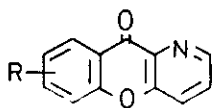
(82) $R^1 = \text{H, NH}_2$
 $R^2 = \text{H, Et, t-Bu, i-Pr, benzo}$

(83) $R^1 = \text{H, NH}_2, \text{NHOMe}$

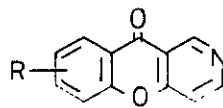


(83a)

[1]Benzopyrano[3,2-b]pyridin-10-ones (84) and [1]benzopyrano[3,2-c]pyridin-10-ones (85) have been prepared⁶⁵ from the corresponding phenoxy pyridinecarboxylic acids by the procedure described earlier.

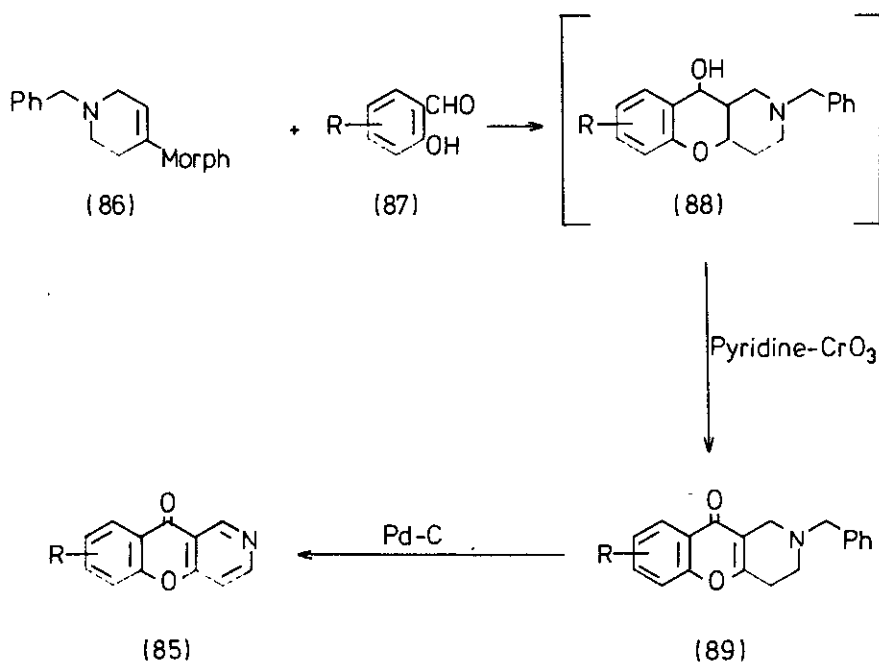


(84) R=Me,NO₂,NH₂,Cl,F



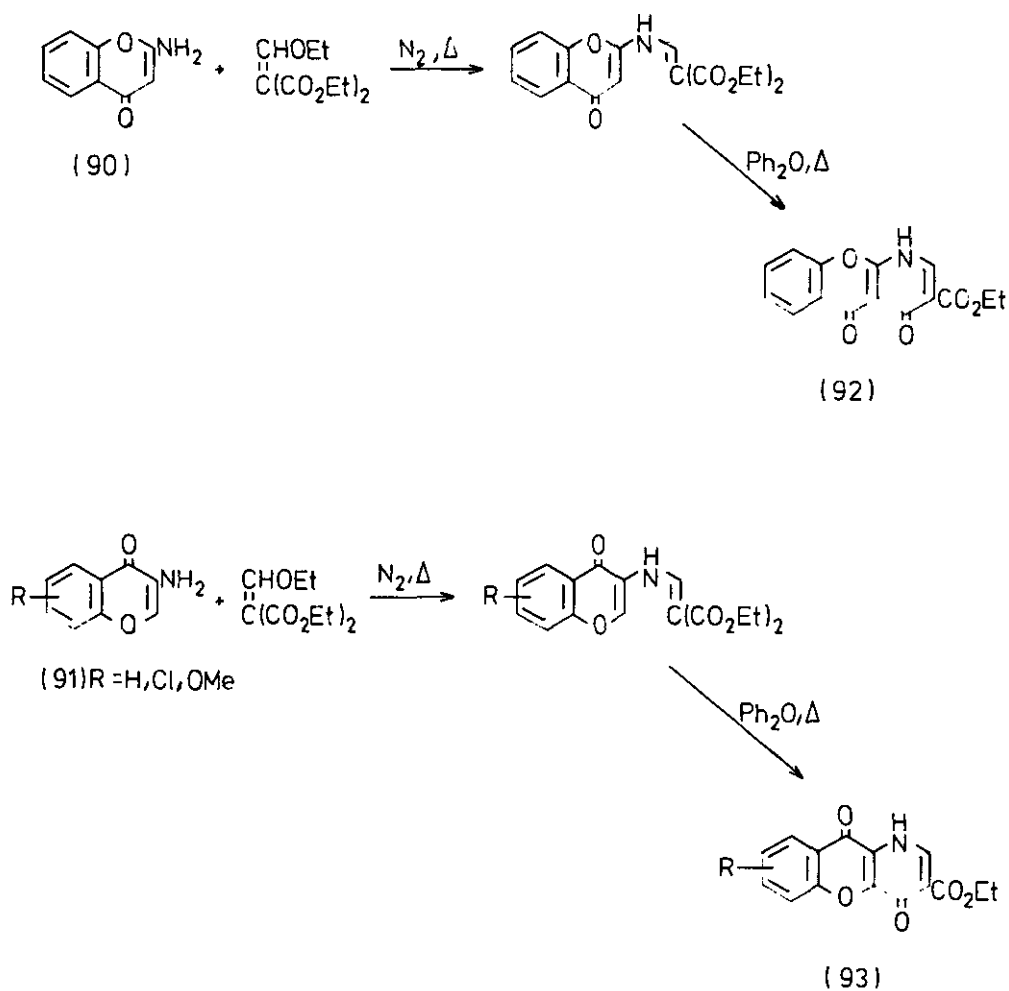
(85) R=H

The synthesis of [1]benzopyrano[3,2-c]pyridin-10-ones (85), by reacting the morpholine enamine of 1-benzyl-4-piperidone (86) and substituted salicylaldehydes (87), has been described⁷⁷. This involved the condensation reaction between the enamine (86) and salicylaldehyde (87), with the carbinol intermediate (88) being directly oxidized with chromium trioxide-pyridine to (89). Debenzylation, using palladium-charcoal, gave (85) in 78% yield (Scheme 12).



