CHEMISTRY OF COUMARINS

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Outline

1.0 Introduction

2.0 Reactions of Coumarins (Benzopyran-2-ones)

2.1 3:4-Fused Coumarins
2.2 Cycloaddition Reactions
2.3 Dibenzo-α-pyrones
2.4 Heterocyclic Coumarins
   2.4.1 Furocoumarins
   2.4.2 Isocoumestan
   2.4.3 Pyranocoumarins
   2.4.4 Chromenocoumarins (Chromans)
   2.4.5 Coumarino-α-pyrone
   2.4.6 Coumarino-γ-pyrone
   2.4.7 Coumarino Coumarins
   2.4.8 Chromones

3.0 Synthesis of Coumarin Heterocycles

3.1 5-Membered Coumarin Heterocycles with One Nitrogen Atom, e.g., Indoles
3.2 6-Membered Coumarin Heterocycles with One Nitrogen Atom, e.g., Coumarinopyridines, Coumarinoquinolines
3.3 5-Membered Coumarin Heterocycles with Two Nitrogen Atoms, e.g., Pyrazoles
3.4 6-Membered Coumarin Heterocycles with Two Nitrogen Atoms, e.g., Pyridazines, Pyrazines
3.5 5-Membered Coumarin Heterocycles with One Oxygen, One Nitrogen and One Sulphur Atom, e.g., Isothiazoles, Thiazoles
3.6 5-Membered Coumarin Heterocycles with One Oxygen and One Nitrogen Atom, e.g., Oxazoles, Isoxazoles, Oxazines
3.7 5-Membered Coumarin Heterocycles with One Oxygen, One Nitrogen and One Sulphur Atom, e.g., Isothiazoles, Thiazoles
3.8 6-Membered Coumarin Heterocycles with One Sulphur and One Nitrogen Atom, e.g., Thiazines

4.0 Naturally Occurring Coumarins
5.0 Biologically Active Coumarins
6.0 Photosensitive Coumarins
7.0 Summary
8.0 Acknowledgement

1.0 Introduction

Coumarins (benzopyran-2-ones) constitute an important class of naturally occurring compounds; they are widely used in the perfume, cosmetic, agrochemical and pharmaceutical industries. Several coumarin derivatives have been synthetically prepared and reported to possess cardiovascular, ageing, antibacterial and photosensitive properties. The chemistry of coumarins has received much attention and is used by chemists to develop several useful products.

2.0 Reactions of Coumarins (Benzopyran-2-ones)

The chemistry of coumarins has centered on performing reactions at the activated C-3,4-double bond of the α,β-unsaturated lactone. Based on this chemistry, heterocyclic
systems have been built. Coumarins with the desired aromatic substitution were built by synthesis starting from appropriate starting material and/or by electrophilic or nucleophilic substitution.

2.1 3:4-Fused Coumarins

Reaction of 3-acetylcoumarin (1, \(X_1 = \text{COCH}_3\)) with phenacyl halide\(^1\)\(^,\)\(^2\) in the presence of NaOEt, according to the procedure of Widman et al.\(^1\) gives 3,4-phenacylidene-3-acetylcoumarin (2, \(X_1 = \text{COCH}_3\)) due to insertion\(^3\) of methylene across the C-3,4-double bond; the product is a 3,4-dihydrocoumarin derivative [Figure I].

2.2 Cycloaddition Reactions

The photodimers of coumarin have been known for nearly 60 years. These have been of interest as furocoumarins, and are known to react with the skin in the presence of light. They have been used for the treatment of skin depigmentation. Photochemical reaction\(^4\)\(^,\)\(^5\)\(^,\)\(^6\)\(^,\)\(^7\) across the double bond of coumarins (1, \(X = \text{H}\)) is reported to give four\(^4\)\(^\text{-}\)\(^10\) and six membered\(^11\)\(^,\)\(^12\) 3,4-dihydrocoumarin dimers 3 and 4, respectively, due to (2+2) and (2+4) cyclo-addition reactions as shown in [Figure I].
2.3 Dibenzo-α-pyrnes

