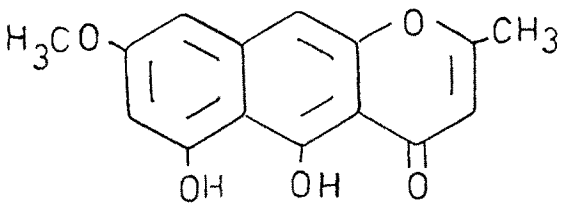
Chapter 1

INTRODUCTION

Benzopyran derivatives[1] are attracting continued attention due to their biological and insecticidal properties. Moreover they occupy a prominent position among the plant products and comprise a body of organic substances of extraordinary variety and interest. Chromones, chromenes and chromanones are also forming the major classes of benzopyran compounds.

A few binaphtho [2,3-b] pyrones are found in nature and are deeply coloured compounds carrying hydroxyl and methoxyl groups.[2] The first of these to be isolated was aurofusarin (2), an orange-yellow compound which does not melt below 360°. Ashley, Hobbs and Raistrick[3] obtained this from Fusarium culmorum; it's structure was elucidated more recently[3,4] by the use of a combination of spectroscopy,[5-7] chemical reaction and degradation and it was shown to be a dimer (2) of an oxidized form of rubrofusarin (1), which is also found in Fusarium. It is a deterrent to termite, but rubrofusarin does not have this property.[8]

A parasitic fungus, Ustilaginoidea vivens (cooke) grows on rice and produced a mixture of binaphthopyrans that was separated on silicic acid in to three compounds called ustilaginoidins A (3), B (4) and C (5) respectively which differ only in substitutents at C-2.[9-12] Their absolute configuration has been shown[13] to be R and racemic ustilaginoidin A has been synthesized[14] by oxidative coupling of nor-rubofusarin



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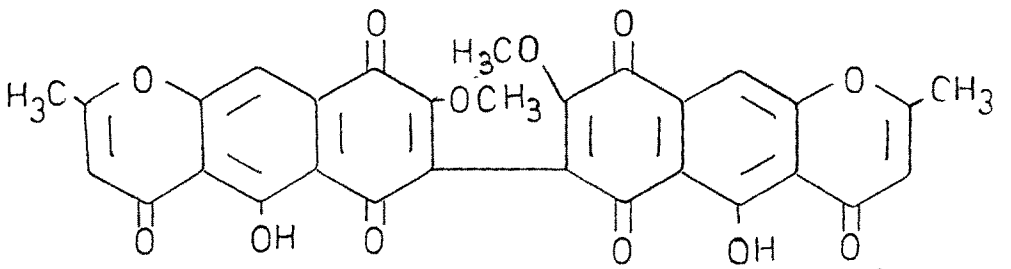

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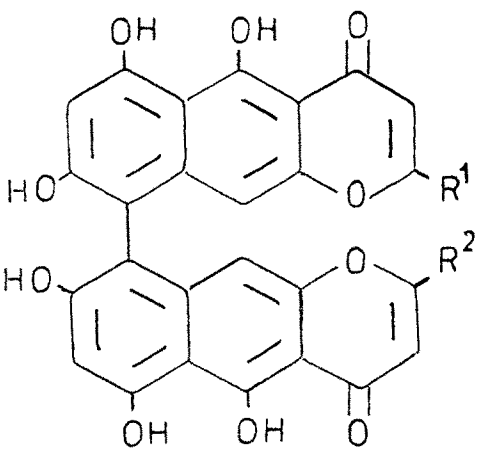


3. $R^1 = R^2 = CH_3$

4. $R^1 = CH_3$, $R^2 = CH_2OH$

5. $R^1 = R^2 = CH_2OH$

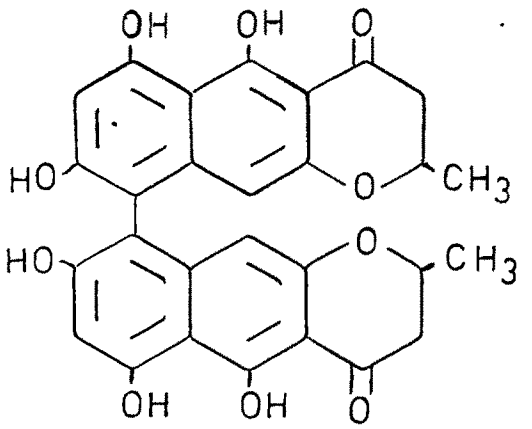
dimethyl ether with ferric chloride in dioxan followed by methylation of the hydroxyl groups and demethylation with hydroiodic acid in acetic anhydride.

