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Xanthyrones, Glaucyrones, and Chelated Magnesium Enolates.

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Contents

1. Introduction

A century has elapsed since Ludwig Claisen[*2] reported that by warming together ethyl ethoxymethyleneacetoacetate and ethyl sodioacetoacetate on a steam bath in the absence of solvent (a 'melt reaction') the sodio-

[*2] Ludwig Claisen 1852-1930. b. Cologne; Ph.D. Bonn (Kekule): Univ. Bonn, Owens College Manchester, Univ. Munich, Aachen, Kiel, Berlin, Godesberg (privae laboratory). Obituary by Richard Anschutz *Ber.* 1936, *69* , 97A - 170A. Xanthophanic acid and glaucophanic acid are not mentioned in the obituary.

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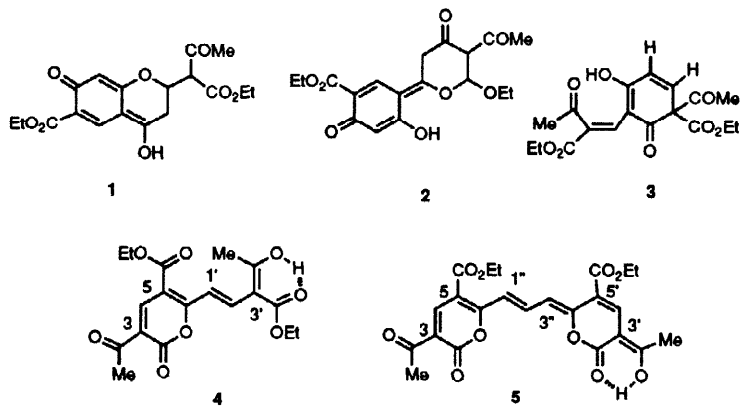
derivatives of two new compounds were formed.[1] Treatment of the mixture with acetic acid gave xanthophanic acid (or enol) as yellow plates from ethanol (~42% yield) or red needles from benzene. When the remaining sodio-derivative was acidified using mineral acid, the second product, black crystalline glaucophanic acid (or enol), deep blue in solution in ethanol, was obtained (~23% yield).[1] Later, a third product, a colourless naphthalene, was found in the reaction mother liquors by Liebermann.[2]

Claisen showed that xanthophanic enol is formed as its sodio-derivative according to the stoicheometry:

$$2C_9H_{14}O_4 + C_6H_9O_3Na = C_{18}H_{19}O_8Na + 3C_2H_5OH.$$

It is a monobasic acid forming an acetate and a benzoate, and minute quantities stain the skin an intense red colour. Liebermann found that when methyl esters are used in the formation reaction, a different, but closely related compound, $C_{16}H_{16}O_8$ is formed. The nature of the alkoxy grouping of the alkoxymethylene-acetoacetate component is immaterial, as it is this which is eliminated. Structural proposals (**1** - **3** respectively) were made by Liebermann *et al.* [2-7], by Weiss and Woidich [8], and by Feist *et al.* [9,10], but the α-pyrone [11] structures accepted today, **4** for diethyl xanthophanic enol, and **5** for diethyl glaucophanic enol (Scheme 1), were not proposed until 1964 on the basis of chemical and spectroscopic evidence.[12]



Scheme 1. Formulations for xanthophanic and glaucophanic acids

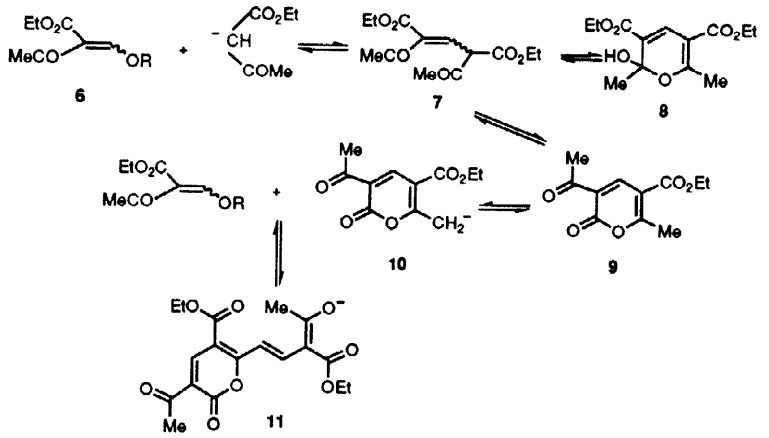
2. The Xanthyrones.

2.1.Xanthophanic enol - Mechanism of Formation and Spectral Data.

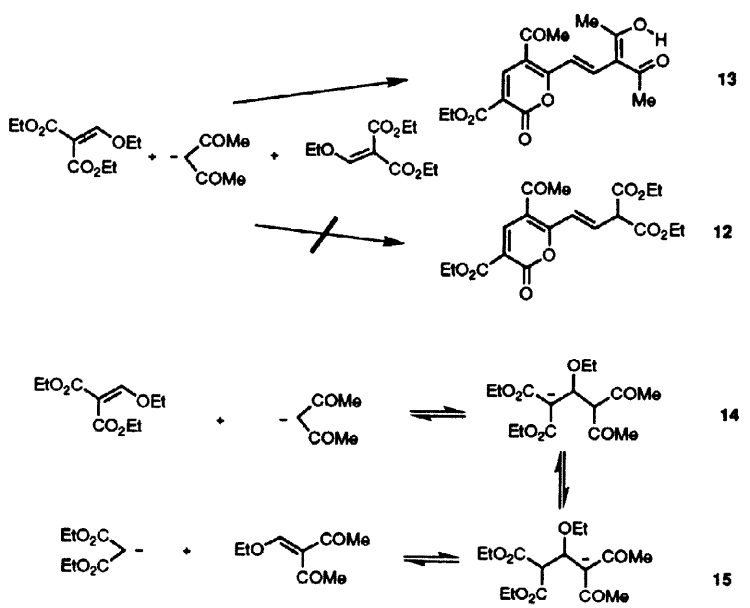
Treatment of an alkoxymethylene-acetoacetate **6** with sodioacetoacetate at 20°C gives a diacetylglutaconate **7** by Michael addition and elimination of OR: diacetylglutaconic ester is conveniently written as **7** though it actually exists mainly as the cyclic hemi-ketal form **8** in solution.[13] Further treatment with base converts the glutaconate into an electron deficient a-pyrone **9** which on treatment with alkoxymethylene-

acetoacetate and base forms, via anion **10**, the xanthyrone[*3] **11** as its sodium salt (Scheme 2). The xanthyrone, a thermodynamically stable (acidic) product, is formed from the equilibria of the melt reaction' through irreversible loss of alcohol. In a melt reaction under thermodynamic control, the product may not be that predicted at first sight however (Scheme 3}. Thus ethoxymethylene-malonate and sodioacetylacetone do not give **12** but xanthyrone **13** with the enolised side chain confering enhanced stability. Transference of the ethoxymethylene grouping between components comes about through equilibration *via* **14** and **15**.[12]

In place of the melt procedure, the required a-pyrone may be independently synthesised and then treated

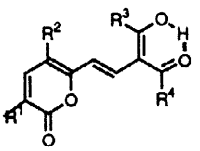


Scheme 2. Mechanism for the formation of diethyl xanthophanic enol.



Scheme 3.. Exchange of xanthyrone termini during preparation, with mechanism.

[3] The class name xanthyrone is given to derivatives of 6-propenyl–α–pyrone **17a** carrying enolisable or electron withdrawing substituents at C-3'. Glaucyrones are based on bispyrone **17b** carrying an enolisable or electron withdrawing C-3' substituent.

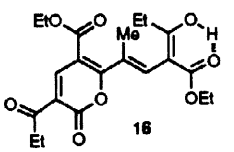


R^1	R^2	R^3	R^4
CO_2Me	CO_2Me	Me	OMe
CO_2Me	CO_2Me	Me	Me
COMe	CO_2Me	Me	OMe
COMe	CO_2Me	Me	Me
CO_2Me	COMe	Me	Me
COMe	COMe	Me	Me
H	CO_2Me	Me	OMe
H	CO_2Me	Me	OEt
H	CO_2Et	Me	OEt
CO_2Me	H	Me	OEt
CO_2Et	COMe	Me	Me
COMe	CO_2Met	Me	OEt
COMe	CO_2Et	Me	OMe
CO_2Et	CO_2Et	Me	OEt
COMe	CO_2Et	Me	OEt
COMe	CO_2Et	Ph	OEt

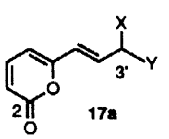
Table 1. Enolic xanthyrones available.

with base (NaOMe, or $KOBu^t$) and the alkoxymethylene component. The compounds listed in Table 1 were made by one or other of these procedure. [14] Attempts to make **16** were not successful, presumably for steric reasons.[12]

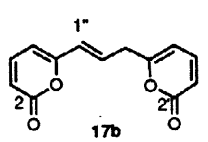
All the compounds in Table 1 have highly enolised propenyl termini. Extensive ^1H and ^{13}C NMR data