The preparation of 3:4-fused 5-member ring coumarins have been accomplished mostly by two protocols. The first and popular one is condensation of the appropriate phenol with cyclopentanone-2-carboxylate under Pechmann condensation reaction conditions as depicted in [Figure II]. Phenols $5^{13-16}$ bearing various substituents (Me, HO, COOH) at C-2 and C-5 were condensed with cyclic β-ketoesters $6^{17,18}$ (n = 1) by use of POCl$_3$ or H$_2$SO$_4$ to give 1, 2, 3, 4-tetrahydro cyclopetta [c][2] benzopyran 7 (n = 1) derivatives [Figure II]. Pechmann reaction conditions leading to the synthesis of colchicines have been reported.$^{19,20}$ In the second approach, straight chain β-ketoesters $8$ were condensed with phenols $5$, initially resulting in propionic acid residue at C-4; cyclization followed by reduction gives the 5-membered ring containing coumarins $7^{21,22}$ (n = 1) [Figure II].

In an analogous way, the corresponding six membered ring containing coumarins $7$ (n = 2) have been prepared by Pechmann condensation. Thus, reaction of various phenols $5$ with ethyl cyclohexanone-2-carboxylate $6$ under acidic conditions$^{7,8,9,10-12}$ gives tetrahydrodibenzo-α-pyrnes $7^{13, 15, 16, 23-30-33}$ (n = 2) [Figure II] in yields ranging from 5 to 75 %.
Condensation of phenols 9 with \( o \)-halobenzoic acid (10, \( Y = \text{Br} \)), catalyzed by copper salts, gives fair yields of dibenzo-\( \alpha \)-pyrones 11\textsuperscript{34} as shown in [Figure III]. Ethanol has been found to be a suitable solvent for the reaction of 2-chloro-,\textsuperscript{34} 2-bromo-\textsuperscript{34} and 2-bromo-4-methyl benzoic acid.\textsuperscript{35-37} The yield of 11 decreased in the order 2-bromo->2-chloro-> 2-iodobenzoic acid.\textsuperscript{38} The condensation reaction of phenols 9 with diazoanthranilic acids \( (10, Y = \text{N}_2^+ \) ), demethylative cyclization of 2-methoxy-2’-carboxybiphenyl\textsuperscript{42,43} 12 and oxidative cyclization of 2’-carboxy biphenyl 13\textsuperscript{44} gives dibenzo-2-pyrones 11 [Figure III]. For oxidative cyclization, chromic acid\textsuperscript{44}, \( \text{I}_2/\text{CCl}_4 \), and peracetic acid\textsuperscript{44} are added to silver salts of biphenyl carboxylic acids. Oxidation was also effected by use of aroyl peroxides,\textsuperscript{44,45,46} cobalt-(II)-catalyst/molecular oxygen and di-tert-butylperoxide,\textsuperscript{47} \( \text{Pb(IV)OAc} \textsuperscript{48} \) and \( \text{K}_2\text{S}_2\text{O}_8 \textsuperscript{49,50} \) [Figure III]. The potassium salt of 2’-nitrophenyl-2-carboxylate 13 (\( X=2’\)-NO\textsubscript{2} ) gives 11(\( X=1\)-NO\textsubscript{2} ), due to facile intramolecular displacement\textsuperscript{45a}. The presence of fluorine or bromine in place of the nitro group gives lower yields of 11. Among other methods, dehydrogenation of 3:4-cyclohexenocoumarins 14 by \( \text{Pd/C} \textsuperscript{51} \) and Baeyer-Villiger oxidation\textsuperscript{52} of fluorenones gives 11.\textsuperscript{43} The reaction of 2-methoxycarbonyl-1,4-benzoquinone 15 with substituted phenols 16 catalyzed by acid in regiospecific way gives substituted dibenzo-\( \alpha \)-pyrones 17.\textsuperscript{53} Regiospecific cyclization leading to the formation of 3-chloro-dibenzo-\( \alpha \)-pyrone 17 (\( X = 3\)-Cl; A, B, C = H) has been reported.\textsuperscript{53}
Reaction of 3-methoxycoumarin derivative 18 with primary amine and acetone gives dibenzo-α-pyrone derivative 17.\(^{43}\) Cycloaddition reaction (2+2) of 3-cyano/ethoxycarbonyl coumarin derivative 19 with diene 20 (xylene/heat) followed by dehydrogenation (Pd/C) gives dibenzo-α-pyrone 11 [Figure III]. Oxidation of dibenzopyran derivative 21 with CrO\(_3\) or H\(_2\)O\(_2\)/AcOH gives 11.\(^{40}\)