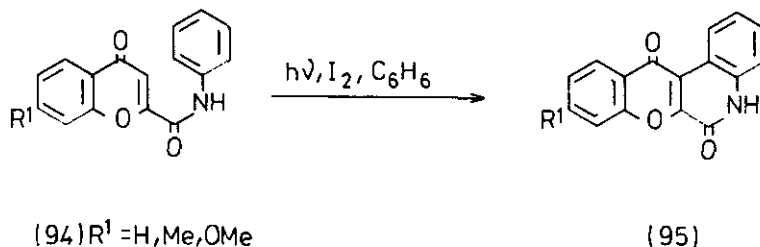
Scheme 12

Thomae⁷⁸ has also prepared compounds of type (85) from enamines, and these have been claimed to exhibit sedative properties. The reaction of both 2-amino-4H-1-benzopyran-4-one (90) and 3-amino-4H-1-benzopyran-4-one (91) with diethyl ethoxymethylenemalonate gave 4,5-dihydro-4,5-dioxo-1H-[1]benzopyrano[2,3-b]pyridine-3-carboxylate (92) and 4,10-dihydro-4,10-dioxo-1H-[1]benzopyrano[3,2-b]pyridine-3-carboxylates (93), respectively, via intermediates, in 52-93% yields⁷⁹ (Scheme 13).

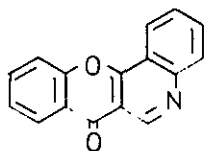


Scheme 13

The synthesis of [1]benzopyrano[2,3-c]quinoline-6,12-diones (95) has been described⁸⁰. N-Phenyl-4-oxo-4H-1-benzopyran-2-carboxamides (94), on photooxidation in the presence of iodine in benzene, gave compounds of type (95) in low yields.

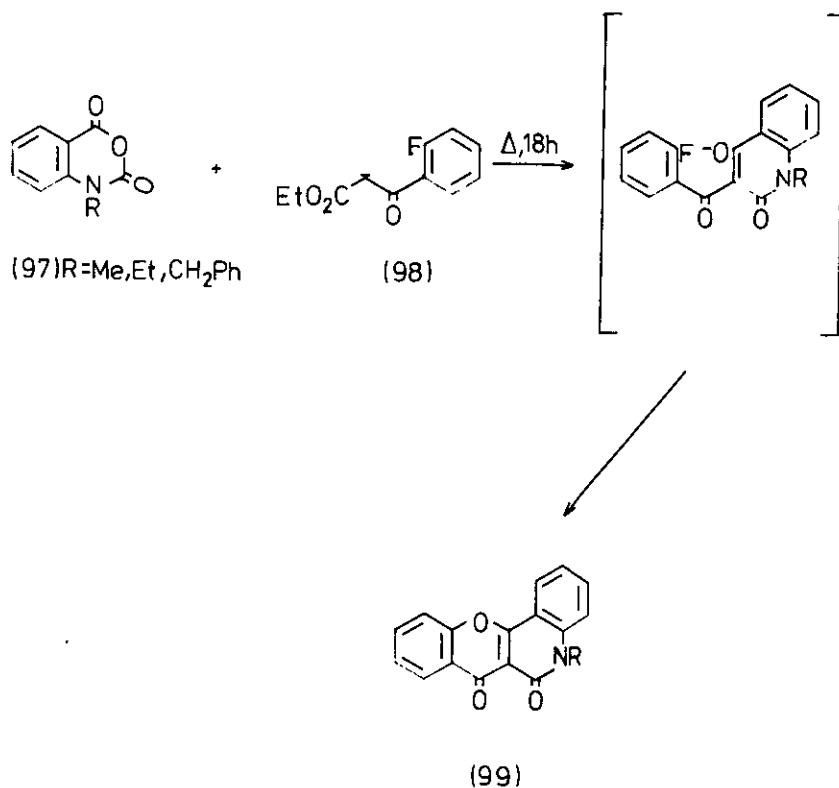


Derivatives of the isomeric ring system, [1]benzopyrano[3,2-c]quinolin-7-one (96), have also been synthesized^{81, 82}. Thus, the thermal condensation of a 4-hydroxyquinoline-3-ester and a phenol gave (96)⁸¹.

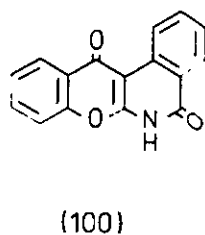


(96)

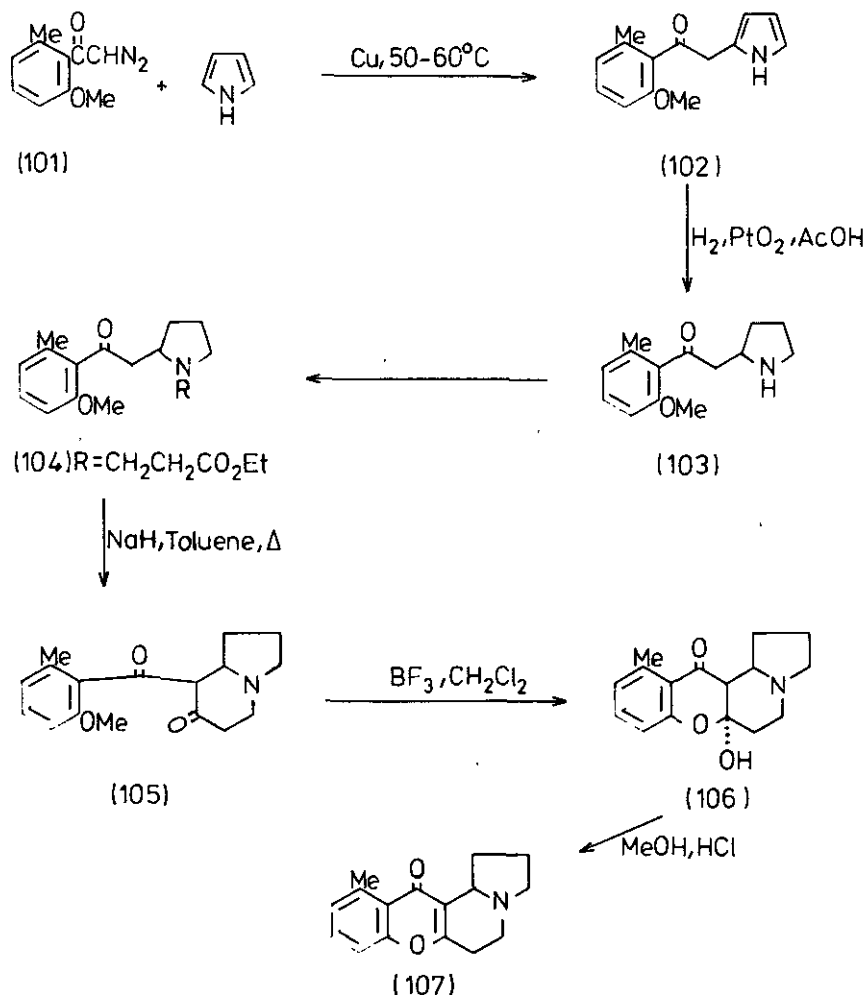
Coppola and Hardtmann^{83, 84} reacted isatoic anhydrides (97) with the anion of ethyl o-fluorobenzoylacetate (98) to give 5-substituted-6H-[1]benzopyrano[3,2-c]quinoline-6,7(5H)-diones (99) in good yields.