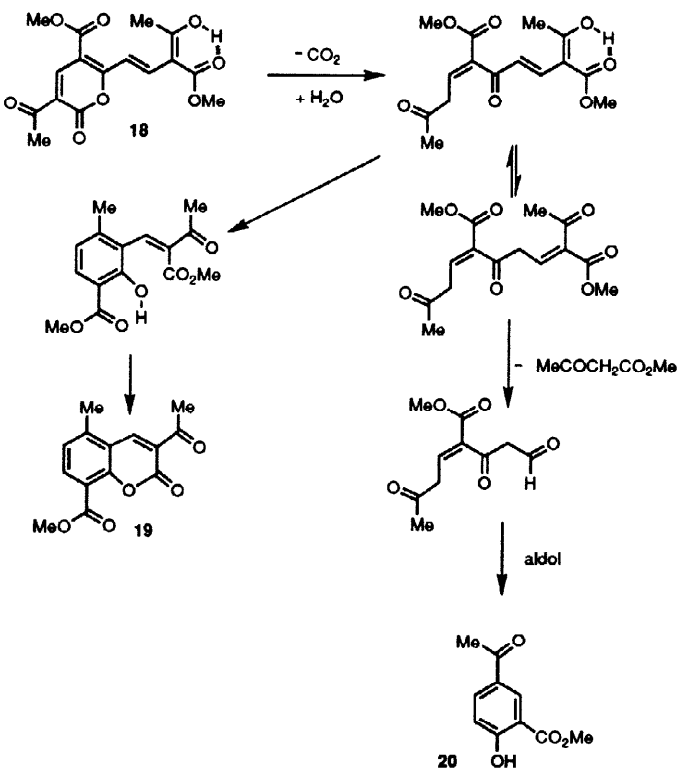
16



17a



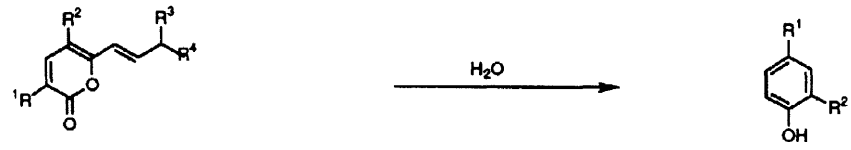
17b



Scheme 4. Reaction of dimethyl xanthophanic enol with boiling water

for the xanthyrones are available in the literature, along with IR and UV Tables and data for electron deficient pyrones themselves for comparison. [14] In the ^1H NMR the AB system is characteristic and the proton of the enolised xanthyrone terminus resonates as low field as δ 18.05 for 3'-diacetyl and 14.75 for 3'-acetyl-3'-carboalkoxy. IR data (cm^{-1}; $CHCl_3$) are mostly in the range 1745 -1773 (α-pyrone C=O), 1700 - 1730 (pyrone ester C=O), 1680 - 1690 (pyrone acetyl C=O) cm^{-1}. Unsaturation gives rise to absorptions at 1640-1650 (weak) and 1600 - 1630 cm^{-1} whilst the chelated terminus of xanthyrones is represented by two strong absorptions at 1565 - 1595 and 1500 - 1530 cm^{-1}. In the UV, xanthyrones having 3-ester-5-acetyl, or 3-acetyl-5-ester substitution have two major absorptions in 0.01M-acid ethanol near λ_{max} 300 nm (e 10,000 - 14,000) and near λ_{max} 430 nm (e 13,000 - 25,000) with an inflection in the 520 - 530 nm region. In xanthyrones lacking a 3-acetyl or a 3-ester the long wavelength absorption near λ_{max} 430 nm is absent but is replaced by maximal absorption at 385 - 350 nm. With 0.01M-alkaline ethanol as solvent, xanthyrones having 3- and 5-carbonyl or ester substituents show a strong absorption at λ_{max} 510 - 540 nm (e 40,000 - 70,000).

When boiled with water, decarboxylation of the orange dimethyl xanthophanic enol ensues and the reactive chain released cyclises to give a substituted coumarin **19** or its precursor,and a phenol **20** (Scheme 4).[15] The nature



R^1	R^2	R^3	R^4	R^1	R^2
COMe	CO_2Me	COMe	CO_2Me	COMe	CO_2Me
CO_2Me	CO_2Me	COMe	CO_2Me	CO_2Me	CO_2Me
CO_2Me	CO_2Me	COMe	COMe	CO_2Me	CO_2Me
COMe	CO_2Me	COMe	COMe	COMe	CO_2Me
CO_2Me	COMe	COMe	COMe	CO_2Me	COMe
COMe	COMe	COMe	COMw	COMe	COMe

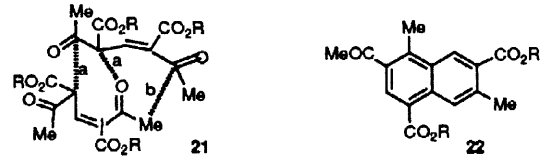
Table 2. Substituted phenols from xanthyrones and boiling water, demonstrating the nature and orientation of the pyrone substituents.

and position of the substituents on the simple phenol formed can be used to deduce the nature and position of the substituents on the original xanthyrone as indicated in Table 2.[14]

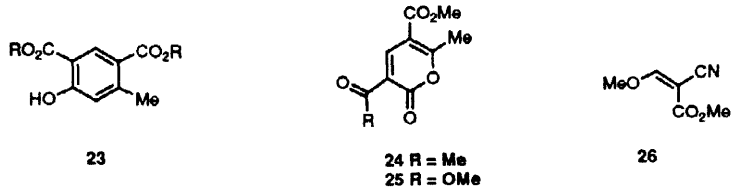
The naphthalene by-product found in the synthesis of xanthophanic and glaucophanic enols is **22** (Scheme 5) and originates from a 'dimeric' condensation **21** of the glutaconate under mild base conditions.[16,17] Treated with a more concentrated sodium methoxide, the glutaconate gives instead the isophthalate **23**.[13]

2.2. Xanthyrones Lacking Highly Enolisable Side-Chains.[18,19]

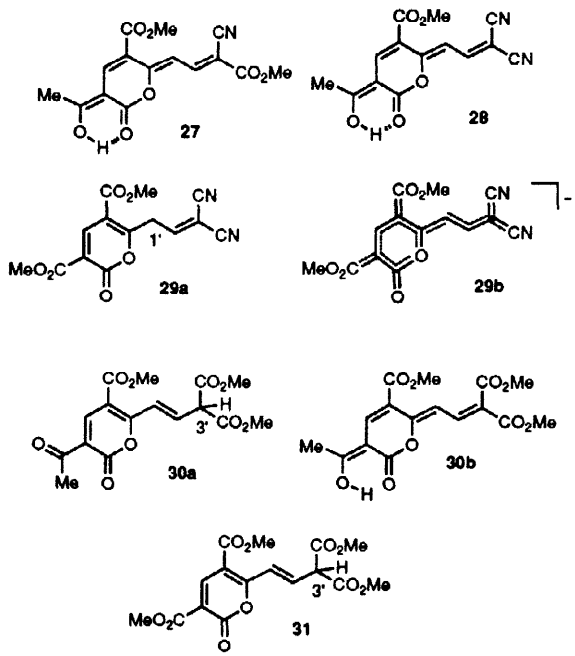
Xanthyrones lacking highly enolisable substituents attached to the propenyl side chain of the pyrone (Scheme 6) have been made by condensing the acetyl - ester pyrone **24** with methyl methoxymethylene-cyanoacetate **26**. Spectroscopic examination of the dark red product, highly ionised in ethanol, shows it to have



Scheme 5. Formation of the naphthalene by-product



23 **24 R = Me** **25 R = OMe** **26**



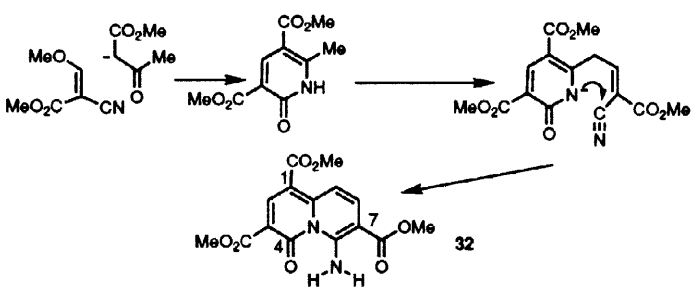
Scheme 6. Xanthyrone anions and positions of protonation.

the enolic pyrone structure **27**. Employing methoxymethylene-malononitrile and pyrone **24** similarly gave a highly acidic purple - black compound having structure **28** with an enolic pyrone unit in $CDCl_3$ (NMR), but almost fully ionised in ethanol. The rather insoluble red xanthyrone type made from the bis-methoxycarbonyl pyrone **25** and methoxymethylene-malononitrile was identified by ^1H NMR as being in the 1'-H form **29a** in $CDCl_3$ - trifluoroacetic acid solution but in d_6-dimethylsulfoxide it was highly ionised as **29b**. The UV spectrum is the same in neutral ethanol as in acidic or basic (O.O1M) ethanol, supporting this highly ionised and delocalised structure.

A' melt reaction' between the pyrone **24**, dry sodium methoxide and dimethyl methoxymethylene-malonate gave (after removal of the glaucyrone - see later) yellow crystals of 3-acetyl-3',3',5-trimethoxycarbonyl-xanthyrone. The NMR spectrum ($CDCl_3$) of this indicated a 4:1 mixture of the 3'-protonated form **30a** and its enol **30b** in this solvent (Scheme 6). A "melt reaction' between 3,5-bismethoxycarbonyl-6-methyl-2-pyrone **25**, dimethylmethoxymethylene malonate and sodium methoxide gave, on work up, 3,3',5,5'-tetramethoxycarbonyl-glaucyrone together with a small yield of the golden yellow 3,3'.3',5-tetramethoxycarbonylxanthyrone **31**. In contrast to the dinitrile case **29a**, protonation of the anion is here at the 3'- rather than at the 1'-position in the side-chain. In ethanol it is 80% ionised.

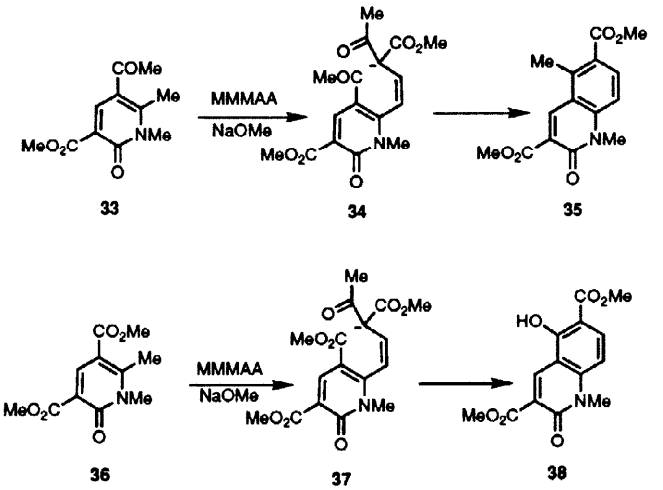
2.3. Pyridone-Containing Xanthyrone Types. [20]

In order to extend xanthyrone types to nitrogen - containing examples having a pyridone nucleus, methyl methoxymethylene cyanoacetate was treated with sodioacetoacetate in a 'melt reaction (Scheme 7),but the yellow crystalline product was clearly not of the xanthyrone type and proved to be the novel 6-amino-1,3,7-trismethoxycarbonyl-4-quinolizone. The N-methylated pyridone **33** was therefore employed with methyl methoxymethylene-acetoacetate (MMMAA)in the presence of sodium methoxide, but again did not give a pyridone-based xanthyrone (Scheme 8), but the quinolone **35** and its demethylation product. However, the desired xanthyrone type **34** had apparently been formed as an intermediate, but was then disposed of by internal aldol cyclisation. The bis-methoxycarbonyl substituted pyridone **36** reacted with methyl methoxymethylene-malonate (MMMM) to give an analogous hydroxy-quinolinone **38**, again implicating a xanthyrone type intermediate **37**, with cyclisation *via* a Claisen pathway. The pyrone ring of dimethylxanthophanic enol is much more readily opened and recyclised to a carbocyclic aromatic (see Scheme 23 later) than is that of the pyridone. Condensation of methyl methoxymethylene cyanoacetate (MMMCA) with the dimethyl ester of *N*-methylpyridone **36** gives colourless crystalline **39** in which the olefinic bond is in conjugation with the unenolised cyano-ester moiety, destroying the overall chromophore (Scheme 9). In alkaline solution, however, a highly delocalised anion is formed with absorption in the visible region λ_{max} (nm) 255 (e 17,800), 322 (4,300), 488 (65.000). In dilute acid the long wavelength absorption was shifted to λ_{max} (nm) 336 (e 8,120). The

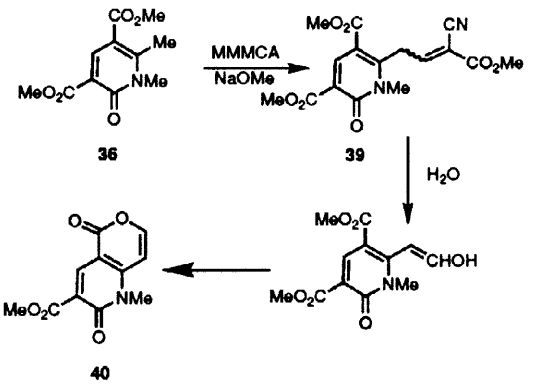


Scheme 7. Cyclisation of pyridone - xanthyrone to a quinolizone.