Cycloaddition of 4-vinyl coumarin derivative 22 with maleic anhydride (23, \(Y = \text{O}\)) and maleimide (23, \(Y = \text{N}\)) separately (xylene/heat) gives the coumarin adducts 24 and 25,\(^{54}\) respectively as shown in [eq 1].
2.4 Heterocyclic Coumarins

2.4.1 Furanocoumarins

Coumarins bearing a heterocyclic system fused at C-3, 4 have been prepared. Heteroatoms such as oxygen, nitrogen, sulphur or combinations thereof have been incorporated into the heterocycle. A five-membered ring containing oxygen atoms can fuse to C-3,4 of coumarin in two possible ways to form furan isomers. Both the isomers can be prepared, starting from 3- or 4-hydroxycoumarin, or directly by decarboxylation of carboxy derivatives as shown in [Figure IV].

Condensation of two moles of 4-hydroxy coumarin derivative 26 with one mole of α-chloro acetaldehyde diethyl acetal gives\(^55\) 3-(hydroxycoumarin-3-yl)-[3,2-b] dihydrofuranyl coumarin 27. Two moles of 26 condenses with one mole of oximino acetone and\(^56\) undergoes dehydration (Ac\(_2\)O/NaOAc) to give furano coumarin derivative 28. A similar reaction of 26 with glycerol gives the hydroxymethyl analog 29.\(^57\) A-ring-fused furan derivative 30 was obtained from 3-propargyl-4-hydroxy coumarin derivative (26, \(R = CH_2CH=CH\)) due to addition followed by dehydration\(^58\). Alternatively, the furan derivative 30 was obtained from the 4-\(O\)-allyl coumarin derivative 31 by Claisen migration.\(^59-61\) Reaction of 3-phenylcarbonyl coumarin 26 (\(R = CO\text{COPh}\)) with acetone, followed by treatment with alkali (NaOH/EtOH) and Cu/quinoline, gives substituted furano coumarin 30\(^62\) (\(R_1 = COOEt, COOH, H; R_2 = C_6H_5; X = H, Me\)).
Reaction of the 3-β-hydroxymethyl-4-hydroxycoumarin derivative 32 gives the dihydropyran derivative of coumarin on reaction with HCl/MeOH. Bromination (NBS) followed by elimination of HBr gives the furano coumarin 30\textsuperscript{63, 64} (R\textsubscript{1} = R\textsubscript{2} = X = H) [Scheme IV]. The same product, α,β-unsaturated pyrone 30, was also obtained by condensation of 4-hydroxy succinic acid in conc. H\textsubscript{2}SO\textsubscript{4}. Treatment of the pyrone with NBS gives the corresponding 3-bromo derivative 33. The bromo derivative 33, on treatment with alkali, gives furan-α-carboxylic acid derivative 34 which, on decarboxylation (Cu/quinioline) at 240°C, gives the furano coumarin derivative 30\textsuperscript{65-69}.

\textbf{2.4.2 Isocoumestan}

Pechmann condensation of ethyl 3-oxo-2,3-dihydrobenzofuran-2-carboxylate derivative 35 with resorcinol 36 (X = 3-HO) using 85% aq. H\textsubscript{2}SO\textsubscript{4} gives 9-hydroxybenzofuro[2,3-c][1]benzopyran-6-one 37\textsuperscript{70-72} (isocoumestan) as shown in [eq 2]. 3-Hydroxy coumarin 38, on dehydrogenative coupling with catechol 39 in NaOAc/KIO\textsubscript{3} in acetone, gives isocoumestan 40\textsuperscript{72} as depicted in [eq. 3].