Recently three binaphthopyrans[15] were isolated from a culture of a species of the imperfect fungus Verticillum (Strain K-113). Chromatography on silicic acid and silica gel impregnated with O.5N oxalic acid gave three compounds, cephalochromin (6) isoustiaginoidin A (7) and dihydroisoustilaginoidin A (8).

Fuscofusarin (9) is a minor constitutent of Fusarium culmorum (W.G. Smith) Sacc. and is a brownish red, high melting, unsymmetrical binaphthopyran. Its spectral & chemical properties have been described.[16]

In addition to the angular naphthopyran, flavasperone (10), cultures of Aspergillus niger contain a linear binaphthopyran called aurasperone A (11). This yellow optically active compound was also isolated from A. awamori and it's structure was deduced from it's properties.[16-19] Dehydration of an analogue aurasperone C (12) which is a 2-hydroxychromanone found in A. awamori, gave the unsymmetrical bichromone (13).

Pharmacological activity has been the incentive to synthesize the majority of the bischromones and many of the bichro-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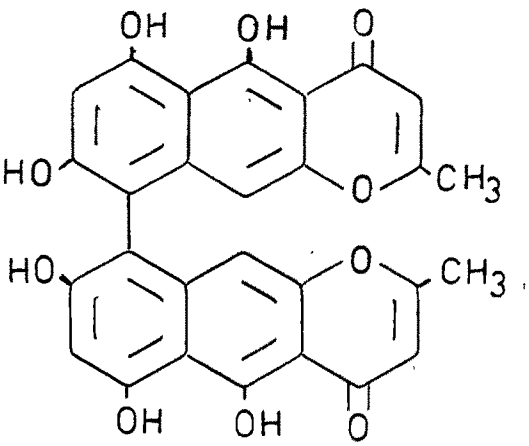
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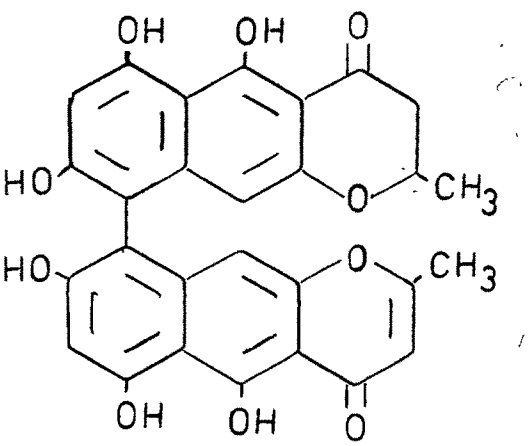
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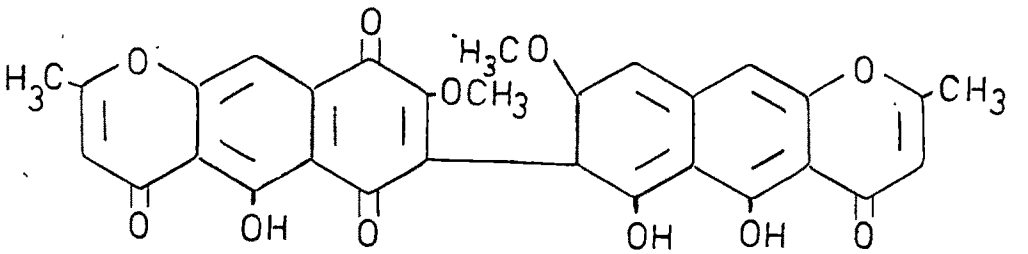

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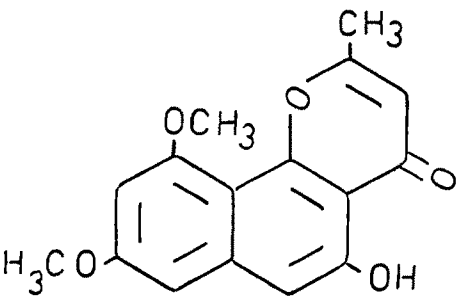

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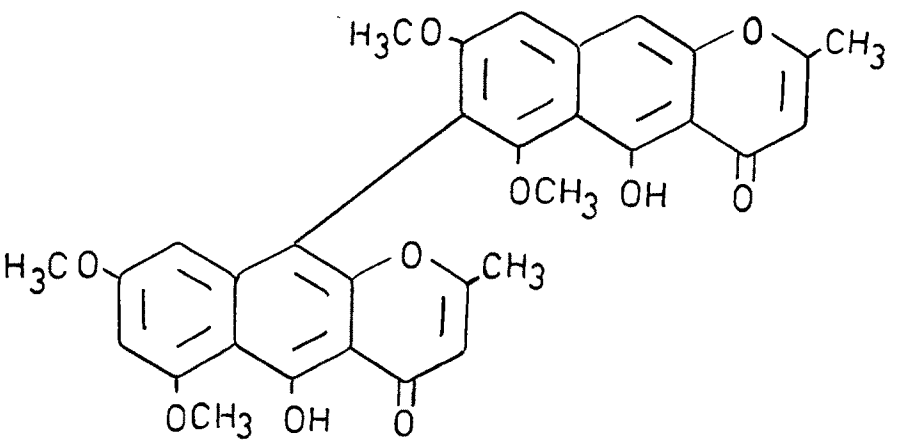