'pyridone-xanthyrone' relative **39** is reactive to boiling water giving an α-pyrano-*N*-methyl-α-pyridone **40**, cyclisation again involving the side-chain, but this time a partially degraded side chain.



Scheme 8. Quinolinones from attempted N-methylpyridone - xanthyrone preparations.



Scheme 9 Synthesis of an N-methylpyridino - xanthyrone and its reaction with boiling water.

3. The Glaucyrones.

3.1. Glaucophanic Enol - Structure, X-Ray Data and Spectra.

Unlike diethyl xanthophanic enol, no attempt was made by earlier reasearchers to formulate diethyl glaucophanic enol until 1964 when it was shown to be **5** on the basis of chemical and spectroscopic evidence [12,21] This structure was later confirmed by X-ray single crystal studies (Fig. 1 and 2).[22,23] Diethyl glaucophanic enol forms glittering black crystals from benzene. Its solution in benzene is red but in ethanol or dimethyl sulfoxide it is blue. The colour in some solvents such as acetone is red, becoming blue on the addition of a small amount of water: there can also be colour changes in solution dependent on temperature. Dimethyl glaucophanic enol, although normally crystallising from benzene in the blue-black form, can give a red

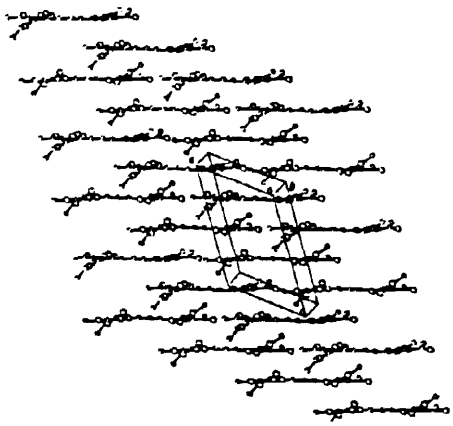


Figure 1. Diethyl glaucophanic enol. Projection showing stair-like arrangement of molecules.

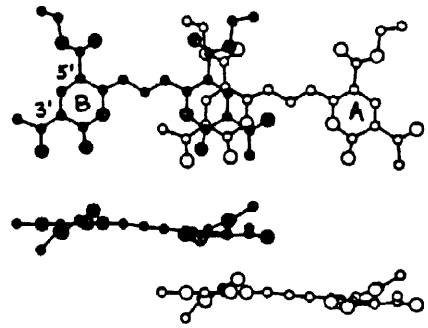


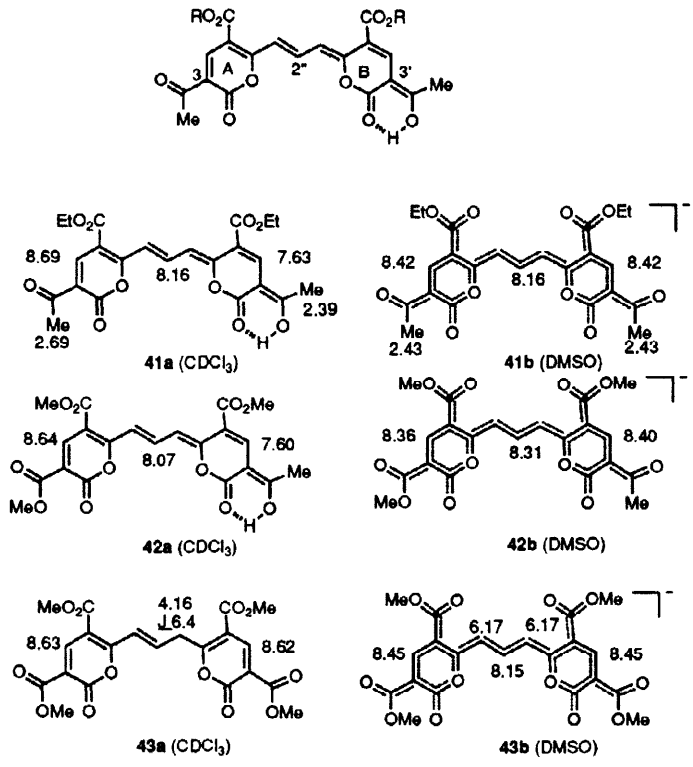
Figure 2. Arrangement of pairs of glaucophanic enol molecules showing close contacts.

crystalline form, apparently solvated , from chloroform. The red solution of the diethyl ester in benzene crystallises in the refrigerator in blue-black form, the process being reversed on warming.

The electronic solution spectra of diethyl glaucophanic enol vary with the solvent. There are two extremes. In benzene or chloroform (red solutions) there is strong absorption near λ_{max} 500 nm but in the most polar solvents, EtOH, DMF, DMSO (blue solutions) there is a narrow intense absorption near λ_{max} 680nm corresponding to that of the sodium salt and indicating almost complete ionisation. UV spectra of an intermediate type are given in acetonitrile or acetone (concentrated solutions red, becoming blue on adding a little water).

The X-ray structure shows an essentially planar core with the acetyl of ring-B enolised and hydrogen bonded and the carbonyl of ring-A turned away from interaction of the lactonic carbonyl and twisted 16^{o} from the plane. The ester addenda to the glaucyrone core lie out of plane by 20^{o} at the ketonic end and 30^{o} at the enolic end. The crystal structure shows an interesting short carbon-carbon interaction (3.27 Å, shorter than the sum of the van der Waals distances) apparently caused by the enolic ring-B acting as a donor. Positions of higher electron density are thought to be associated with positions 3' and 5' of ring-B with carbons 2 and 4 of ring A being positions of electrical deficiency. A stair-like structure is formed.

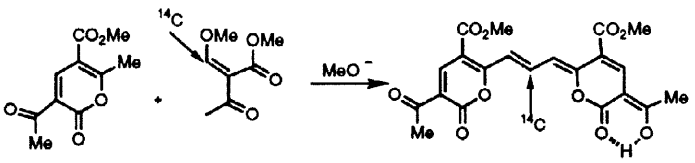
Some ^{1}H NMR assignments for 3,3"-diacetyl-5,5'-bisethoxycarbonyl glaucyrone in pure dry deuteriochloroform are shown in **41a** and are in agreement with the unsymmetrical X-ray structure: there are two types of pyrone ring connected by an AMX system (Scheme 10).[23] Measurement in damp $CDCl_3$ (or addition of a trace of $F_3C.CO_2H$) gives a slow exchange spectrum with the 4-H and 4'-H, the acetyl methyls, and 1"- and 3"-H becoming broad and ill-defined: only the central 2"-H remains sharp, along with signal for the ester



Scheme 10. ^{1}H NMR spectra of glaucyrone types and their ionised products. (For full assignments see ref..[23])

ethyls. Similar slow exchange of a proton between the two ends of the molecule can be followed using ^{13}C NMR spectra. In the ^{1}H NMR experiments, addition of a little cyclohexylamine to the $CDCl_3$ causes complete ionisation, as does measurement in damp [$^2H_6$]-DMSO,and the spectrum **41b** is now that of a molecule symmetrical about the central carbon-2"

The tautomerically unsymmetrical 3'-acetyl-3,5,5'-trismethoxycarbonyl-glaucyrone **42a**,black plates, was obtained as one of the products from a melt reaction between an equimolecular mixture of the pyrones **24** and **25** and dimethyl methoxymethylene-malonate. As expected it had, both in unionised **42a** and ionised **42b** forms, spectra characteristic of an unsymmetrical structure. In pure dry $CDCl_3$ the ^{1}H NMR spectrum of 3,3',5,5'-tetramethoxycarbonyl-glaucyrone **43a** (made by a similar melt procedure) contrasts with those for **41a** and **42a** as there is no enolised carbalkoxy and no AMX system. The proton resides on C-3" but in damp [$^2H_6$]-DMSO or $CDCl_3$ containing a trace of cyclohexylamine the spectrum becomes symmetrical about the C-2" axis **43b**.



Scheme 11. Origin of the central carbon atom in dimethyl glaucophanic enol by isotopic labelling.

3.2. Mechanism of Formation of Glaucophanic Enol.[24,25]

The problem of the mechanism of formation of glaucophanic enol required identification of the source of the central 2" carbon atom of the molecule. As shown by ^{14}C labelling, and labelled atom extraction by degradation, it proved to be the methoxymethylene carbon as in Scheme 11 Study of the relative yields of glaucyrones *versus* xanthyrones as given in Table 3 shows that they are correlated with the acidity of the leaving groups: poorer leaving groups give better yields of glaucyrones. On this basis the formation mechanisms for xanthophanic and glaucophanic enols may be unified as in Scheme 12. Michael addition of the pyrone anion **P** to the methoxymethylene gives the anion **44a** and loss of $^{-}$OMe from this produces the xanthyrone. However the anion **44a** will equilibrate with its protonated form **44b** and the relative amounts of each will be related to the acidity of the terminus. Displacement by pyrone anion, or elimination followed by addition, leads to competitive formation of glaucyrone as shown.

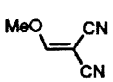
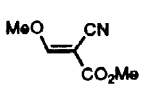
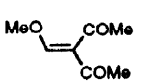
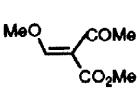
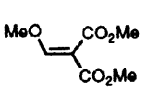
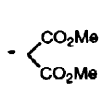
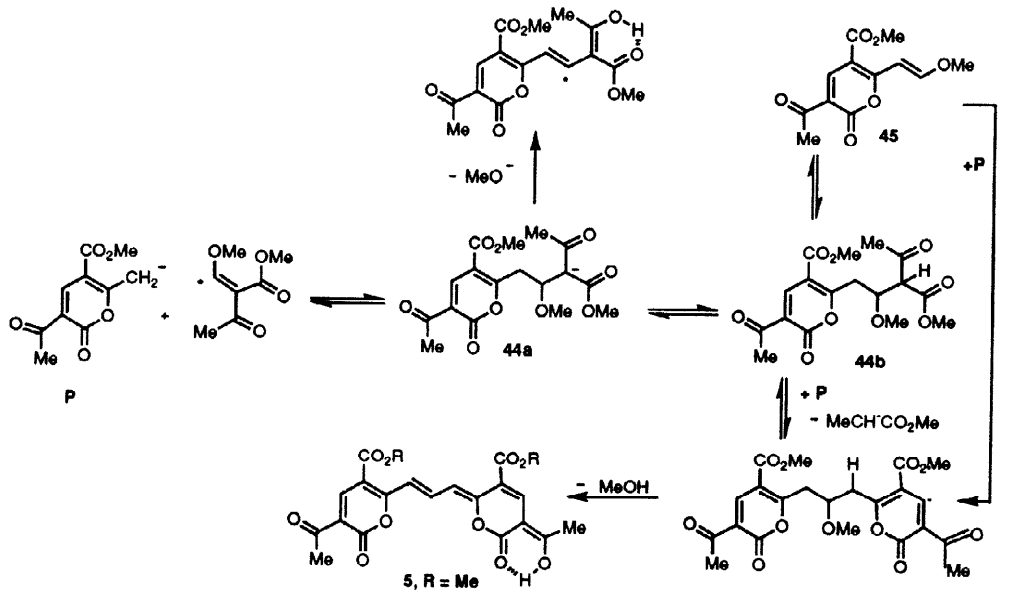
Carbon source	Leavig group	Yield of glaucyrone %	Yield of xanthyrone %
		nil	86
		trace	88
		2	85
		49	44
		56	4

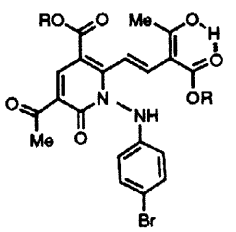
Table 3. Dependence of xanthyrone / glaucyrone yields on the relative acidity of the leaving group.