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2.4.3 Pyranocoumarins

A number of pyranocoumarins have been readily synthesized from 4-hydroxycoumarin 41 [Figure V]. Michael addition of 4-hydroxycoumarin 41 to \( \alpha,\beta \)-unsaturated ketones or aldehydes (pyridine/reflux) followed by cyclization in \( R_4\)-OH/HCl gives various hemiacetals of pyranocoumarins 42.\(^{73-78}\) Many of these compounds have anti-coagulant properties. In a similar way, condensation of 4-hydroxyxoumarin 41 with unsaturated nitriles 43 gives 2-imino-3-ethoxy carbonyl pyranocoumarins 44.\(^{79}\) Reaction of 41 with cinnamyl bromide 45 gives 3-alkylated coumarin derivative which, on reaction with bromine in CHCl\(_3\), yields 2-phenyl-3-bromo pyranobenzopyran 46.\(^{80}\) Warfarin 47 on reflux in Ac\(_2\)O/HClO\(_4\) gives the corresponding acetal 48 (20%) and pyran 49\(^{81}\) (50%).
2.4.4 Chromenocoumarins (Chromans)

Chromenocoumarins have been prepared by i) Pechmann condensation, ii) Michael addition of coumarins to α,β-unsaturated ketones, iii) condensation of Mannich bases, and iv) condensation reactions of aromatic aldehydes as shown in [Figure VI].

Thus, Pechmann reaction of resorcinol with 3-hydroxy-6,7-dimethoxy-A3-chromene-4-carboxylate in 85% H₂SO₄ gives chromenocoumarin. In the second method, Michael addition of 4-hydroxycoumarin 41 to α,β-unsaturated ketones 50 in pyridine gives 6-oxo-7-acetonylbenzopyrano-[4,3-b][1]benzopyran 51b. In the third method, reaction of 4-hydroxycoumarin 41 with HCHO/PhCH₂NH₂ gives Mannich base 52 which, on heating...
with phenol, gives coumarinochroman 53.\textsuperscript{84} In the fourth method, reaction of 41 with aldehydes such as citral, citronellal 54 in pyridine, gives chromenocoumarin 55.\textsuperscript{84} Reaction of two moles of 41 with glyceraldehydes 56 by refluxing in dioxane gives chromenocoumarin 57\textsuperscript{[Figure VI]}, and on reaction with \(o\)-chlorobenzaldehyde derivative 58, by first refluxing in ethanol and then heating to 200\(^\circ\)C in xylene, gives chromenocoumarin 59.\textsuperscript{85} Under similar reaction conditions, heterocyclic chromenocoumarins containing nitrogen 60 have also been prepared\textsuperscript{85-85} by reaction of 41 with 2-pyridine-2-aldehyde derivatives 61. Reaction of 41 with \(o\)-halophenol 62 in pyridine followed by reflux in MeOH/HCl gives chromenocoumarin 63 in good yield.\textsuperscript{73} The same product has also been prepared by reaction of 41 (HCl and POCl\(_3\)) with hydroxyl \(\alpha\)-phenyl ethyl alcohol 64\textsuperscript{88} as shown in [Figure VI].
2.4.5 Coumarino-α-pyrones

Coumarino-α-pyrones have been synthesized by: i) condensation of o-hydroxyphenylacetic acid with benzylpyruvic acid, ii) condensation of 4-hydroxycoumarin with either benzylidene malononitrile or malonic acid under Pechmann conditions, iii) cyclisation of 4-hydroxycoumarin-3-propionic acid, and iv) by acylation of 3-acyl-4-hydroxycoumarin as shown in [Figure VII]. Condensation of 4-hydroxycoumarin (41) with benzylidene malononitrile 65 in pyridine and AcOH/HCl/Ac₂O gives 4-phenylcoumarino-3,4-dihydro-α-pyrone 66.