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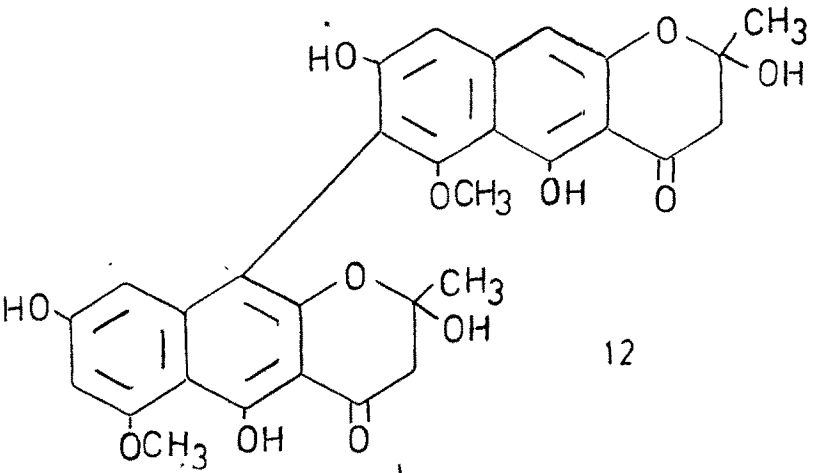
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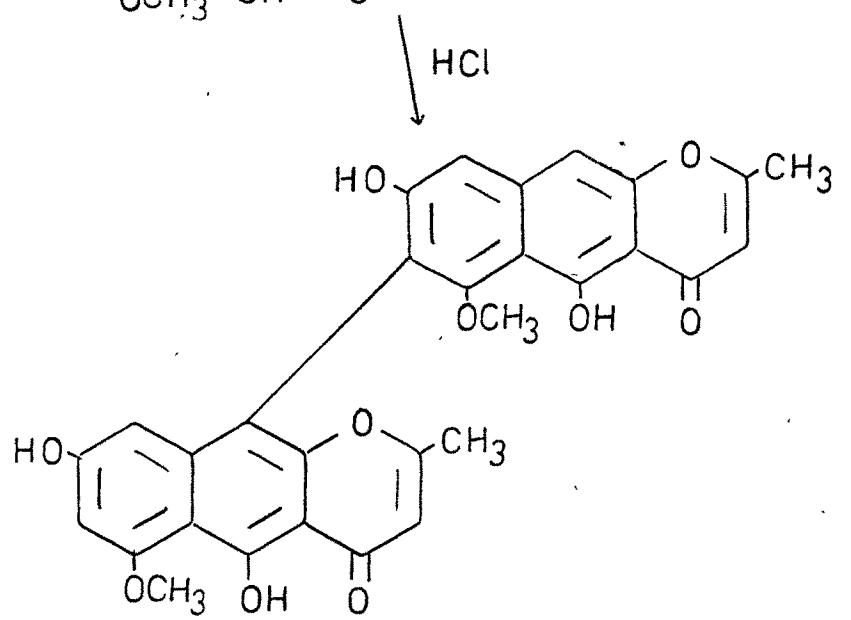
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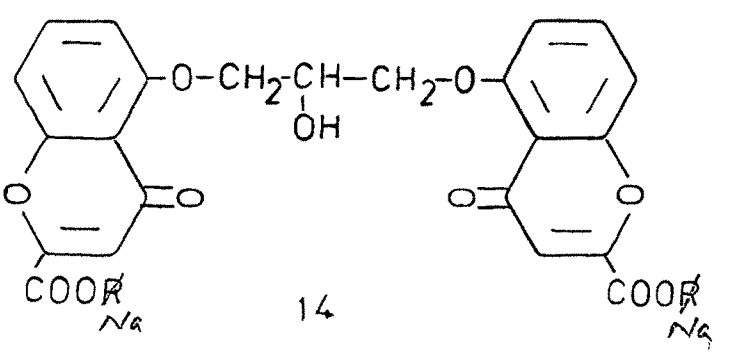
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14

mones. Consequently much of the information is available only in patents. Disodium cromoglycate (14) possesses very potential antiasthematic activity. Various aspects of the biological characteristics and clinical use of disodium chromoglycate are discussed in reviews.[21-23] The structure activity relationships between cromoglycic acid and it's analogues have been discussed.[24]