Scheme 12. A combined mechanism for the formation of xanthophanic and glaucophanic enols.

4. Some Reactions of Xanthyrones and Glaucyrones

The reactions of xanthyrones and glaucyrones with sodium amd magnesium methoxides will be dealt with in a separate section later. Diethyl or dimethyl xanthophanic enols react with p-bromophenylhydrazine to give pyridones e.g.**46** but the reaction with alcoholic hydrazine is different, leading to the diazine acid **47** by the extrusion process of Scheme 13.[15] The same product is obtained when diethylglaucophanic enol is treated with hydrazine.[21]



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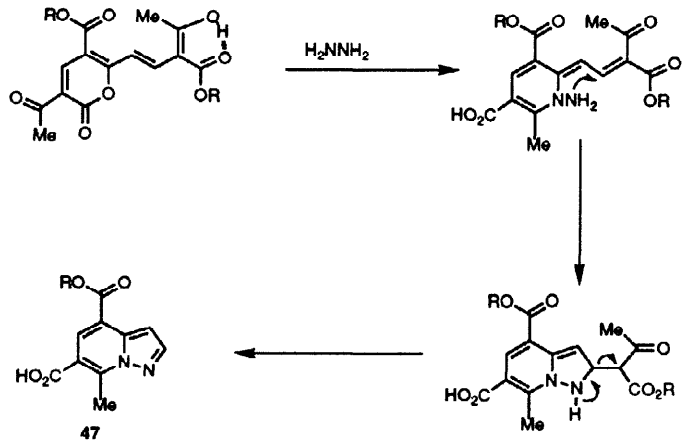
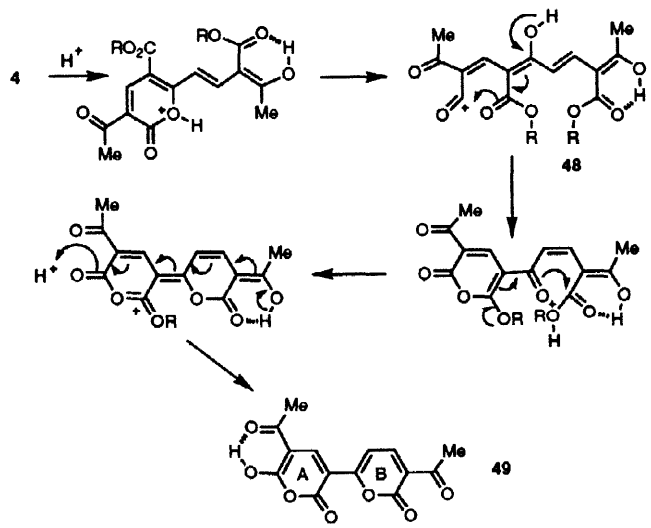


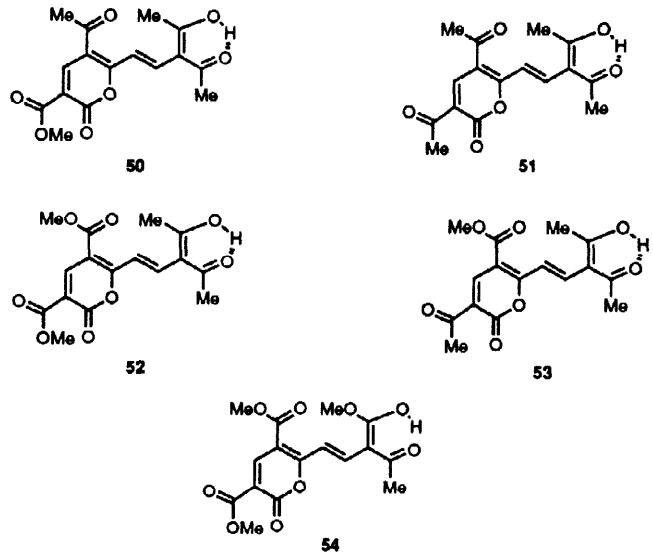
Scheme 13. Reaction of dialkyl xanthophanic enol with hydrazine.

4.1. Formation of GP Compounds from Xanthyrones.

An intriguing reaction occurs when either diethyl or dimethyl xanthophanic enol is dissolved in concentrated sulfuric acid [2,15] or trifluoroacetic acid, the golden plates produced being a glutaconic anhydride - α-pyrone (GP1) **49**, formed (Scheme 14) by rearrangement involving an acylium ion **48**.[26,27] In accord with this mechanism the same treatment of **54** gave a similar compound (GP2) but such products could not be isolated from **50**, **51**,**52** or **53** (Scheme 15). When the reaction giving GP1 was carried out with D_2SO_4 the product was the tetradeuterio compound **55**, but dissolution of unlabelled **49** in D_2SO_4 inserted only the three protons of one of the methyl groups, forming **56**. This indicates that the fourth deuterium is inserted as part of the

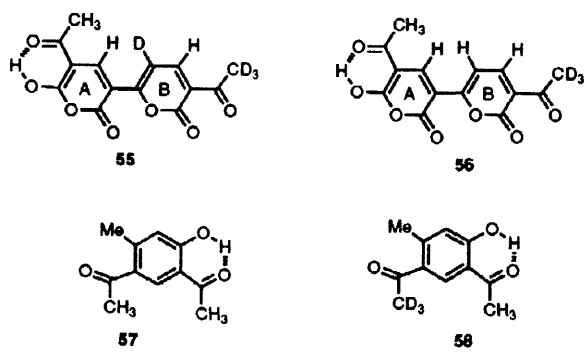


Scheme 14. The formation of GP 1 from dialkyl xanthophanic enols in concentrated sulfuric acid medium.

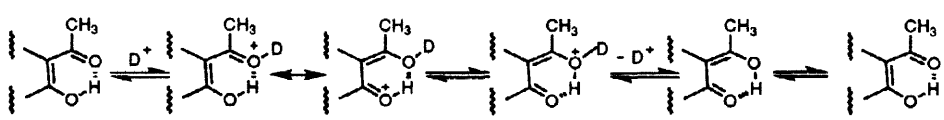


Scheme 15. Xanthyrones tested for possible GP formation.

formation mechanism (Schemes 14 and 16).[27] The labelling of the methyl of only one of the acetyls in **55** or **56** seemed surprising at first sight, but the conclusion was reached that chelation must be protecting one of the acetyl methyls. This was confirmed by experiments with model systems (Scheme 16). For example, treatment of **57** with D_2SO_4 gave **58**, the chelated acetyl remaining unaffected. The process by which enolisation into the chelated methyl, a necessary preliminary to deuteriation, is subverted, is shown in Scheme 17.[27]



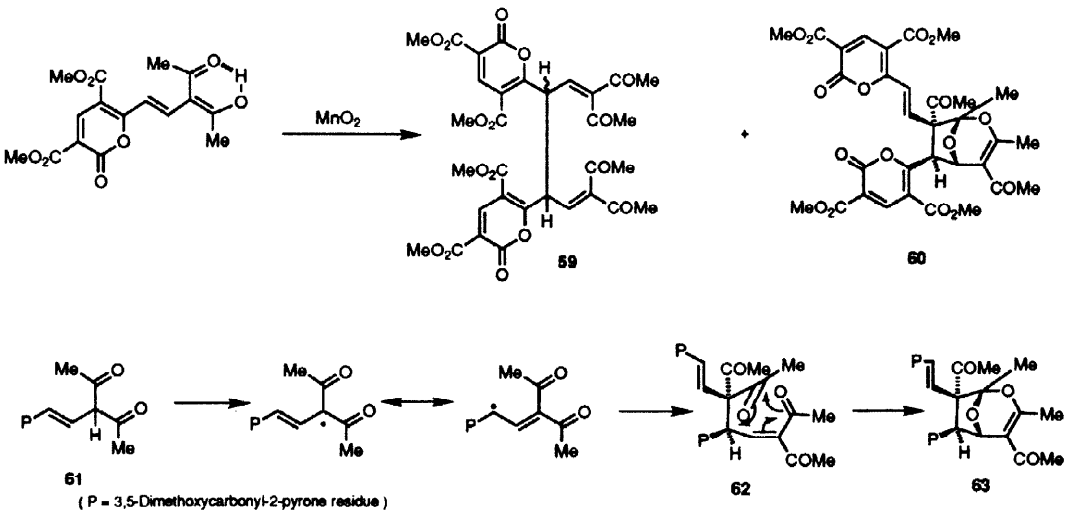
Scheme 16. Deuteriation studies relevant to GP1 formation.



Scheme 17. Mechanism accounting for the failure of a chelated acetyl to deuteriate in acid solution.