Compounds of type (99) have been claimed to be useful as inflammation-inhibiting substances⁸⁴. [1]Benzopyrano[2,3-b]isoquinoline-5,12-dione (100) was synthesized by Glozman and co-workers⁶⁸ using the same procedure as used to synthesize the [1]benzopyrano[2,3-b]pyridine (66).

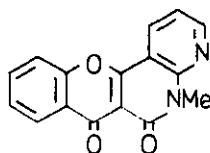


[1]Benzopyrano[2,3-g]indolizin-12-one (107) was an intermediate in the total synthesis of (±)elaecarpine and (±)isoelaecarpine^{85, 86}. The diazoketone (101), prepared by reacting diazomethane with the acid chloride of 6-methoxy-2-methylbenzoic acid, was condensed with excess pyrrole, in the presence of copper powder. This gave the 2-pyrrolylmethyl ketone (102) which was converted to the 2-pyrrolidinylmethyl ketone (103) by catalytic hydrogenation. Addition of ethyl acrylate to (103) gave the aminoester (104). The Dieckmann condensation of (104), using sodium hydride, resulted in the diketoindolizidine (105). Cyclization in the presence of boron trifluoride gave (106) which was dehydrated to the benzopyran-4-one (107), in 78% yield using methanolic hydrogen chloride (Scheme 14).



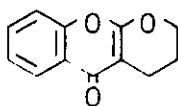
Scheme 14

The synthesis of [1]benzopyrano[3,2-c][1,8]naphthyridine-6,7(5H)-dione (108) has been reported⁸³ and involved the reaction of 3-azaisatoic anhydride with the anion derived from ethyl *o*-fluorobenzoylacetate.

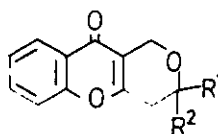


(108)

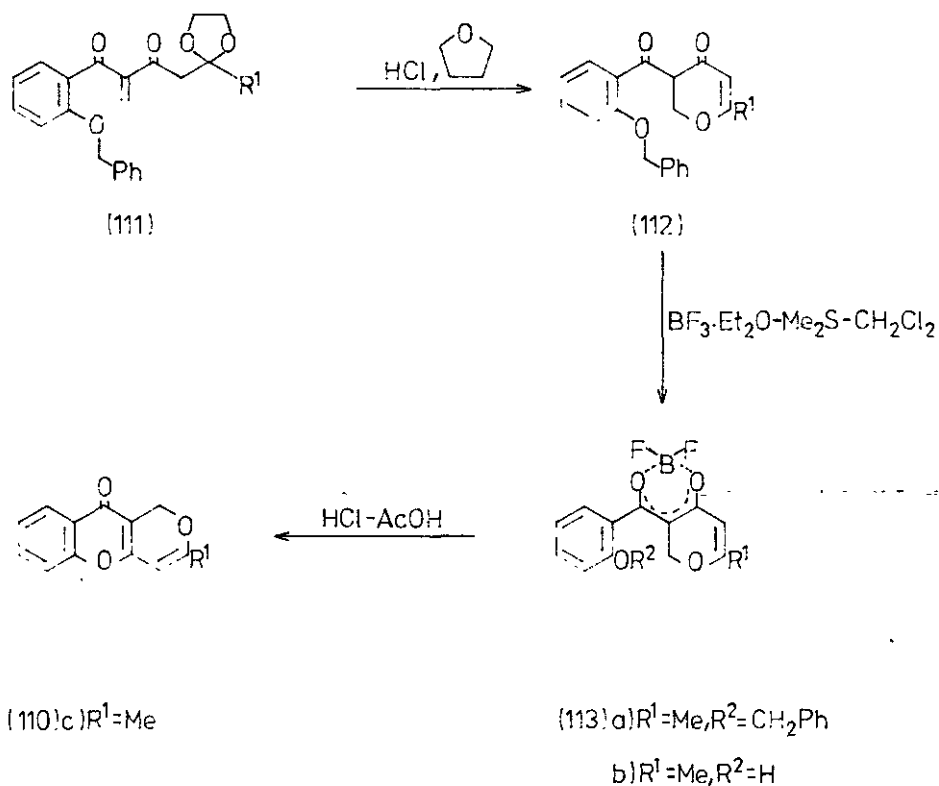
Numerous natural and synthetic compounds in which the third ring is a pyran have been described. The simplest examples of these are the pyrano[2,3-b][1]benzopyran-5-ones (109)²⁸ and the pyrano[4,3-b][1]benzopyran-10-ones (110a)^{87, 88}.



(109)

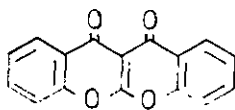
(110) a) $R^1 = R^2 = H$ b) $R^1 = Me, R^2 = OH$

Yamauchi and co-workers⁸⁸ have prepared 3,4-dihydro-3-hydroxy-3-methyl-1H,3H-pyrano[4,3-b][1]benzopyran-10-one (110b), the basic skeleton in fulvic acid. Treatment of the acetal (111) with 5% HCl-tetrahydrofuran gave the pyrone (112) in 97% yield. This gave the boron complex (113a) in 70% yield on treatment with boron trifluoride-diethyl ether in dichloromethane. Application of Fujita's method⁸⁹ ($BF_3 \cdot Et_2O - Me_2S - CH_2Cl_2$) to (113a) gave the phenol (113b) in 88% yield and the acid catalysed cyclization of (113b) with concentrated HCl-acetic acid gave (110c) in 79% yield (Scheme 15). Treatment of (110c) with HCl-acetone gave (110b) in 78% yield.