The position at which the chromone rings are attached to the bridging chain is important, the 6,6' and 5,7' positions giving the most potent and the 8,8' the least active compounds. Variation in the length and character of the bridge between the two chromone nuclei produced compounds of varying activity. The antiallergic activity and pharmacological properties of few other bischromones has been reported.[25,26,27]

Chrom-3-enes (2H-1-benzopyrans) are also widely occuring in nature. In the 2H-1-benzopyran the only isolable natural products are 2,2-disubstituted - 2H-1-benzopyrans, primarily, 2,2-dimethyl substituted resulting from the combination of phenol and an isoprene unit. No naturally occuring 2H-1-benzopyran have been isolated which are mono or non substituted in the 2-position. This may be also due to their inherent instability. 2H-1-benzopyrans occuring in nature are isolated by simple extraction of the plants of rhizomes with ether,

dichloroethylene or boiling benzene followed by column chromatography on alumina or silica gel or another method is steam distillation of the plant to yield the essential oil, either as a pure distillate or as a mixture requiring column chromatography.

Acetovanillochromene (15) is one of the many natural 2H-1-benzopyrans isolated from plants of the family Rutaceae and sub family Rutoideae.[28] This product is from a Jamaican weed Euputorium riparium Regel.

Demethoxyageratochromene or Precocene I (16) and ageratochromene or Precocene II (17) were isolated while plants of the family compositae were being studied.[29] The plant that contain this products are Ageratum mexicum sims[29,30] Ageratum conyzoides L[30] and Agertum houstonianum mill.[31] These compounds possesses anti-juvenile hormone like effects.[32,33] The structures were determined by spectral studies and by comparing the dihydroproduct formed by hydrogenation with chromans of known structure.[34] Ageratochromene was synthesized from the corresponding arylpropargyl ether.[35]

Eupatoriochromene (18) is found in variety of Australian Weeds : Helianthella uniflora Torr. and Grey. Eupatorium riparium Regel, and Encelia Californica Nutt. Eupatoriochromene is one of the six 2H-1-benzopyrans isolated from the extract of these weeds.

Methyleupatoriochromene (Encecalin) (19). This methylated product of eupatoriochromene is found and isolated with eupatoriochromene from the same plants and also from Eupatorium glandulosum H.B. and K. (Syn. E. adenophorum spr.). It's structure was determined by comparison with the product of eupatoriochromene and dimethyl sulphate-potassium carbonate.

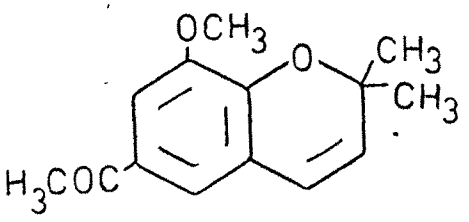
. Mundulone[36] (20) is a complex natural product extracted from the bark of a Mundulia serica tree; structure of Mundulone was determined by spectral studies and degradation studies.

Tecol[37-39] (21)

Tecol results from the methanolic extraction of the roots of Tetona grandis L.f. (better known as teakwood)[38] and was shown to contain a 2,2-dimethyl-2H-1-benzopyran moiety, by chemical reaction with dimethyl acetylene dicarboxylate, a chemical test for specific benzopyrans, which yield acetone.[37,38] Chemical reactions and product identification were used to identify tecol as a dimer of lapachenole in which methyl ether groups were replaced by free hydroxyl groups.[37-39]

Uses of 2H-1-benzopyrans

2H-1-benzopyrans were considered to be analgesics[40-42] and antidepressants[40-42] as well as antianxietal[40,41] antihypertensive[40,41,43] and hypoglycemic agents.[44] These species have been claimed to be reactivators for cytochrome C reductase[45], and antioxidants[45-47] for food and vitamin preparations.[45-47]



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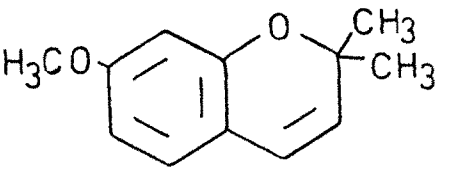

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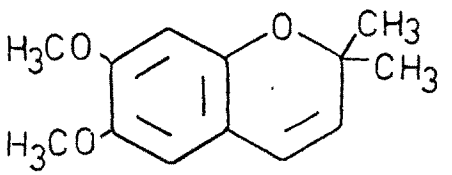

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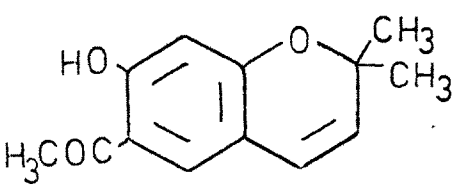