Pechmann condensation of 41 with ethylacetoacetate (R = H) gives coumarino-α-pyrone 67, in the presence of condensing agents such as AlCl₃, 80% H₂SO₄ and POCl₃. Reaction of 41 with diaryl malonates 68 and AlCl₃, or malic acid 69 and cyanoacetic...
acid 70 catalyzed by acid, gives coumarino-\(\alpha\)-pyrones 71 and 72, respectively. Reaction of 4-hydroxy coumarin 41 with \(\alpha,\beta\)-unsaturated esters 73, catalyzed by piperidine and acetic acid, gives 74.\(^{92,93}\) Reaction of 4-hydroxy coumarin 41 with triethyl orthoformate in the presence of aniline gives 75.\(^{93b}\) Reaction of 41 with 2-acetyl diethyl malonate 76 in AlCl\(_3\)/C\(_6\)H\(_2\)NO\(_2\) at 110°\(\text{C}\) gives 77.\(^{90}\) Chlorine containing derivatives of coumarino-\(\alpha\)-pyrones (78, \(R_1 = R_2 = \text{Cl}\)) were prepared by reaction of 41 with hexachloroethylene 79 in AlCl\(_3\)/CS\(_2\).\(^{94}\) Several 3-cyano-3-carboethoxy and 3-carbamido coumarino-\(\alpha\)-pyrones 80 were prepared by reaction of 41 with the corresponding malonic acid derivatives 81 (\(X_1\)-CH\(_2\)-\(X_2\)) in pyridine at room temperature.\(^{95}\)
2.4.6 Coumarino-γ-pyriones

The synthesis of coumarino-γ-pyriones 82, 83 have been described by: i) Michael addition of 4-hydroxy-coumarin 41 to α,β-unsaturated carboxylic acids 84 or acid chlorides followed by cyclization in PPA to give dihydro-γ-pyriones 8296,97 as depicted in [Scheme VIII], ii) reaction of 2-acetyl coumarins 85 with acetic anhydride in the presence of NaOAc or KOAc,98-100 and iii) by reaction of 41 with ethylacetoacetate/CF3COOH.35a

Reaction of 41 with isoxazole 86 by refluxing in pyridine/CuCl2 gives coumarino-γ-pyrone 87, containing the isoxazole ring.101

2.4.7 Coumarino Coumarins:

Reaction of 3-hydroxyflavone with Ac2O/NaOAc, followed by photolysis, gives bis-3,3’-oxaaindane derivative 88 which, on oxidation with KMnO4, gives coumarino coumarins 89102 [Figure IX]. Alternatively, demethylative ring closure of 3-(2’methoxyphenyl)-4-ethoxycarbonyl coumarins 90 in pyridine/HCl also gives 88.103 A new synthesis of 88 has been described from 2, 2’-dimethoxydiphenyl succinonitrile 91 by reaction with pyridine hydrochloride at 210°C.103 A simple 3,3’-bis-oxaaindnone 92, on reduction with 10 % NaOH, gives 88.103 Condensation reaction of 4-hydroxycoumarin 41 with o-halobenzoic acid derivatives 93 in alkaline aq.CuSO4 gives 89.104

2.4.8 Chromones

Condensation of resorcinol 5 with coumarin 3-carboxylic acid chloride 94 under Friedel-Craft’s conditions (AlCl3/C6H5-NO2), followed by oxidation with Pb(IV)OAc/AcOH, gives chromone 95105 as shown in [eq 6]. Coumarino benzopyrans 96 on oxidation with (CrO3/AcOH) also gives 95.104,106

November 2008

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Oxidation of active methylene containing rotenone 97 by CrO$_3$/AcOH gives the oxidized product of rotenone 98 [eq 7].$^{106}$ Acid catalyzed reaction of isoflavone 99 with HBr/AcOH gives [1] benzopyrano-[3,4-b][1]benzopyran-6,12-dione 100 [eq 8].
3.0 Synthesis of Coumarino Heterocycles