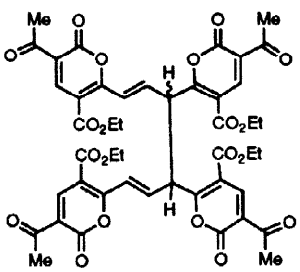
4.2. Radical Reactions of Xanthophanic and Glaucophanic Enols. [28]

When a xanthophanic enol is shaken with manganese dioxide in chloroform three compounds are formed by electron transfer. Two of these are products of formal radical coupling at 1' and are the *erythro-* and *threo-* forms of dehydrodimer **59** (Scheme 18). A radical addition mechanism can alternatively be written. A similar dehydrodimer **64**, isolated as one stereoisomer from 3',3'-coupling, was obtained when diethyl glaucophanic



Scheme 18. Reactions of dimethyl xanthophanic enol initiated by manganese dioxide.

enol was treated with manganese dioxide and it was also formed photochemically by sunlight irradiation of a solution containing acetone. The third product from the xanthyrone (Scheme 18) is structurally more subtle, and was shown to be **60** by X-ray structure analysis. It was also found that a low yield of a dehydrodimer analogous to **60** could be obtained from diethyl 2,4-diacetylglutaconate. It seems most likely that the mechanism is a formal radical coupling followed by an intramolecular [4+2]cycloaddition **62**,leading to **63**



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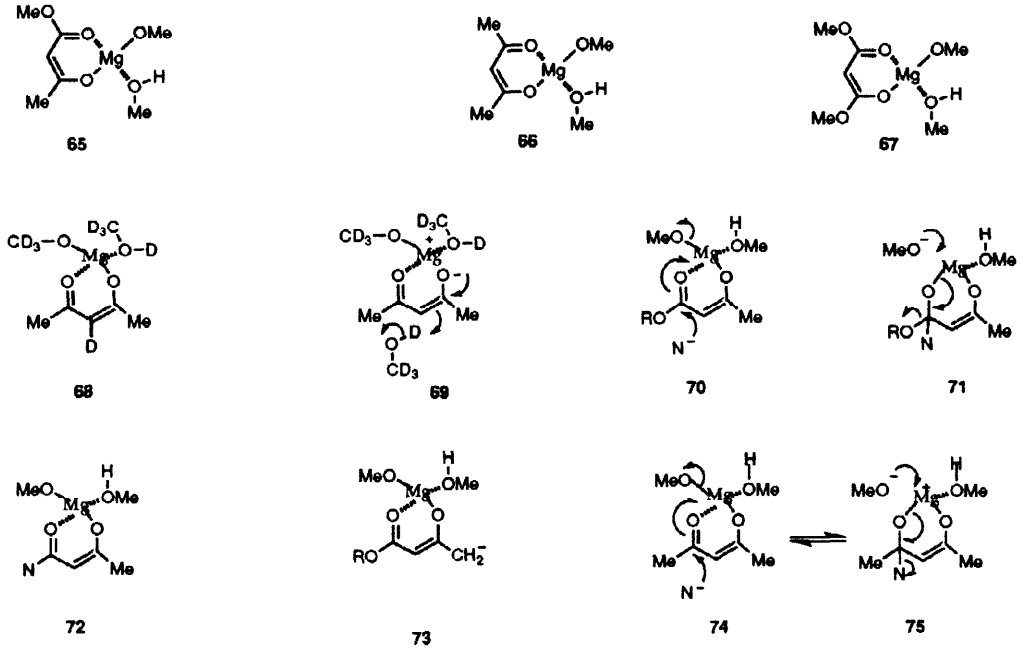
5. Chelated Magnesium Enolates and their Reactions.

During work on the xanthyrones [2] and glaucyrones it was apparent that magnesium methoxide, as compared with sodium methoxide,often gave quite different products, usually purer and in higher yields. It was surprising that the merits of this long known chelating base had not been properly appreciated, and over the years we have explored its potential.

5.1. Model Magnesio-Chelates and their Deuteriation.[29]

For solubility reasons multicomplexed systems can cause difficulties and we have examined some simple models for spectroscopic data. The magnesium complexes from acetyl acetone **66**, acetoacetate **65** and malonate **67** can be isolated and crystallised, and when excess magnesium methoxide is used to prepare them they are all of the 1:1 type. ^{1}H NMR data for the magnesium chelates in deuteriobenzene accord with the structures shown, though there may additionally be some aggregation in solution. It seems likely that the complexes are of the distorted tetrahedral (D_{2d}) type, though X-ray data are not available. Magnesium displacement can occur amongst different competing chelate sites. Thus acetylacetone or methyl acetoacetate completely scavenges the magnesium from dimethyl magnesio-malonate.



Scheme 19. Properties of magnesium chelates.

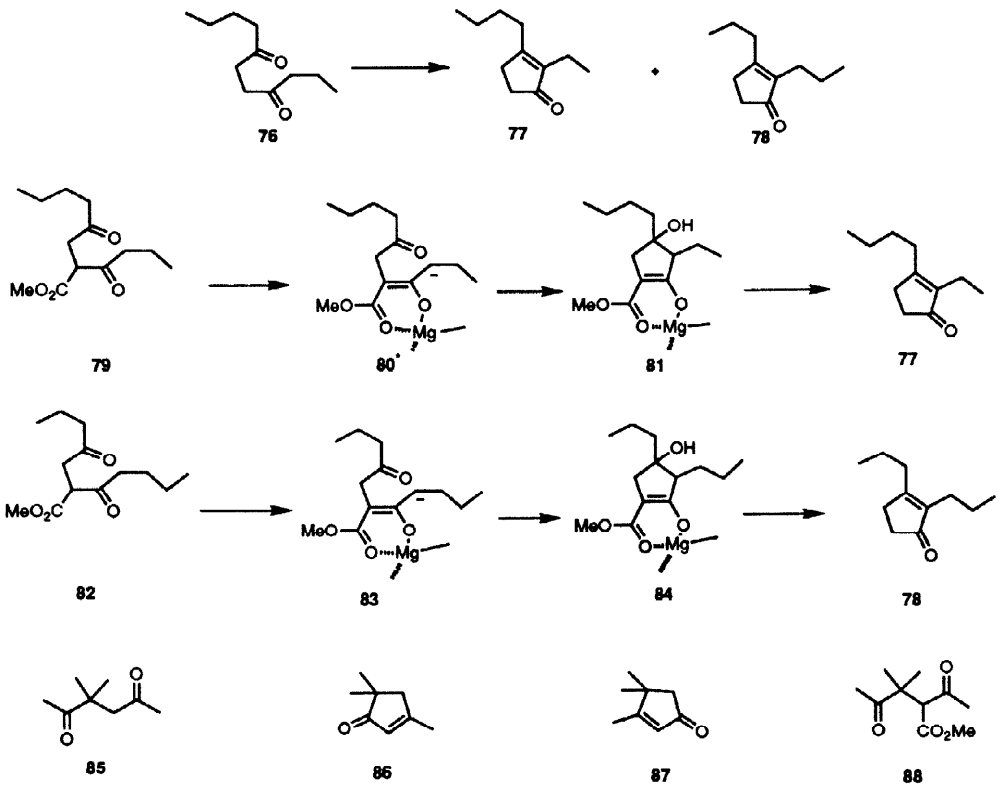
Deuteriaton of magnesio-acetylacetone **66** in benzene, as effected by adding d_4-methanol, results first in the disappearance of the methanol ligand signal from the ^1H NMR spectrum, followed by that of the methoxy, and finally, and more slowly, that of the olefinic proton (see **68**). The exchange of the latter is thought to involve an ion pair **69** and alkylation and acylation at this position in magnesium chelates, especially malonate, is well known.[30] Deuteriation of the acetyl methyl protons to any appreciable extent was not observed - extra base (which can be magnesium methoxide or another base) - is needed. Methyl magnesio-acetoacetate **65** shows a similar sequence of deuteriation and in the presence of another mol of magnesium methoxide, deuteriation of the acetyl methyl, as well as exchange of the ester methoxyl for deuteriomethoxyl, occurs. The latter models the Claisen condensation (**70**,**71** and **72**) which is so characteristic of magnesium chelates of this type. Exchange of the acetyl methyl protons occurs *via* a carbanion stabilised by delocalisation into the adjacent chelate system **73**. In chemistry involving magnesium chelates this models the mode of action as the nucleophilic partner in aldol condensations. The chelate itself is screened from attack as an acceptor in the reversible aldol reaction, since the intermediate (see **74**, **75**) (Scheme 19) does not lead to product.

5.2. Directed Aldol Construction of Cyclopentenones Using Magnesium chelation.[31]

The above findings have led to investigation of a chemoselective method for the aldol condensation of γ-diketones. Sodium hydroxide catalysed cyclisation of the diketone **76** gives an essentially 1:1 mixture of the two possible cyclopentenones **77** and **78** as expected (Scheme 20). Insertion of a methoxycarbonyl as in **79**, followed by treatment with magnesium methoxide in methanol (**80**, **81**) and then aqueous sodium hydroxide to complete the dehydration of the aldol, along with hydrolysis and decarboxylation of the ester, gives the cyclopentenones **77** and **78** in 9 : 1 ratio. On the other hand similar treatment of **82***via* **83** and **84**, gives cyclopentenones **77** and **78** in a 1 : 9 ratio. Non-chelating base catalysed cyclisation of diketone **85** gives **86** and **87** in a ratio of 2.2 : 1 but insertion of a methoxycarbonyl group **88** and treatment with magnesium methoxide in methanol, followed by work-up as above, gives **86** and **87** in a ratio of 1 : 49

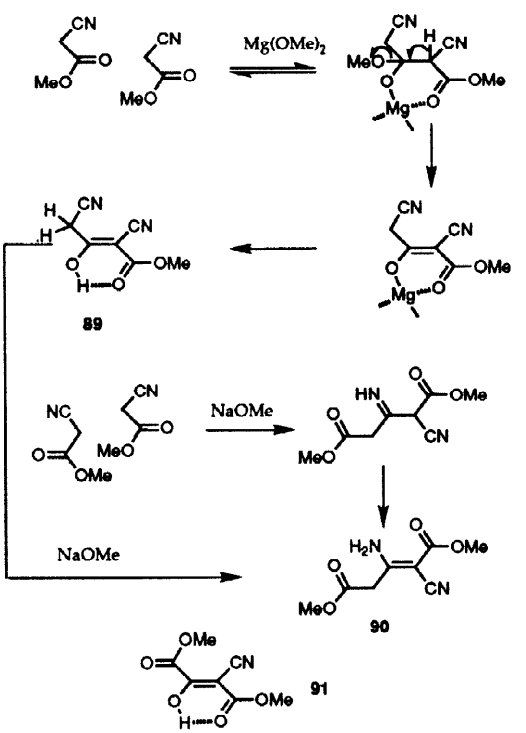
5.3. Interception of a New Kinetic Product by Magnesium Chelation.[29,32]

Some of the xanthyrones possess cyanoester termini so methyl cyanoacetate was also treated with magnesium methoxide in methanol, and here the results were unexpected (Scheme 21). Treatment at room temperature with 1 equivalent of magnesium methoxide gave a precipitate, which on decomposition with acid produced methyl 2,4-dicyano-3-hydroxybut-2-enoate **89** in 78% yield. On the other hand, if sodium methoxide was used, the product was dimethyl (Z)-3-amino-2-cyanopent-2-enedioate **90**. If compound **89** is treated with sodium methoxide it is converted into **90**, but treatment of **90** with magnesium methoxide does not convert it



*When shown in this way, the two remaining ligands are OR and ROH as appropriate.

Scheme 20. Synthesis of cyclopentenones by magnesium chelate directed aldol condensation.

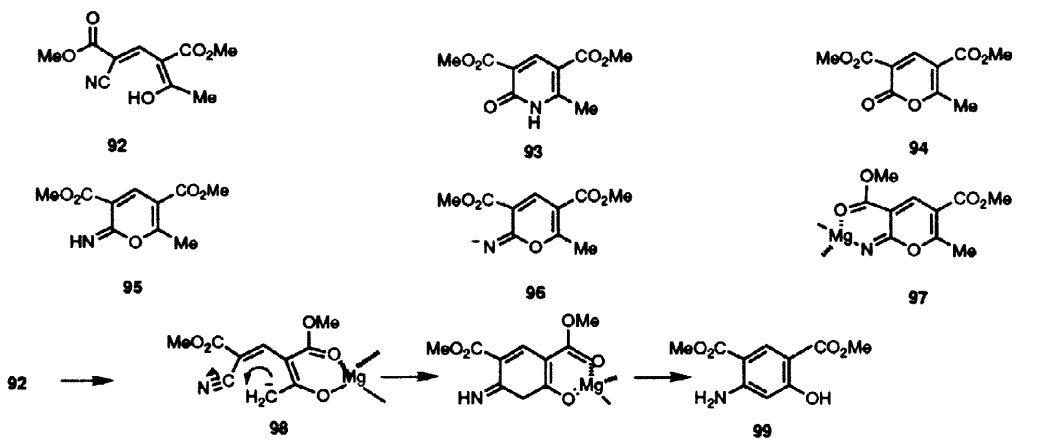


Scheme 21. Sequestration of the kinetic product from the condensation by magnesium chelation.