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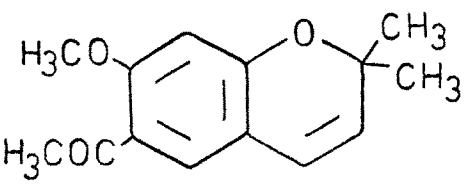

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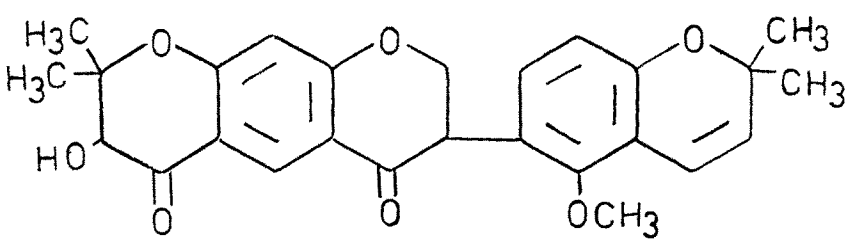

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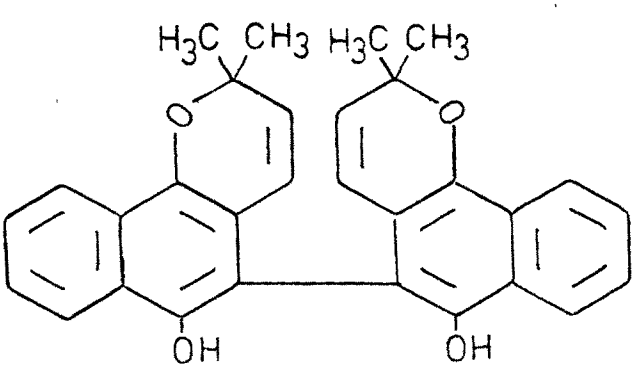

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They have been cited as promising antitumor agents.[48,49] Early cultures undoubtedly used 2H-1-benzopyran containing herbs such as Tzotzil, which is widely used in Mexico for treatment of diarrhea.[50,51] the chinese drug Wu-Chu-Yu is used as a stimulant carminative, beobstrunet, stomachic astingent, and anthelmintic remedy[52] and the East African drug called Wars (Wurrus or black Kamala) is used as cosmetic, dye and drug.

Photochromic properties have been described for 2H-1-benzopyrans.[54,55]

In contrast to the related flavones, the occurrence of 4-chromanones in nature is very rare. 5-Hydroxy-2-methyl-4-chromanone has been shown to be produced by a stain of the ascomycete, Daldinia concentrica a parasie of the ash tree but only after repeated subculturing.[56] Rosellinic acid, a plant growth inhibitor isolated by chloroform extraction from the culture filtrate of Rosellinia pecatrix Berlese has been postulated to have the structure of 8-hydroxy-2-methyl-4-chromanone-6-carboxylic acid.[57] Considerable work has been carried out on calophyllum ingredients. Calphylloide, obtained from the nuts of Calophyllum inophyllum, has been assigned 5,7-dihydroxy-2,3-dimethyl-4-chromanone.[58-60] This compound has been converted to 5-hydroxy-7-methoxy-2,3-dimethyl-4-chromanone by the action of diazomethane.[60]

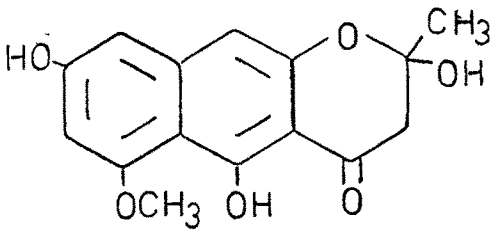
A compound that is worthy of note is fonsecin, a yellow pigment produced by an ultraviolent mutant of fungus Aspergillus fonsecaeus. This pigment has been assigned the structure (22). Myrochromanone (23) together with it's 4-chromanol analogue has been isolated from cultures of Myrothecium Todex ex fr.[61]

The fungus phoma pigmentivora has been shown to produce (2R)-5-hydroxy-6-(2-hydroxymethyl)-7-methoxy-2-methyl-4-chromanone (24, R=H) in good yield in both still fermentation in the presence of beachwood shavings and in agitated fermentations. In surface fermentation, the culture also produced the monoaceate (25, R=Ac) in lower yield, while agitated fermentation afforded lower yields of the dihydrofurochromanone (26). The latter was produced on treating (24) with H_2SO_4.[62]

Dehydroisostoebenone (27) has been isolated from Stoebe plumosa.[63] A further substance that was isolated, the diketone (28), was converted to the chromanone (29) by the action of methanolic potassium hydroxide. Subsequent oxidation with manganese dioxide in carbon tetrachloride afforded dehydroisostoebenone (27).