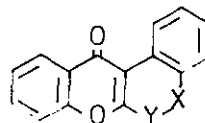


Scheme 15

Eiden and Schweiger⁹⁰ have described the synthesis of [1]benzopyrano[2,3-b]-benzopyran-11,12-dione (114) whilst [1]benzopyrano[3,4-b][1]benzopyran-12-ones (115)⁹¹⁻⁹³, [2]benzopyrano[3,4-b][1]benzopyran-12-one (116)⁹⁴, [1]benzopyrano[3,4-b][1]benzopyran-6,12-diones (117)⁹⁵⁻⁹⁹, [1]benzopyrano[4,3-b][1]benzopyran-7-one (118)¹⁰⁰, [2]benzopyrano[4,3-b][1]benzopyran-7-one (119)¹⁰¹, [1]benzopyrano[4,3-b]-[1]benzopyran-6,7-dione (120)¹⁰² and [2]benzopyrano[4,3-b][1]benzopyran-5,7-diones (121)¹⁰³⁻¹⁰⁶ have been reported.



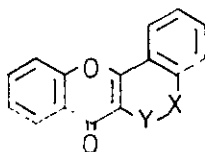
(114)



(115) X=O, Y=CH₂

(116) X=CH₂, Y=O

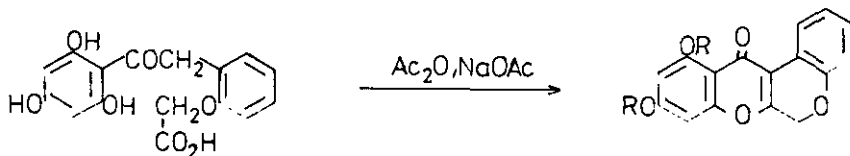
(117) X=O, Y=CO



(118) X=O, Y=CH₂; (120) X=O, Y=CO

(119) X=CH₂, Y=O ; (121) X=CO, Y=O

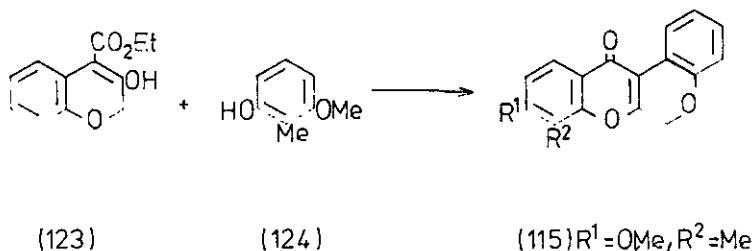
The synthesis of [1]benzopyrano[3,4-*b*][1]benzopyran-12-one (115), a compound analogous in structure to rotenone, has been described by George and Robertson⁹¹, and involved the reaction of the keto acid (122) with acetic anhydride and sodium acetate to give the diacetate (115a, R=Ac) which was deacetylated, using hydrochloric acid, to give (115b, R=H) in low yield.



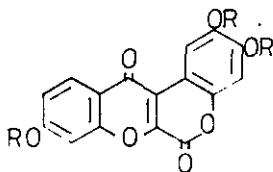
(122)

(115)

Peet and Sunder⁹³ have also synthesized the ring system (115) in low yield. Ethyl 3-hydroxy-2H-1-benzopyran-4-carboxylate (123) was heated with 3-methoxy-2-methylphenol (124) at 180°C for 6 h.

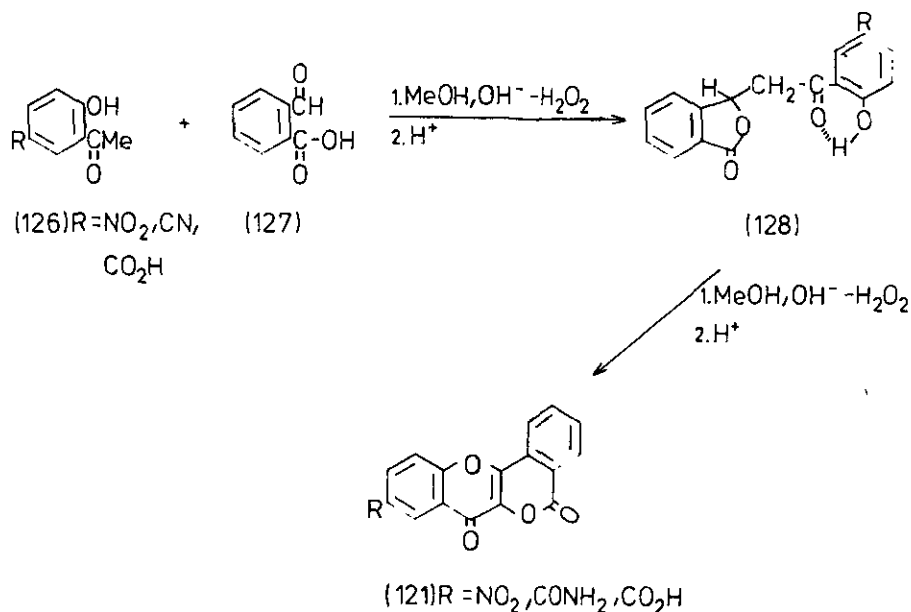


(+)-Munduserone (125), a [1]benzopyrano[3,4-b][1]benzopyran-6,12-dione, has been isolated from the bark of *Mundulea sericea* and shown to be useful as an insecticide⁹⁷.



(125)R=Me

Wurm and Geres¹⁰⁶ prepared several [2]benzopyrano[4,3-b][1]benzopyran-5,7-diones (121) as potential anti-anaphylactics. 5'-Substituted-2'-hydroxyacetophenones (126) and 2-formylbenzoic acid (127) underwent a Claisen-Schmidt condensation to give (128) which, when subjected to the Algar-Flynn-Oyamada oxidation, using hydrogen peroxide, gave (121). The nitro-group was reduced to the amine (Scheme 16).