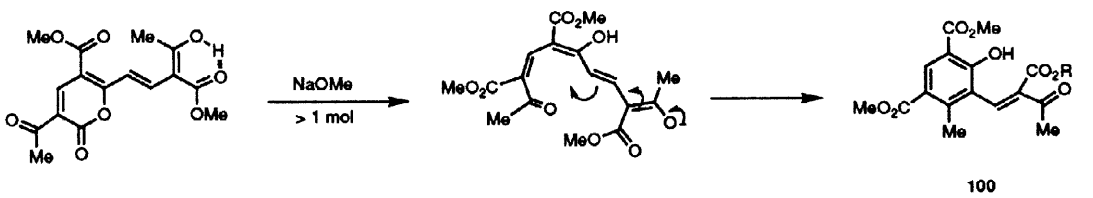
into **89**. The kinetic product **89** from the 1,2-addition / Claisen competition is intercepted and captured from solution as the magnesium complex in a reaction that with sodium methoxide as the base leads to the thermodynamic product **90**. A magnesium methoxide catalysed reaction between diethyl oxalate and methyl cyanoacetate also gave Claisen product **91** in 85% yield without precipitation of the magnesio complex from solution.

5.4. Diversion to Hydroxyanilines in the Cyclisation of Glutaconate Nitrile Types.[29,33]

Condensation of methyl methoxymethylene-acetoacetate with methyl cyanoacetate in the presence of sodium methoxide forms the propenyl **92** which at low base concentrations cyclises to give mainly the pyridone **93** (0.05 mol gives 77%) but at high base concentrations the pyrone **94** (4 mol, 67%) is the major product (Scheme 22). The propene **92** is in equilibrium with the imine **95** which at high sodium methoxide concentrations remains in the ionised imine form **96** and gives the pyrone **94** on work up. At low base concentrations the imine is largely protonated and then forms the pyridone **93** irreversibly.[33] If the base is magnesium methoxide, high concentrations (4 mol) give pyrone **94** (16%) along with a new product,the hydroxyaniline **99** (69%). This is explained by the formation of two chelated intermediates, the first of which **97** leads to the pyrone as before, whilst the second (see **98**) locks the precursor conformationally with a geometry and reactivity suitable for cyclisation and hence formation of the hydroxyaniline **99**. Other examples in related systems have been investigated and are also explained on the basis of magnesio - chelation.[29].



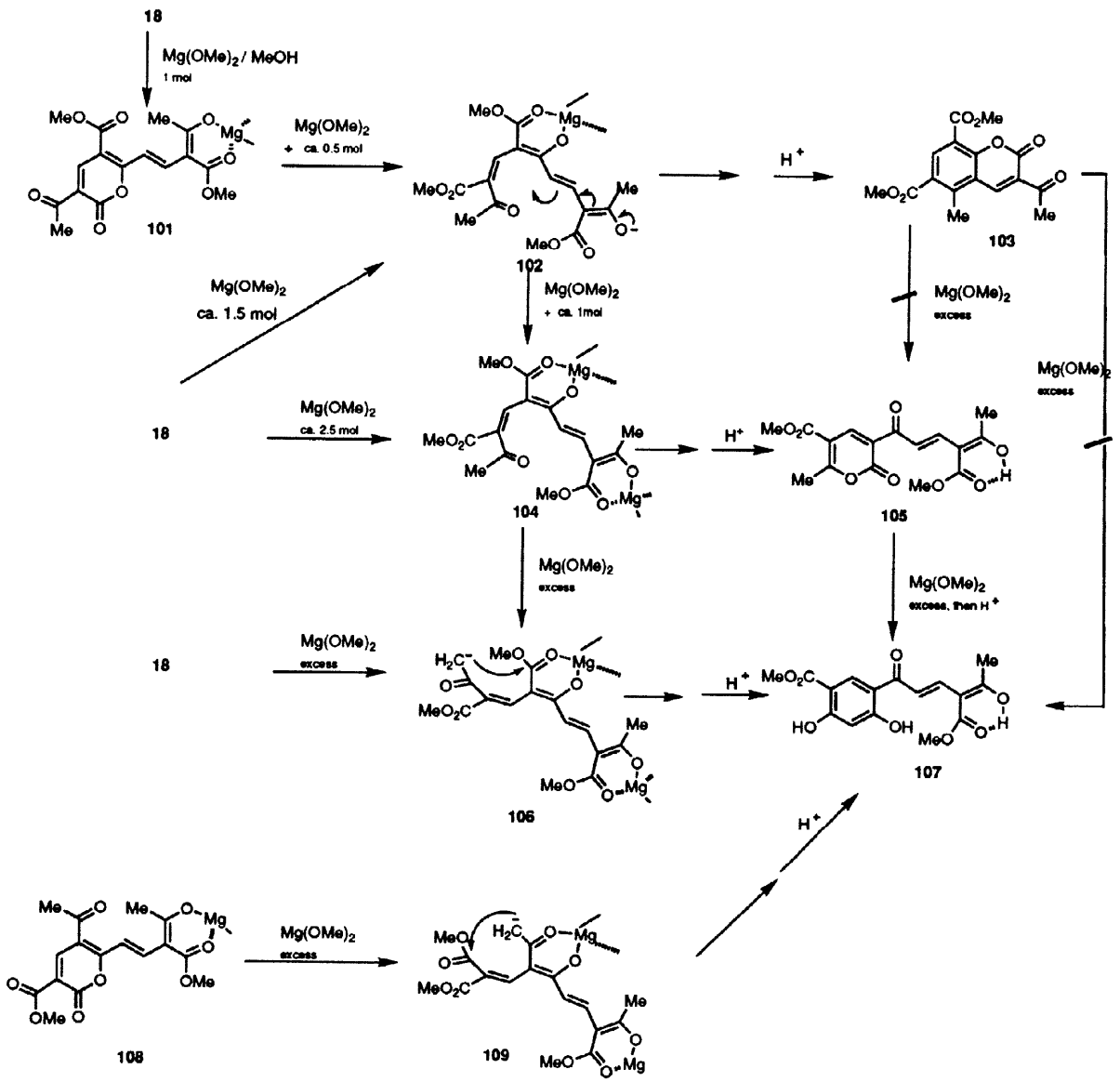
Scheme 22. Role of magnesium chelation in determining the nature of condensation products.



Scheme 23. Treatment of dimethyl xanthophanic enol with 1 to 24 mol of sodium methoxide.

5.5. Xanthophanic Enol - Control of Product Type by Modulation of the Initial Molarity of Added Magnesium Methoxide.[34-36]

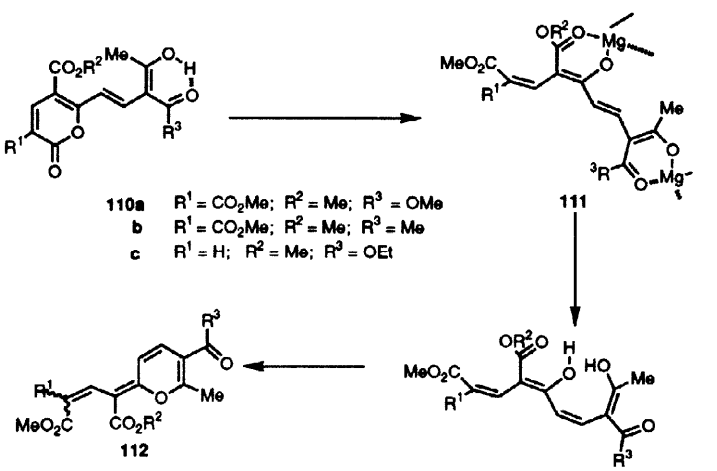
Some of the most interesting reactions of xanthophanic and glaucophanic enols concern their varying behaviour towards the initial amounts of methanolic magnesium methoxide employed. Treatment of dimethyl xanthophanic enol (1 mol) with sodium methoxide in the concentration range 1 - 24 mol forms the isophthalate **100** (Scheme 23).[37] Treatment of the isophthalate with acid converts it into the corresponding coumarin **103** and traces of this are formed on work-up.



Scheme 24. The responses of xanthyrones to varying molar ratios of magnesium methoxide.

The response of dimethyl xanthophanic enol towards varying initial concentrations of magnesium methoxide is more intricate.[37] With the use of up to 1 mol magnesium methoxide in methanol per mol of xanthyrone, it merely forms the chelate **101** and on acidification the enol is recovered unchanged. Somewhat above this ratio the limited excess of magnesium methoxide permits the formation of the coumarin **103** and its acetal. As in the case of the sodium methoxide reaction, these are products of an aldol reaction and it seems likely that when the pyrone ring is opened there is repositioning of the magnesium chelate giving **102** which cyclises in the conformation shown (Scheme 24). Maximal yields (80-85%) are found near, or a little above, the 1 : 1 ratio. As the ratio $Mg(OMe)_2$ / xanthyrone passes through 1.5 : 1, and then 2 : 1, the yields of aldol isophthalate **103** decline and a new pyrone product **105** emerges, reaching its maximum yield (70%) at about 2.5 : 1 when virtually no aldol product is obtained, though some (25-30%) of the resorcylic ester **107** is also observed. The pyrone **105** is considered to be a product of the doubly chelated and protected magnesium chain **104** with the chain stabilising itself by forming the pyrone **105** on work-up.

At a ratio of 3 : 1 magnesium methoxide : dimethyl xanthophanic enol there is 35 - 40% of pyrone **105** and 60 - 65% of resorcinol **107**; corresponding figures of 5 : 95% are found at a ratio of 6 :1. Finally, using a large excess of magnesium methoxide (12 mol) only the resorcinol **107**, a product of a Claisen condensation of **106**, is produced in essentially theoretical yield. None of the other products mentioned above are observed. The resorcinol is derived from the doubly complexed form **104** which in the presence of more than two equivalents of base now forms the anion **106** and cyclises by Claisen condensation. Formation of the pyrone **105** from the 2 mol reaction is reversible, and so if treated with an excess of magnesium methoxide in methanol it is converted into **107** *via* **106**. However, product **103** from the 1 mol reaction cannot be converted into **107** by adding excess magnesium methoxide.[37]

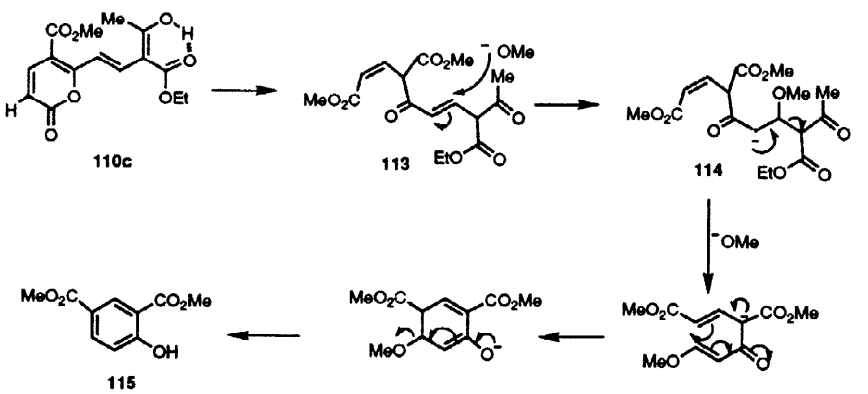


Scheme 25. Pyran from a xanthyrone devoid of a 3-acetyl substituent, by treatment with magnesium methoxide.