Pharmocological activity of 4-chromanones

The Mannich bases of 4-chromanones have probably been more examined for pharmacological activity than any other group of compounds in this field. The various neutral 4-chromanones shows no amoebacidal activity, but the mannich bases showed definite activity in vitro[64] and were claimed to be therapeu-



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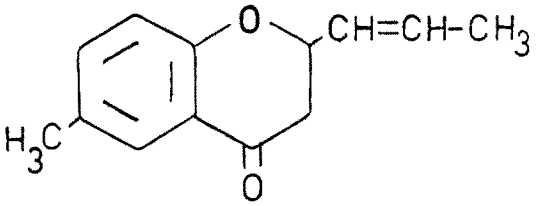

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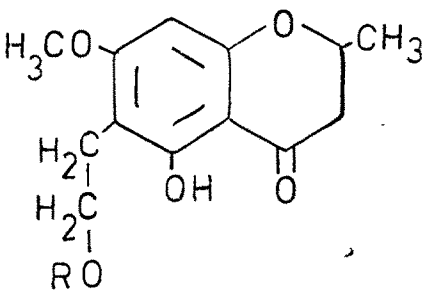
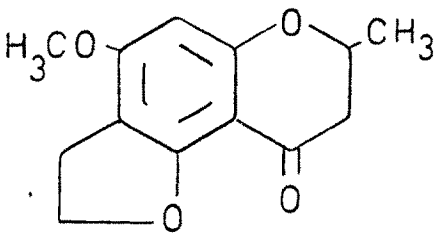


24. R=H

25. R=COCH$_3$



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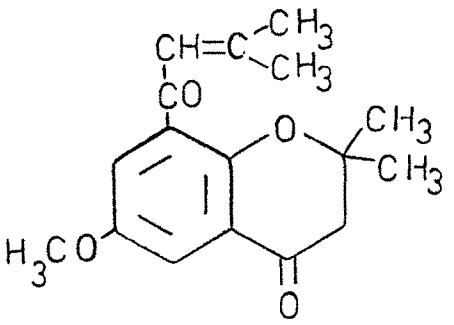

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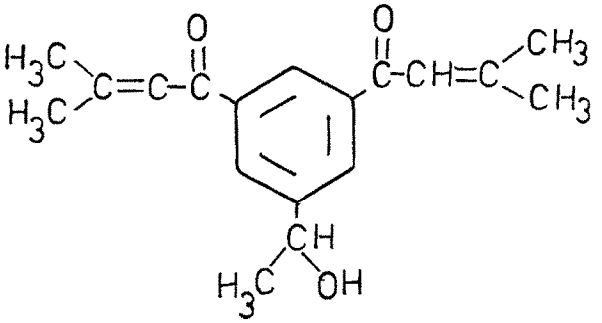

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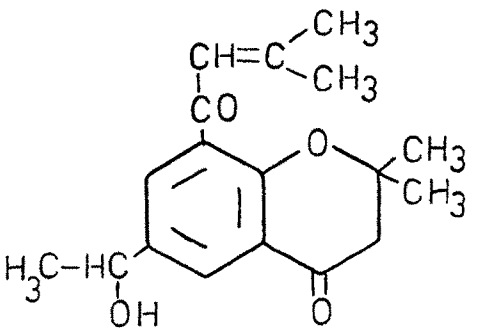

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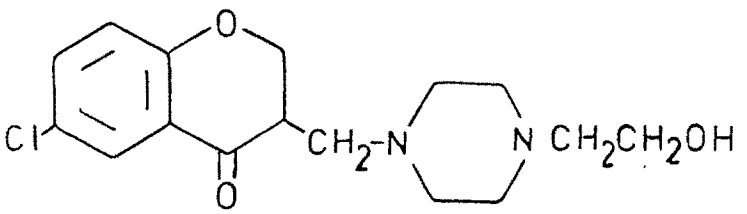
tically useful.[65] Compounds having a 3-dimethylamino methyl group were the most active.[64] 3-(2-Hydroxyethyl) piperazino methyl-6-chloro-4-chromanone (30) has been shown to be an effective bronchodilator in guinea pigs.[66]

While compounds of type (31) have been reported to have psychoanaleptic properties.[67] 3-Phenethylaminomethyl-4-chromanone and 3-(4-methoxyphenoxy) ethylaminomethyl-4-chromanones hydrochlorides were among compounds claimed to have β-sympatholytic activity.[68,69] The related mannich base hydrochlorides (32, 33) were claimed to be antidepressants.[70] 3-Amino-4-chromanone hydrochloride showed pronounced activity in a test designed to measure gastric antisecretory properties.[71]

Physical and Spectral Properties

Infrared Spectroscopy :

IR spectra of chromone in solid state shows carbonyl stretching at 1655 cm^{-1} and 1668 cm^{-1} in CCl_4 in solution.[72] Because of the proximity of absorptions due to carbonyl stretching and benzene ring breathing, it is not possible to identify with certainity the absorption of the pyrone ring double bond. Ruvet and Renson[73] have compared the spectra of chromone in different solvents, a significant difference exist between the frequency of the absorptions in the 1700 - 1575 cm^{-1} region as the solvent is changed.