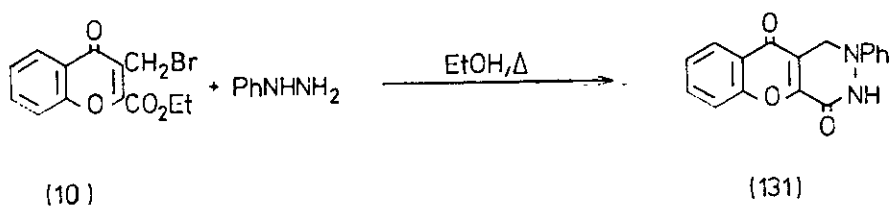
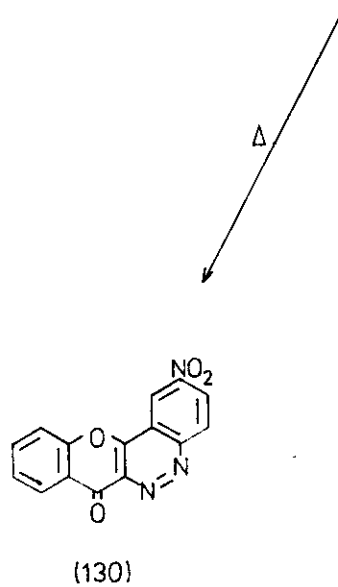
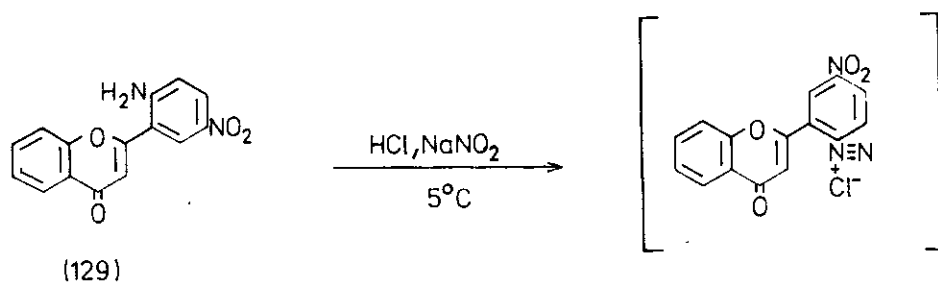
Scheme 16

3.2 Two heteroatoms

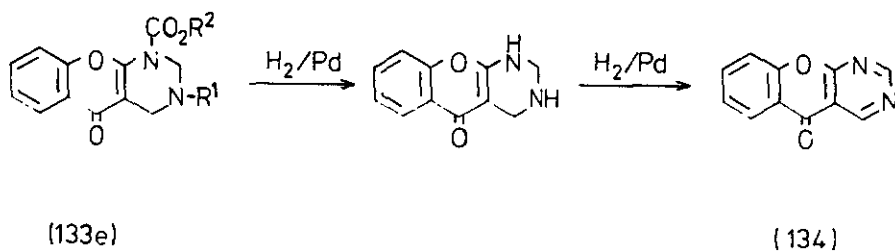
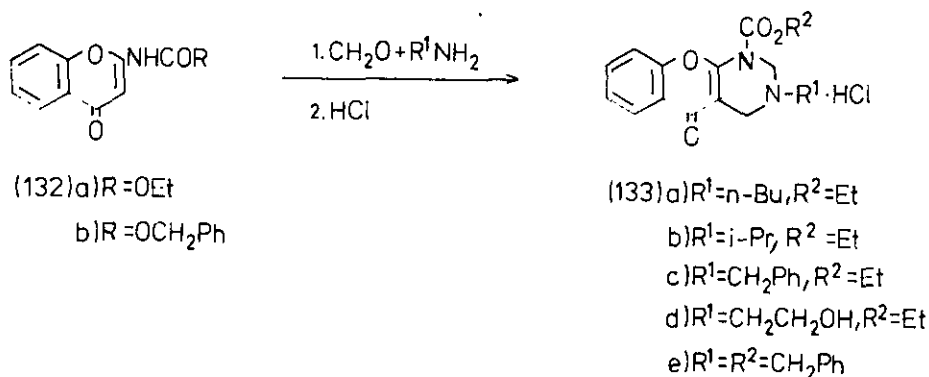
In this category, the benzopyranopyrimidines are the largest group of compounds but several pyridazine-containing compounds have been described.

The preparation of [1]benzopyrano[3,2-c]cinnolin-7-one (130)¹⁰⁷ was achieved by diazotization of 2-(2'-amino-5'-nitrophenyl)-4H-1-benzopyran-4-one (129), followed by thermal cyclization.

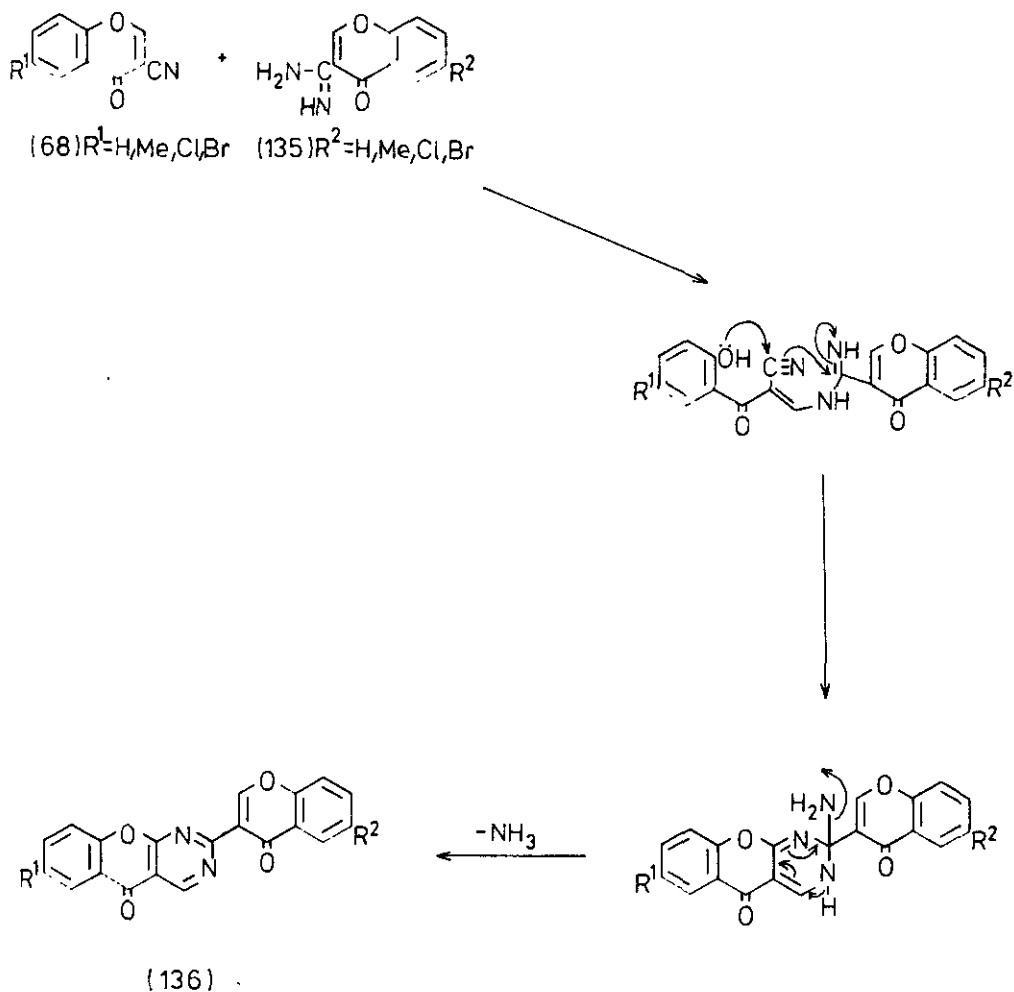
The synthesis of 1,2-dihydro-2-phenyl[1]benzopyrano[2,3-d]pyridazine-4,10-dione (131) has recently been described¹⁵, and involved the reaction between ethyl 3-bromomethyl-4-oxo-4H-1-benzopyran-2-carboxylate (10) and phenylhydrazine under reflux. The yield was very low.