3.1 5-Membered Coumarin Heterocycles with One Nitrogen Atom, e.g., Indoles

Pechmann reaction of resorcinol 5 and substituted resorcinol with pyrrolidine β-ketoester 101 and indole β-ketoester 102, separately in the presence of conc. H$_2$SO$_4$, gives the corresponding 7-(1,2-dimethylheptyl)-9-hydroxypyrrolo [3,4-c] benzopyran-4-one derivative 103 and 3-hydroxy[1]benzopyran[4,3-b]indol-6-one 104 as shown in [eqs 9 & 10], respectively. Reaction of 3-aminocoumarin 105 with NaNO$_2$/HCl (diazotization), followed by reduction with Sn(II)Cl, gives coumarin-3-yl hydrazine which, without isolation, reacts with various carbonyl compounds in a Fischer indole synthesis to yield [1] benzopyran [3,4-b]pyrrol-4(3H,4H)-one 106 [eq 11].

3.2 6-Membered Coumarin Heterocycles with One Nitrogen Atom, e.g., Coumarinopyridines, Coumarinoquinolines
Coumarins having 3:4-fused six membered heterocycles having one nitrogen atom have been reported.\textsuperscript{109,110} The best method developed reacts 4-(\(o\)-methylphenyl)-lutidine-3-carboxylic acid sulphate \textsuperscript{107} with AlCl\(_3\) in nitrobenzene to give 2,4-dimethyl[1]benzopyrano [3,4-c]pyridine-5-(2H)-one \textsuperscript{108} as shown in [Scheme X].\textsuperscript{114,109} The same compound \textsuperscript{108} has also been prepared by reaction of 3-acetylcoumarin \textsuperscript{109} with cyanoacetamide and acetone in a sealed tube.\textsuperscript{111} Reaction of \(o\)-cyano substituted 4-phenyl pyridine derivatives \textsuperscript{110}, on reflux in 48 \% aq. HBr, gives the corresponding coumarinopyridine \textsuperscript{108}.\textsuperscript{110,112} Reaction of 3-acetylcoumarin \textsuperscript{109} with cyanoethylacetate and a keto compound at 165\(^\circ\)C gives \textsuperscript{108}.\textsuperscript{113} Reaction of \(o\)-hydroxybenzaldehyde \textsuperscript{111} with dicyanomethane and a ketocompound by heating in NH\(_4\)OAc, followed by reaction with HCl, gives \textsuperscript{108}.\textsuperscript{114} Reaction of the flavonone derivative \textsuperscript{112} with a secondary amine in the presence of acid gives coumarinopyridines \textsuperscript{113}; the same product is formed on reaction of \textsuperscript{112} with cyanoacetamide.\textsuperscript{114}

Reaction of \textsuperscript{111} with 2-cyanoethyl acetate in NH\(_4\)OAc under refluxing conditions gives coumarinopyridine \textsuperscript{114}.\textsuperscript{115} Reaction of 3-coumarino derivative \textsuperscript{115} with \(N\)-[3-ketobutyl] pyridinium bromide \textsuperscript{116} in NH\(_4\)OAc/AcOH, followed by oxidation with CrO\(_3\), gives \textsuperscript{114}. Reaction of 3-aminocoumarin derivative \textsuperscript{117} with unsaturated compounds such as \(\beta\)-ethoxyacrylates \textsuperscript{118} [eq 12], propargylic ester \textsuperscript{119} [eq 13], and ethyl acetoacetate [eq 14] separately, under thermal conditions, gives coumarinopyridine-4-one derivatives \textsuperscript{120, 121 and 122}, respectively.\textsuperscript{116} 2-Aminocoumarins \textsuperscript{117} have been important substrates for preparation of coumarino pyridine derivatives \textsuperscript{123} [eq 15] by reaction with glycerol and H\(_2\)SO\(_4\).
Thus, reaction of 4-hydroxycoumarin 41 with anilines 124 and formaldehyde at high temperature (240°C/0.5 torr) gives dihydro coumarinoquinolines 125,121-123 when 3-amino-6-methoxypyridine 126 was used in place of aniline it gives 9-methoxy [1]
benzopyran[4,3-b][1,5]naphthyridine-6-one \textsuperscript{127}. Reaction of \textsuperscript{41} with \textit{o}-nitrobenzaldehyde derivatives in the presence of AcOH/NaOAc and Zn/AcOH gives coumarinoquinolines \textsuperscript{128} \textbf{[Figure XI]}\textsuperscript{125}. Refluxing 3-(2’-hydroxyaryl)-4-carboxyquinoline (\textsuperscript{129}, R = H) in pyridine hydrochloride gives coumarinoquinoline \textsuperscript{130}\textsuperscript{126,127}.