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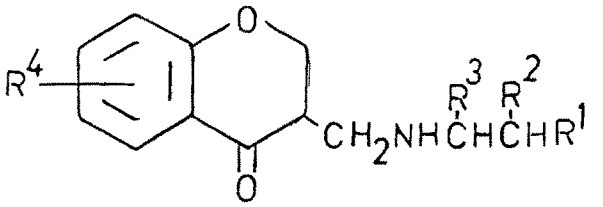


31 R^1=Ph, R^2=R^3=H or Alkyl
R^4=H, Alkyl, Alkoxy or CF_3

32 R^1=Ph, R^2=OH, R^3=CH_3, R^4=H

33 R^1=Ph, R^2=R^4=H, R^3=CH_3

For 2H-1-benzopyans (chrom-3-enes) the following datas have been reported.[74,75] 3040(w), 2970(w), 2840(m) 1644(m), 1613(m), 1495, 1480(s) cm^{-1} and 1230 (aromatic ether) 1610, 1570, 1480, 1360, 1110, 1040, 930 and 750 cm^{-1} . The most valuable diagnostic peaks are the c-c stretch of the carbon-carbon double bond of the pyran ring at 1644 cm^{-1} and the C-O stretch of the aromatic ether of the pyran at 1230 cm^{-1} The position of these two bands is greatly affected by substituents, especially when the substituent are on the C-4 carbon. In natural products containing the 2H-1-benzopyran system[76] the characteristic bands of the gem dimethyl absorption at 1380 - 1360 cm^{-1} , the aromatic ether at 1120 and 1270 cm^{-1} and a band at 899 ± 10 cm^{-1} become more diagnostic for identification of the 2H-1-benzopyran moiety.

The infrared spectrum of 4-chromanones are typical of aromatic alicyclic ketones showing strong carbonyl absorption around 1680 cm^{-1} but the frequency varies somewhat with the position and characteristic of substituents.

Nuclear magnetic resonance spectrscopy

A detailed study of the spectrum of chromone was made by Mathis and Goldstein[77] and is shown in (34). In the spectrum of chromone[78,79] it is possible to identify the signals of the 5-H which is a quartret as a result of spin coupling with the 6- and 7-hydrogens. The doublets arising from the 2-H and 3-H atoms stand out clearly.

For the unsubstituted 2H-1-benzopyran the following NMR assignments have been reported.[75] 4.53 (q, 2H, 2-H) ; 5.38 (m, 1H, 3-H) ; 6.20 (m, 1H, 4-H) ; 6.60 - 7.13 ppm (m, 4H, Ar-H). The pyran ring protons have the following characteristic couplings : $J_{3,2}$ = 3Hz ; $J_{4,2}$ = 2Hz, $J_{3,4}$ = 10Hz.[75] Substitution of one or two alkyl group on the C-2 carbon causes slight shifts in the 3- and 4-positions. Two methyl groups shift both these protons : 3-H to 5.46 ppm and 4-H to 6.21 ppm with the same coupling constants.[80] The two methyl groups appear as a singlet at 1.38 ppm or 1.5 ppm.[80]

The nuclear magnetic resonance spectra of 4-chromanone has been studied in deutrochloroform[81] the C-3 protons appear at 3.02 ppm in 4-chromanone and those at C-2 at 4.67 ppm, the two methylenes producing an A_2X_2 spectrum. There is large number of chromanones for which NMR data have been recorded, these include 2-Methyl-[82], 5-methyl-, 7-methyl-[83], 2,6-dimethyl, 7-hydroxy-2,2,8-trimethyl and the 6-nitro analogue,[84] 7-methoxy,[83-85] 5,7-dimethoxy and 7-methoxy-2,2,8-trimethyl and the 6-nitro-analogues.[84]

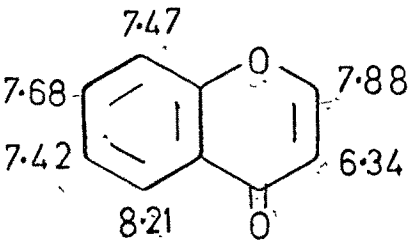
Mass Spectrometry

Chromone fragments under electron bombardment by two main pathways[86-88] loss of CO from the carbonyl group and cleavage of the pyrone ring by a retro - Diels - Alder reaction as shown in Scheme (a), other peaks appear at m/e 90 and 63.