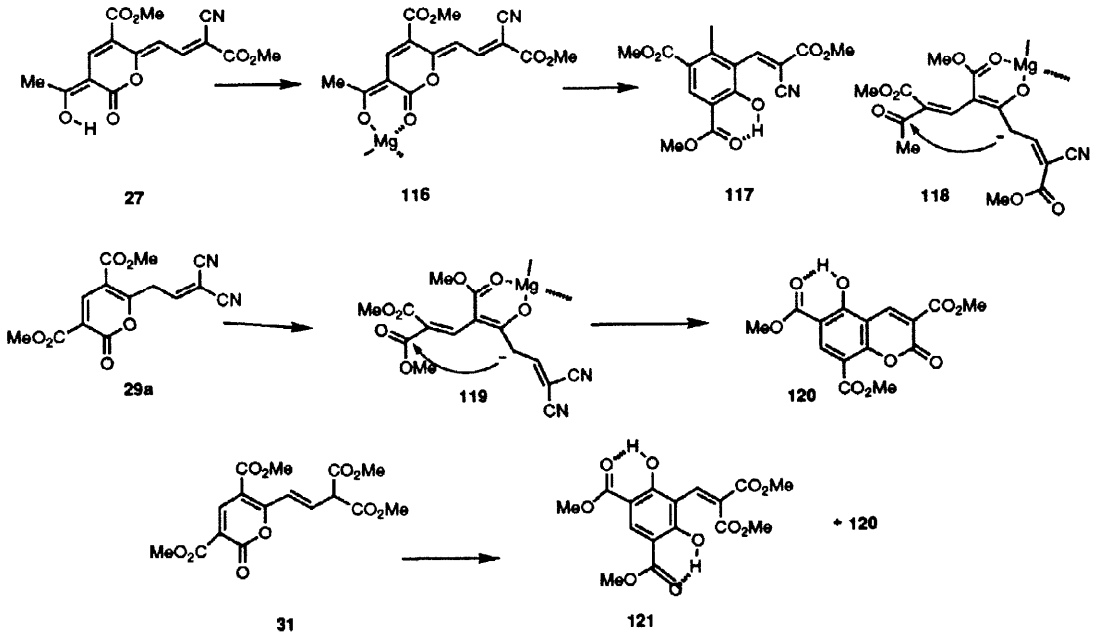
5.6. Reactions of Further Xanthyrones with Magnesium Methoxide.[37,38]

It is of interest to note that the two isomeric xanthyrones **101** and **108** (Scheme 24) give one and the same resorcinol product **107** when treated with excess $Mg(OMe)_2$ in methanol. It is also of interest to note the behaviour of the xanthyrones **110, a-c** under similar conditions (Scheme 25). Here no pyrone acetyl is available to initiate the customary resorcylic cyclisation and instead the bis - complexed chain **111,** when released from the magnesium, stabilises itself by pyran formation at the other end of the chain giving **112.** In view of the simple pyrone opening - pyran closure mechanism, it might be questioned whether magnesium methoxide has a special role in such a transformation so the reaction was performed using excess (10 mol) sodium methoxide in methanol and **110c** as the substrate (Scheme 26). The major product was dimethyl 4-hydroxyisophthalate **115** formed by chain degradation along with extrusion of acetoacetate (**113, 114**), Michael reaction, and aromatisation. The formation of a magnesium chelate has an important function in stabilising and protecting the chain.

The cyanoxanthyrone **27** lacks the usual chelating terminus on the propenyl side chain and can itself only give a conjugated monomagnesium chelate **116** using the pyrone feature (Scheme 27). With further magnesium methoxide it is suggested that the pyrone is cleaved by methoxide ion and that there is chelate rearrangement followed by aldol condensation (**118**) leading to the isophthalate **117.** The isophthalate coumarin **120** is similarly formed *via* **119** from the 3',3'-dinitrile **29a** The 3',3'-dicyanoxanthyrone **29a** has a 3-methoxycarbonyl replacing the 3-acetyl of **27** so parallel cyclisation has to be by Claisen reaction along with nitrile hydrolysis forming the isophthalate coumarin **120.** Refluxing the 3,3',3',5-tetramethoxycarbonyl-xanthyrone **31** with excess magnesium methoxide gave a mixture of **120** and **121,** the latter being readily converted into the former. The malonate terminus does not complex efficiently with magnesium methoxide as compared with an acetoacetate terminus.



Scheme 26. Hydroxy isophthalic ester from a xanthyrone devoid of a 3-acetyl substituent, by treatment with sodium methoxide.

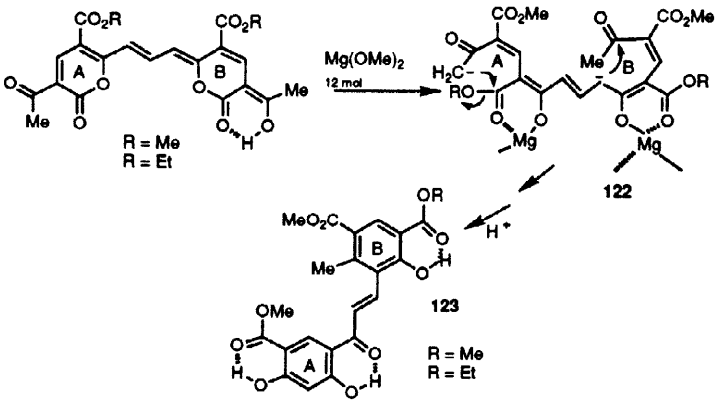


Scheme 27. Reaction of further xanthyrone types with magnesium methoxide.

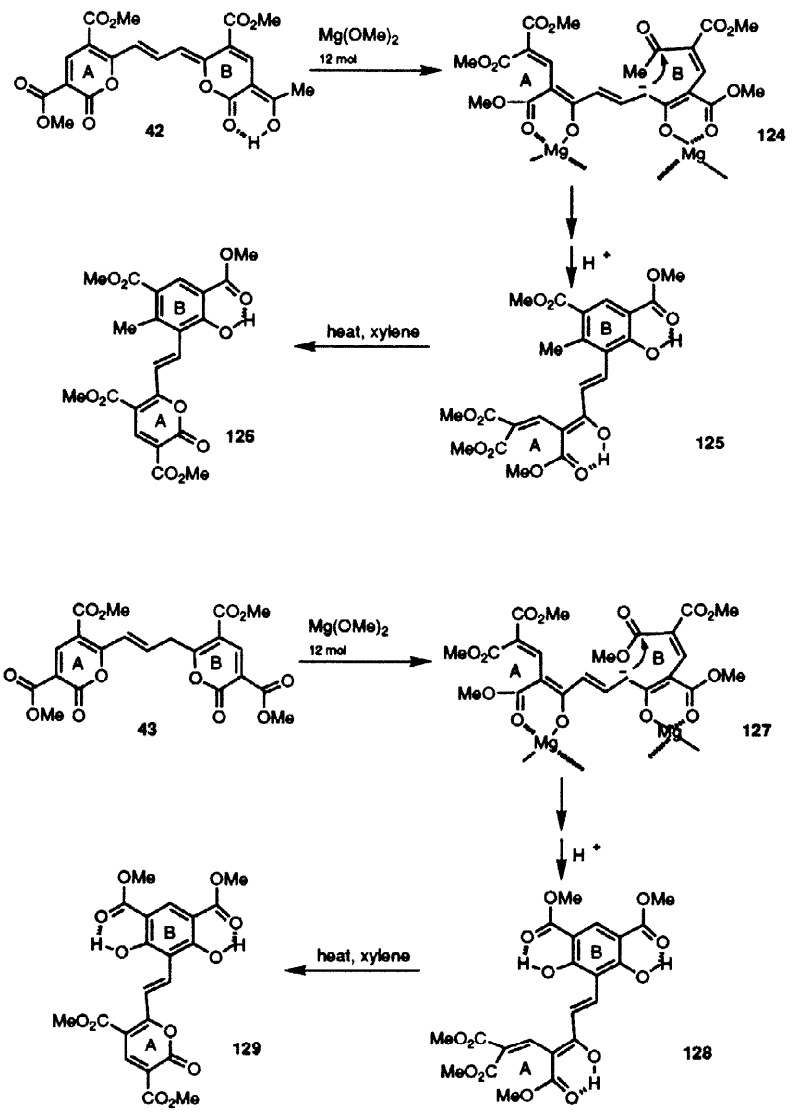
5.7. The Reaction of Glaucophanic Enol and Glaucyrones with Magnesium Methoxide.[39]

On reaction with excess magnesium methoxide in methanol, dimethyl and diethyl glaucophanic enols (Scheme 28) give one and the same product **123** in 78% yield. The two pyrone rings are opened in the usual way with the derived chain being bis-magnesio-complexed **122**. One ring cyclises by aldol reaction, the other by Claisen condensation (see **122**). Equilibration between possible bis-chelates is envisaged. In the case of diethyl glaucophanic enol (R = Et), one ethyl ester is lost in the Claisen cyclisation, the other through ester interchange promoted by its chelated nature. In confirmation,by adjustment of conditions the latter interchange can be partially avoided and **123** (R = Et) obtained.

Reaction of the unsymmetrical glaucyrone **42** with excess magnesium methoxide (12 mol) gave **125** in 90% yield which in refluxing xylene was further cyclised to the interesting compound **126**, containing both an aromatic and a pyrone ring (Scheme 29). The tetraester glaucyrone **43** gives **128** by Claisen condensation (*via* **127**) when treated with excess magnesium methoxide, and on thermolysis in xylene this is converted into **129**, similar to **126**. There is evidence that the aldol cyclisations in these systems are faster than the Claisen condensations.



Scheme 28. Reaction of dimethyl and diethyl glaucophanic enols with magnesium methoxide.