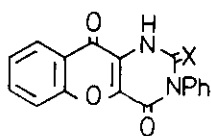
Several examples of [1]benzopyrano[2,3-d]pyrimidin-5-ones (133) have been reported^{47, 49, 70, 71, 108-109a}. Zagorevskii and co-workers¹⁰⁸ prepared 1,2,3,4-tetrahydro-5H-1-benzopyrano[2,3-d]pyrimidin-5-ones (133) in 75-90% yields by the aminomethylation of 2-ethoxycarbonyl- (132a) and 2-benzoyloxycarbonylamino-4H-1-benzopyran-4-one (132b), using primary amines. Debzylation and subsequent dehydrogenation¹⁰⁹ gave the unsubstituted [1]benzopyrano[2,3-d]pyrimidin-5-one (134).



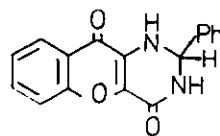
4-Oxo-4H-1-benzopyran-3-carbonitriles (68), when refluxed with ammonium acetate in acetic acid, undergo self-condensation giving 2-(4-oxo-4H-1-benzopyran-3-yl)-[1]-benzopyrano[2,3-d]pyrimidin-5(5H)-ones (136)⁷⁰ in 13-27% yields. It is possible that the nitriles (68) are converted to amidines (135) by ammonia and these further react with the unchanged nitriles (68) to give (136) (Scheme 17).



The synthesis of the [1]benzopyrano[3,2-d]pyrimidine ring system has recently been achieved^{109a}. The treatment of 3-amino-4-oxo-4H-1-benzopyran-2-carboxamide with phenyl isocyanate or phenyl isothiocyanate gave compounds of type (137a) whereas benzaldehyde gave (137b).

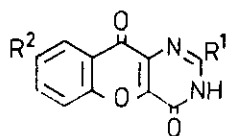


(137a) X=O,S

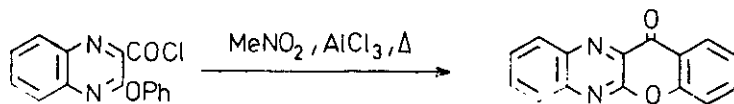


(137b)

A 2,8-disubstituted-[1]benzopyrano[3,2-d]pyrimidine-4,10-dione (138) was also prepared by treating a 6-substituted-3-amino-4-oxo-4H-1-benzopyran-2-carboxamide with diethyl oxalate.

(138) R¹=R²=CO₂Et

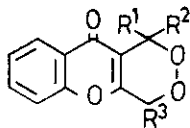
Vinot and Maitte^{110, 111} have described the synthesis of [1]benzopyrano[2,3-b]quinoxalin-12-one (140) in 60% yield. The acid chloride (139) underwent an intramolecular Friedel-Crafts acylation in nitromethane in the presence of aluminum chloride.



(139)

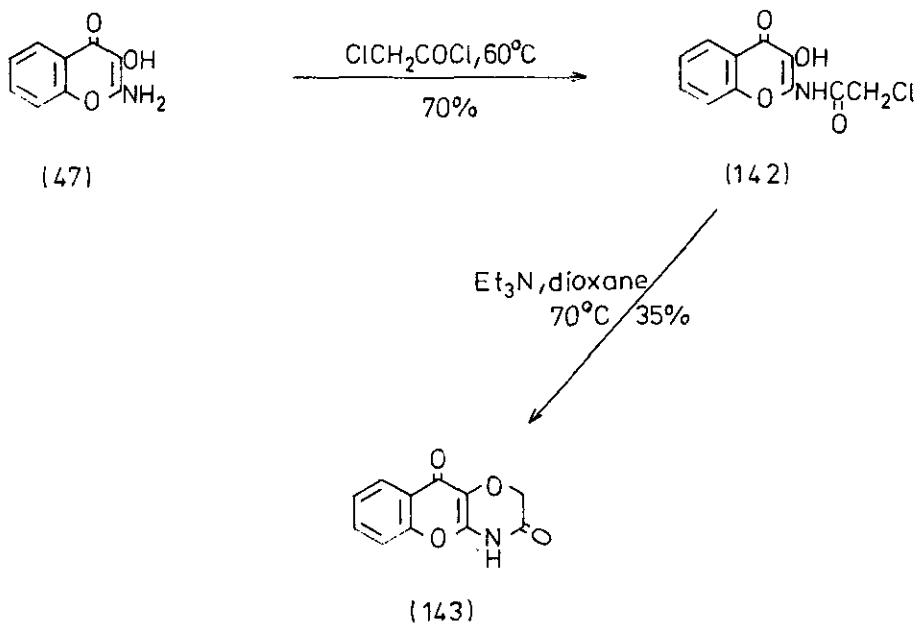
(140)

The photochemical preparation of 1,2-dioxino[4,5-b][1]benzopyran-10-one (141) has been described²⁹.