In the 2H-1-benzopyran series fragmentation pattern have been proposed[89] for the unsubstituted parent compound and for those with one or two dimethyl groups on the C-2 carbon. Scheme (b) shows the characteristic pattern where both C-2 hydrogens are substituted by methyl groups.

The parent ion (35) is formed with a relative intensity of only 10 - 20% of the base ion (36) formed by the loss of methyl radical of again probably by α-cleavage, the disubsituted 2H-1-benzopyran fragment further to give 7.4% indyllium and 4.1% pyropylium ion. For most of the disubstituted 2H-1-benzopyran however, only the molecular ion is given.[90,91]

The principle peak in the mass spectrum of 4-chromanone (m.w. 148) had an m/e ratio of 120, the peak at 148 being 74% of the former. Another significant fragment (53%) had an m/e ratio of 92, the mass spectrum of 5,7-dihydroxy-2,2-dimethyl-4-chromanone has been studied and number of fragments have been identified. In particular the presence of ion with an m/e ratio 96.5 indicated that the ion (37) can exist as a doubly charged species.



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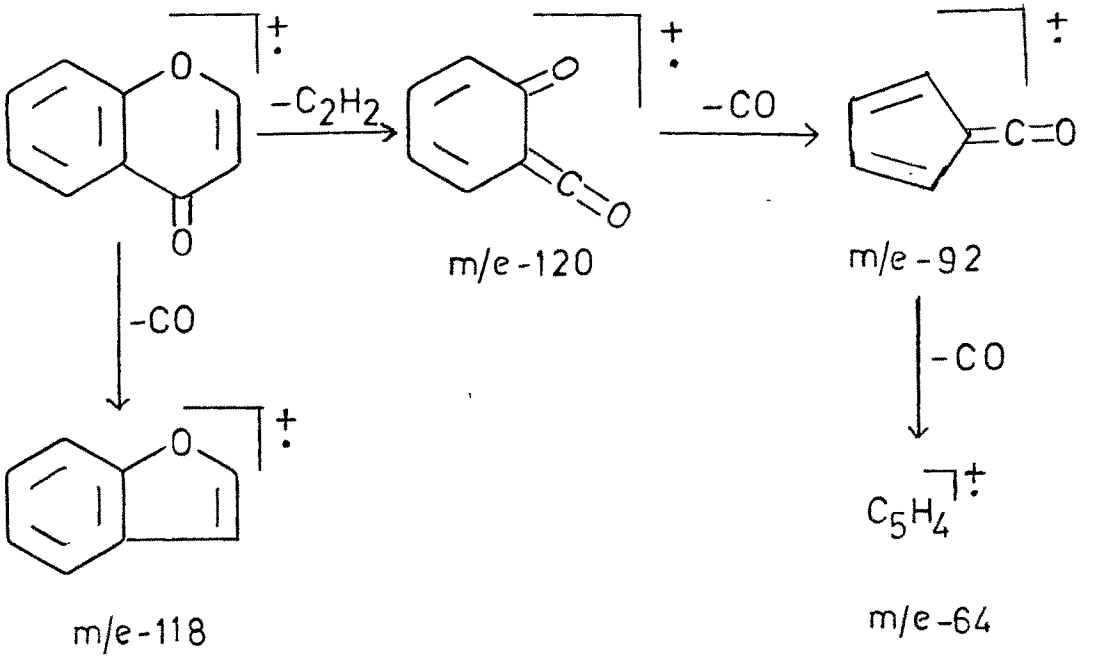
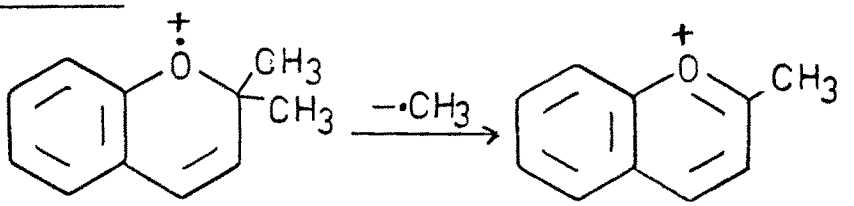
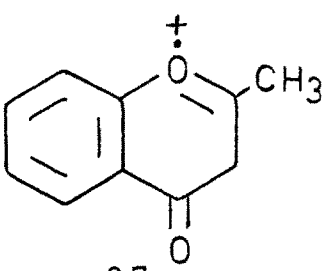
Scheme (a)



Scheme (b)



35 36



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