Several coumarino piperidone derivatives \textsuperscript{131} have been prepared starting from 3-carboethoxy coumarin \textsuperscript{132}. Thus, reaction of \textsuperscript{132} with several keto compounds (R\textsubscript{1}CH\textsubscript{2}COR\textsubscript{2}) and primary amines (R-NH\textsubscript{2}) or NH\textsubscript{4}OAc at 170\degree C gives coumarinopyridinones \textsuperscript{131} \textbf{[eq 16]}\textsuperscript{117}.

Pechmann condensation of resorcinol derivative \textsuperscript{133} with 4-carboethoxy-3-keto piperidine derivative \textsuperscript{134} in H\textsubscript{2}SO\textsubscript{4} or POCl\textsubscript{3} gives 3:4-fused coumarino piperidines \textsuperscript{135}\textsuperscript{118,119}. Mannich reaction of \textsuperscript{135} gives aminomethyl coumarino piperidine \textsuperscript{136} \textbf{[eq 17]}\textsuperscript{120}.
3.3 5-Membered Coumarin Heterocycles with Two Nitrogen Atoms, e.g., Pyrazoles

Reaction of 4-chloro-3-formyl coumarin 137 with phenylhydrazine [eq 18] and phenylsulfoxy coumarin 138 with diazomethane [eq 19] separately gives the corresponding coumarinopyrazoles 139 and 140, respectively.\textsuperscript{130,131} Coumarins bearing cyano, carboxamido and formyl substitutents at C-3 and halo at C-4 are suitable substrates for preparation of coumarinopyrazolines.

\begin{equation}
  \text{i) NH}_2\text{OAc, }170^\circ\text{C} \quad \begin{array}{c}
  \text{+ R}_1\text{CH}_2\text{COR}_2 (R_1 = \text{H, } \text{C}_6\text{H}_5; R_2 = \text{Me}) \\
  \text{+ R}_3\text{CH}_2\text{COR}_2 \\
  \text{+ R}_4\text{NH}_2 (R_1 = R_2 = \text{H, Me}; \\
  \text{R}_3 = 4\text{-Me-C}_6\text{H}_4)
  \end{array} \quad \rightarrow \quad \text{eq. 16}
\end{equation}

\begin{equation}
  \text{eq. 17}
\end{equation}

\begin{equation}
  \text{R}_4 = \text{n-C}_6\text{H}_{11}, \text{4-F-C}_6\text{H}_4(\text{CH}_2)-\text{CH}_2(\text{CH}_3) \\
  \text{R}_3 = \text{Me, C}_6\text{H}_2\text{CH}_2
\end{equation}

\begin{equation}
  \text{eq. 18}
\end{equation}

\begin{equation}
  \text{eq. 19}
\end{equation}

\begin{equation}
  137 R_1 = R_2 = R_3 = \text{H, Me, Cl}
\end{equation}

\begin{equation}
  138 \text{i) CH}_2\text{N}_2/\text{THF/0}^\circ\text{C} \quad \text{ii) heat} \quad \rightarrow \quad 140 R_1 = \text{Me, } R_2 = \text{H}
\end{equation}
3.4 6-Membered Coumarin Heterocycles with Two Nitrogen Atoms, e.g., Pyridazines, Pyrazines