(141) $R^1=OH, R^2=R^3=Ph$

Compounds which contain different heteroatoms include [1]benzopyrano[3,2-b]-1,4-oxazine-3,10(2H,4H)-dione (143)⁵⁴ which was prepared from 2-amino-3-hydroxy-4H-1-benzopyran-4-one (47) via the acetamide derivative (142) which was cyclized in the presence of triethylamine.

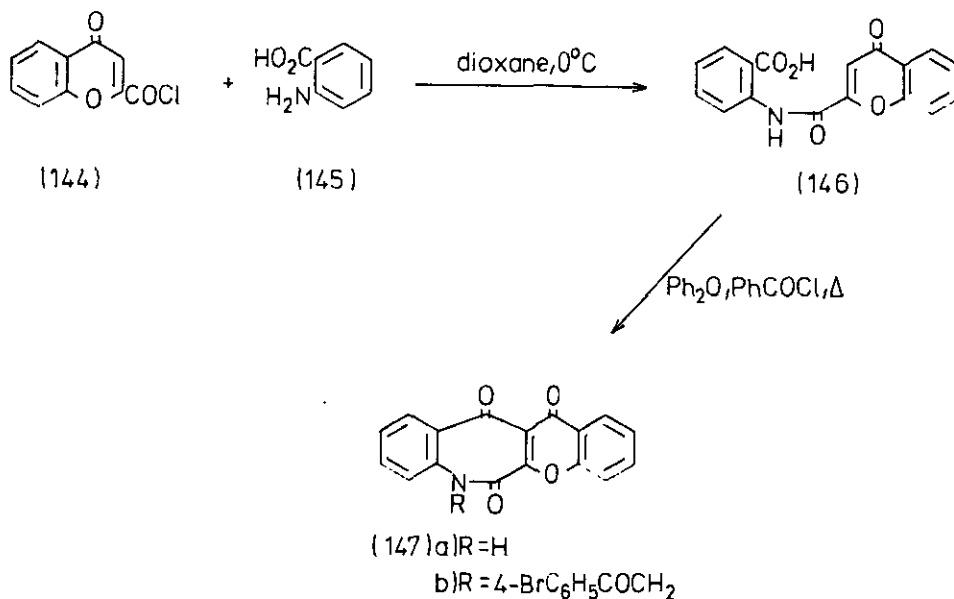


4. Compounds containing a 7-membered heterocyclic ring

These compounds have only been synthesized or isolated in the past few years, with workers concentrating mainly on the [1]benzopyrano[2,3]benzodiazepines.

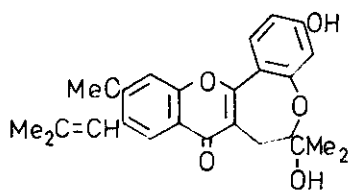
4.1 One heteroatom

Ellis and Romney-Alexander¹⁵ recently described the synthesis of [1]benzopyrano[2,3-c][1]benzazepine-6,12,13-trione (147a). 4-Oxo-4H-1-benzopyran-2-carbonyl chloride (144) reacted with anthranilic acid (145) to give the expected carboxylic acid (146) which was cyclized, by refluxing in diphenyl ether containing benzoyl chloride, in moderate yield. Alkylation of the lactam nitrogen was achieved in the presence of sodium hydride to give (147b) (Scheme 18).

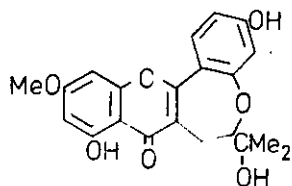


Scheme 18

Benzopyran-4-ones in which the 2,3-fused heterocyclic ring contains oxygen as the heteroatom occur naturally. Two [1]benzopyrano[3,2-d][1]benzoxepin-8-ones are known, namely, chaplashin (148)¹¹², which has been isolated from the heartwood of A. Chaplasha, and oxyisocyclointegrin (149)¹¹³, isolated from the heartwood of A. integer.



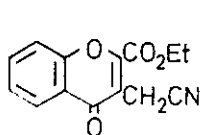
(148)



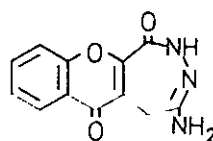
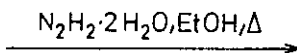
(149)

4.2 Two heteroatoms

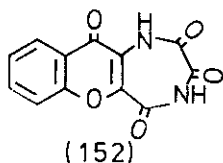
The synthesis of 4-amino[1]benzopyrano[2,3-d][1,2]diazepine-1,6-dione (151) in low yield was achieved by reaction of ethyl 3-cyanomethyl-4-oxo-4H-1-benzopyran-2-carboxylate (150) with hydrazine hydrate¹⁵. A [1]benzopyrano[3,2-e][1,4]-diazepine-2,3,5,11-tetraone (152) has recently been prepared^{109a}.



(150)

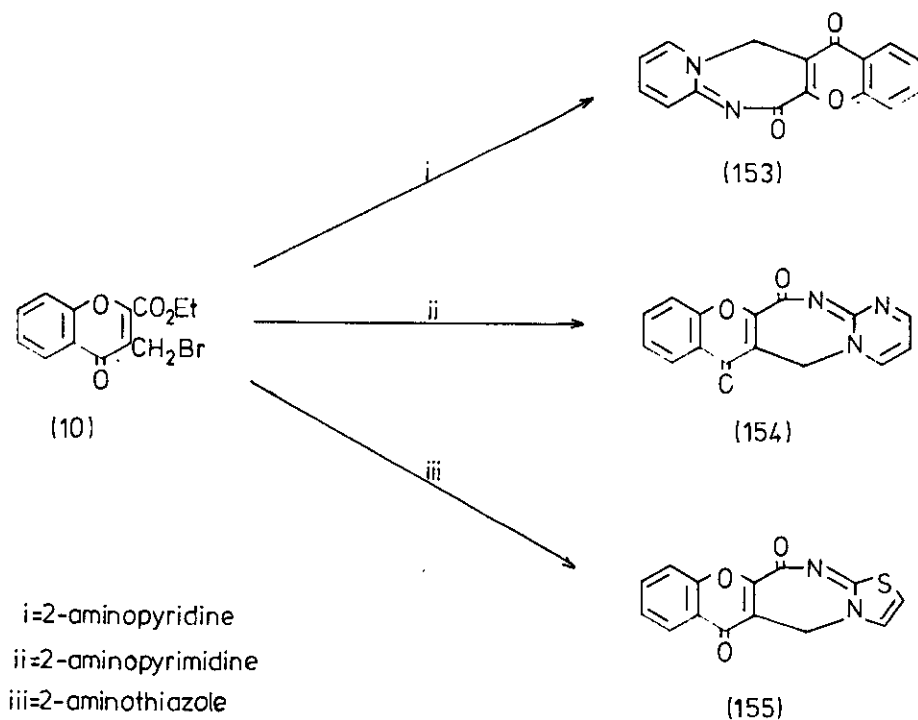


(151)