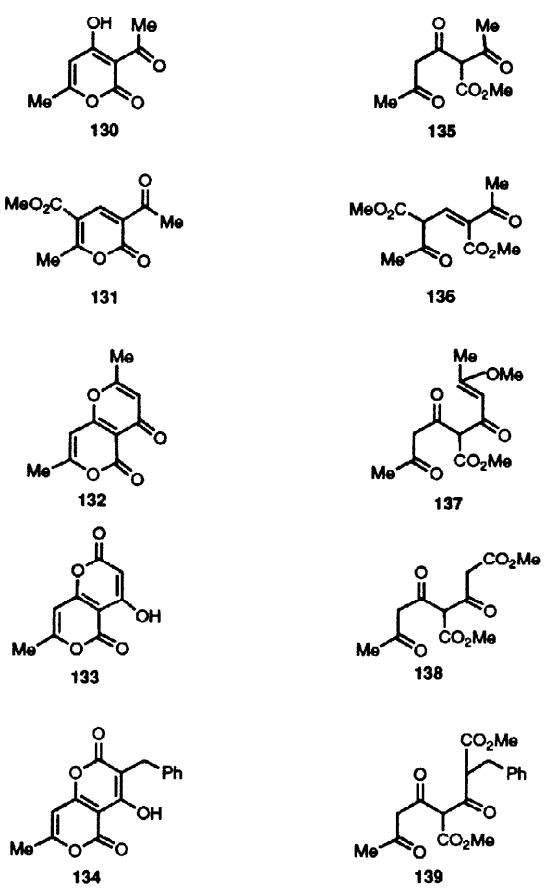


Scheme 29. Products from the treatment of glaucyrones with excess magnesium methoxide, and their further conversion by thermolysis.

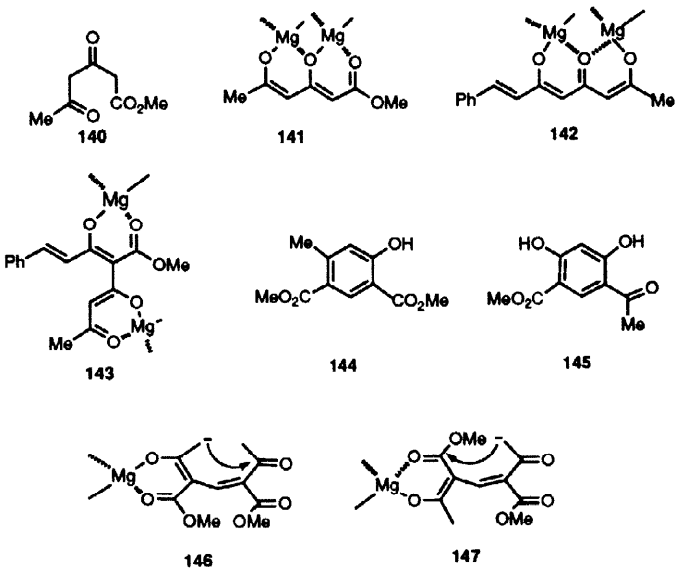
5.8. Pyrone Surrogates for β-Ketoester Systems: Reactions with Magnesium Methoxide.[40]

The products from reactions between a series of fused and unfused α-pyrones **130** - **134** (Scheme 30), methanolic sodium methoxide, magnesium methoxide, and hot water, provide further information on the scope of these reagents. The series of lactones may be viewed as being made up of β-ketoester units which reveal themselves on methanolysis (**136** - **139**) and can complex with magnesium methoxide. On treatment of dehydroacetic acid **130** with the methoxide of either sodium or magnesium, deacylation takes place. [41] However,the yield of methyl triacetate **140** is considerably poorer on using the sodium reagent,there being extensive retro-Claisen chain degradation not found with the magnesium reagent. It is believed that the latter complexes and protects the product **141** from further base degradation. A related example is the complexed trione **142** which can be refluxed with excess magnesium methoxide for 24 h yet recovered unchanged on work-up. A similar case is the complexed trione ester **143** which also does not have suitable geometry for cyclisation.

Treatment of 3-acetyl-5-methoxycarbonyl-6-methylpyrone **131** with 12 equivalents of sodium



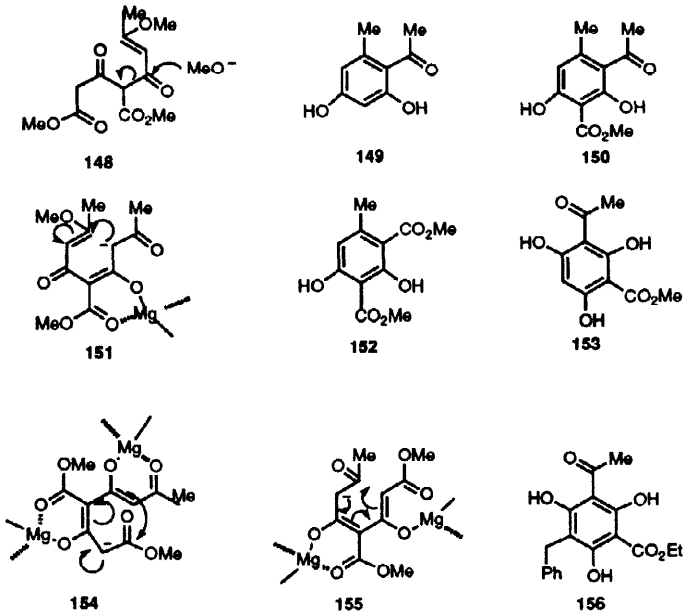
Scheme 30. Pyrones and methanolysed 'equivalents' studied.



methoxide.gave a 61% yield of the *o*-hydroxyester **144** and its corresponding acid formed by aldol condensation from the glutaconate available by opening the pyrone. By contrast, when treated with excess magnesium methoxide, the pyrone gave a 4:1 mixture of aldol **144** and Claisen **145** products. None of the latter was formed in the sodium methoxide reaction. Neither product appeared until > 1 mol of $Mg(OMe)_2$ was used, confirming that the first mol is used for complexation. Two pathways leading to aromatic products are now available: aldol condensation **146** to give **144** and Claisen condensation **147** to give **145** with the chelate system providing screening against a role as an aldol acceptor.

When the α,γ-bispyrone **132** [42,43] was refluxed with sodium methoxide in methanol, aliphatic cleavage (**148**) took place and the main product was methyl triacetate **140** (52%) together with aliphatic degradation products. Very little cyclised aromatic material was formed. On the other hand similar treatment with magnesium methoxide produced four aromatic products, the most prevalent (23%) being the acetyl resorcinol **149**, which along with **150**, may be derived from the chelated species **151** *via* internal Michael reaction. The carbon chain is protected from cleavage in the sense of **148** by magnesium chelation.

Refluxing the α,α-bis-pyrone **133** [44] with sodium methoxide gave the resorcylic diester **152** as the major product (46%) but magnesium methoxide gave the Claisen-derived phloroglucinol ester **153** (55%) together with the aldol-derived **152**. Phloroglucinol **153** may be derived from complex **154** by means of Claisen condensation, while complex **155** might account for resorcinol **152**, the acetyl group not now being protected by chelation. The phloroglucinol **156**, analogous to **153**, was formed when the pyrone **134** was treated with magnesium, but not with sodium ethoxide.[40]



5.9. Magnesium methoxide as a Reagent: A Summary.

Magnesium methoxide, simply made by dissolving magnesium in dry methanol in the presence of a crystal of iodine, can be used without a blanketing gas: it is a mild reagent, cheap and easy to use on a large scale. Compared with alkyl magnesium halides the reagent has not received extensive attention. Prepared from magnesium methoxide in the usual way, the magnesium chelate of a β-diketone or β-ketoester shows high stability towards a refluxing solution of the reagent (cf. **141-143**) and base catalysed operations can sometimes be carried out elsewhere on a complex molecule in the presence of the protected β-dicarbonyl system.

The magnesium chelate formed from a β-keto-ester protects the carbonyl group from participation as the acceptor in aldol condensations (**74,75** and Scheme 20). By contrast, attack at the carbon of the complexed ester proceeds smoothly with displacement of alkoxide, a Claisen condensation (**70,71**). This leads to phloroglucinol or dihydroxyacetophenone oxygenation patterns in some subsequently formed aromatics (e.g. **153,107**). Resorcinols (e.g.**150**), but not phloroglucinols, may be formed by aldol or Michael-aldol mechanisms under sodium methoxide catalysis. Ester exchange is readily effected by using magnesium alkoxide (e.g. **4** to the methyl ester series in Scheme 24). In the presence of excess magnesium methoxide the magnesium derivative of a β-keto-ester forms an anion γ-to the ester group (e.g. **80,83,98**). This is a suitable donor in aldol condensation reactions (Scheme 20 and **122**).

Certain condensations lead, in the presence of sodium methoxide, to a thermodynamically stable product, but with magnesium methoxide as the base initially present, a kinetic product may sometimes be sequestered and isolated as the stable chelate (Scheme 21).

The geometry of magnesium chelates limits the conformational flexibility available to a carbon chain. This, combined with the altered reactivity of the chelate, can provide selectivity for one of a number of outcomes as illustrated in xanthyrone chemistry. Reactive centres of a molecule may be kept apart geometrically by magnesium chelation (e.g. **141-143**). On the other hand the geometry of the magnesium chelate leads to hydroxy-anilines from appropriate glutaconates in the presence of excess reagent (e.g. **98**), contrasting with behaviour towards sodium methoxide (Scheme 22).

The magnesium-chelated starting material is a quite different entity from the un-complexed, so it is hardly surprising that the nature of the products is affected. As indicated by experiments with simple chelates, positional chelate exchange must also be taken into account in substrates or products having multiple chelation sites: differential solubilities may also play a part. Compounds with more than a single chelation site may, in the presence of excess reagent, have more than one possible arrangement of magnesium chelated sites, but it is those arrangements which can lead to products that are significant.

Restrictions on the amount of magnesium methoxide initially added to a compound having more than one chelation site may lead to one product, but give a different product when more initial reagent is used (Scheme 24). The isolated first product obtained at lower magnesium methoxide concentrations is not necessarily converted into the later product just by adding further magnesium methoxide reagent (Scheme 24).

6. Concluding Remarks.

Although from the perspective of a century ago Claisen could not explain his accurate experimental observations, and it was 67 years before xanthophanic and glaucophanic enols were correctly formulated, his work was eventually responsible for initiating some interesting and varied heterocyclic chemistry. Not least, the work on magnesio-chelated enolates is of general application and usefulness when applied to appropriate organic systems.

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Biographical sketch

Leslie Crombie was born in York and brought up in Southern England. He took his B.Sc.degree with first class honours at Portsmouth Municipal College (now Portsmouth University) as a part-time external student of the University of London, and his Ph.D. degree from Kings College, University of London. He held successively appointments as lecturer at Imperial College, London, Reader at Kings College, London, and Professor at the University of Wales, Cardiff. He was then appointed to the Sir Jesse Boot Chair of Organic Chemistry at the University of Nottingham where he is now Emeritus Professor. He was elected to the Royal Society in 1973. Professor Crombie has published some 400 scientific papers, mainly in the Natural Products area covering structure, stereochemistry, synthesis and biosynthesis and frequently using isotopic methods. Some of the natural products are the pyrethrins, rotenoids, mammeins, lipid amides and fatty acids, cannabis, alkaloids of khat and the homaline group, phorbol, various terpenes and natural fungicides. Apart from xanthophanic and glaucophanic enols, some non-natural product interests are carbon suboxide, allene-cyclopropanes, catalytic hydrogenation and cyclic β-halogeno-ether scissions.

Professor Crombie has held various lectureships and awards from the Royal Society of Chemistry and the Phytochemical Society of Erope, and is the current recipient of the American Chemical Society International Award for Research in Agricultural Chemistry.