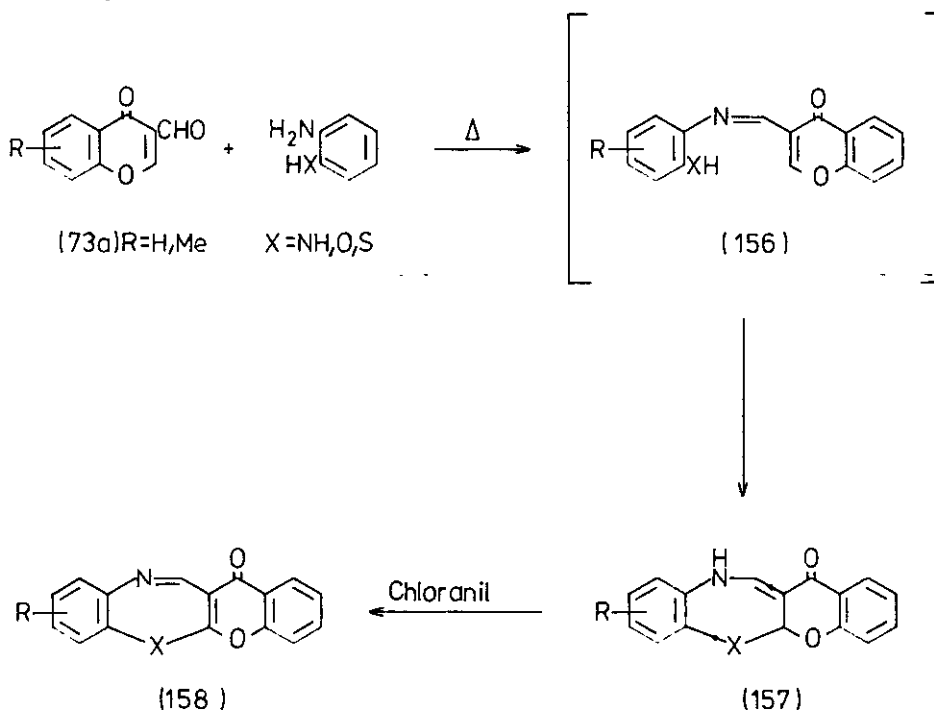
(152)

[1]Benzopyrano[2,3]benzodiazepines have been synthesized by various methods^{15, 47, 114-117}. The reaction between ethyl 3-bromomethyl-4-oxo-4H-1-benzopyran-2-carboxylate (10) and 2-aminoheterocycles (such as 2-aminopyridine, 2-aminopyrimidine or 2-aminothiazole) in the presence of sodium acetate gave [1]benzopyrano[2,3-*e*]pyrido[1,2-*a*][1,3]diazepine-6,14-dione (153), [1]benzopyrano[2,3-*e*]pyrimido[1,2-*a*][1,3]diazepine-7,13-dione (154) and [1]benzopyrano[2,3-*e*]thiazolo[3,2-*a*][1,3]diazepine-6,12-dione (155), respectively, in low to moderate yield (Scheme 19).



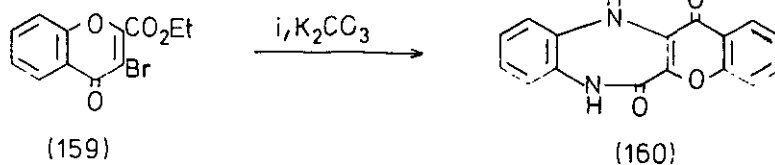
Scheme 19

Fitton and co-workers¹¹⁴ reported the synthesis of [1]benzopyrano[2,3-*b*][1,5]-benzodiazepin-13-one (158) by heating 4-oxo-4H-1-benzopyran-3-carboxaldehyde (73a) with *o*-phenylenediamine. The reaction gave the dihydro compound (157) via the anil (156). Dehydrogenation, using chloranil, gave (158, X=NH). 2-Aminophenol and 2-aminobenzenethiol similarly gave the oxazepine (158, X=O) and the thiazepine (158, X=S) (Scheme 20). However, the structure of the compounds prepared by this procedure has been disputed¹¹⁸. Analogous compounds^{116, 117} which have been prepared using the same procedure may also be questionable.



Scheme 20

The isomeric [1]benzopyrano[3,2-*b*][1,5]benzodiazepine-6,13-dione (160) has recently been prepared by treating ethyl 3-bromo-4-oxo-4H-1-benzopyran-2-carboxylate (159) with *o*-phenylenediamine in the presence of potassium carbonate.

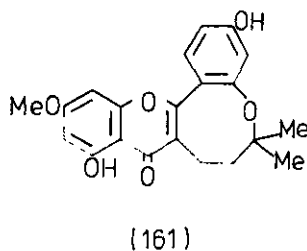


i-o-phenylenediamine

5. Compounds containing larger heterocyclic rings

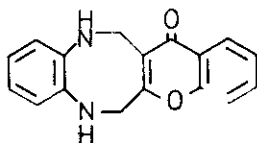
5.1 One heteroatom

In this category, we have a [1]benzopyrano[3,2-e][1]benzoxocin-9-one, cyclo-integrin (161) which was isolated from the heartwood of *A. integer*¹¹³.



5.2 Two heteroatoms

The synthesis of [1]benzopyrano[2,3-c][1,6]benzodiazocine-6,14-dione (162) has been described¹⁵. Ethyl 3-bromomethyl-4-oxo-4H-1-benzopyran-2-carboxylate (10) was reacted with o-phenylenediamine at ambient temperature. Compound (162) was obtained in low yield.



(162)

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