Coumarino pyridazines have been prepared by several methods. Reaction of 4-hydroxycoumarino-γ-pyrone 141 with phenyl diazonium salt followed by cleavage with KOH gives 3-phenylpyridazine intermediate 142 which, on reaction with HBr, yields 1-phenyl[1]benzopyrano [4,3-c]pyridazin-5(4H)-one 143 [eq 23]. In another method, reaction of 3-formyl flavone 144 with cyanamide derivatives 145 in the presence of aq. NaOH gives 146. If one follows this by oxidation with CrO₃/pyridine, one obtains benzopyranopyrimidine 147 [eq 24].

\[
\begin{align*}
\text{141} & \xrightarrow{i) \text{PhN}_2\text{SO}_4} \text{142} \xrightarrow{\text{HBr}} \text{143} \\
\text{144} \text{ R = H, MeO} & \xrightarrow{\text{NaOH, } 70 \degree C} \text{145} \text{ X = H, MeS}
\end{align*}
\]

Reaction of 3,4,6-trichlorocoumarin 148 with o-phenylene diamine 149 in the presence of metallic Na, followed by heating in pyridine, gives 2-chloro[1]benzopyrano[3,4-b]quinoxalin-6-one 150 [eq 25]. Reaction of 3-(4-methylphenylsulphonyl)-coumarin 151 with NaN₃/DMF at 95 °C gives 1-benzopyrano [3,4-d][1,2,3] triazol-4-(1H)-one 152 [eq 26].

\[
\begin{align*}
\text{148} + \text{149} & \xrightarrow{\text{Na}} \text{150} \\
\text{151} & \xrightarrow{\text{NaN₃/DMF}} \text{152}
\end{align*}
\]
Reaction of 7-amino-3-phenylcoumarin with NaNO\textsubscript{2}/H\textsuperscript{+} gives the corresponding 7-diazo salt \textbf{154} which, on coupling with 3-aminocoumarin \textbf{153} followed by oxidation with CuSO\textsubscript{4}, gives fluorescent whitener coumarinotriazole \textbf{155} [eq 27].\textsuperscript{136}

\[ \text{eq 27} \]

3.5 5-Membered Coumarin Heterocycles with One Oxygen, One Nitrogen, and One Sulphur Atom, e.g., Isothiazoles, Thiazoles

3:4-Fused coumarinothiophene derivatives were prepared by Pechmann condensation\textsuperscript{119-119b} of substituted resorcinol with \(\beta\)-ketoesters and thio keto esters. They have also been prepared by reaction of \(o\)-hydroxybenzaldehyde derivatives with thiolactones\textsuperscript{137} or via 4-thiocoumarin derivatives.\textsuperscript{138}

Pechmann reaction of resorcinol \textbf{156} with cyclic thio \(\beta\)-ketoesters \textbf{157}, \textbf{158} separately on heating with acid gives the corresponding coumarinothiophenes \textbf{159} and \textbf{160},\textsuperscript{119} respectively [eq 28]. Alternatively, reaction of \(o\)-hydroxybenzaldehyde \textbf{161} with thiolactones \textbf{162}, \textbf{163} separately under acid catalyzed cyclization gives the corresponding coumarinothiophenes \textbf{164} and \textbf{165}, respectively. A similar reaction of \textbf{161} with benzothiolactone \textbf{166} gives the coumarinothiophene derivative \textbf{167}\textsuperscript{137} [eq 29].
eq. 28

\[
\begin{align*}
156 & \xrightarrow{\text{157} n=1,2} 159 \\
158 & \xrightarrow{\text{158} n=1,2} 160
\end{align*}
\]

eq. 29

\[
\begin{align*}
161 & \xrightarrow{\text{163} i) \text{HCl} \ ii) \text{E}_{5}N/\text{C}_{6}H_{5}NO_{2}} 164 \\
162 & \xrightarrow{\text{162}} 165 \\
166 & \xrightarrow{\text{i) Py/EtOH ii) DDQ}} 167
\end{align*}
\]

eq. 30

\[
\begin{align*}
168 & \xrightarrow{\text{H}_{3}\text{PO}_{4} / 200^\circ\text{C}} 169
\end{align*}
\]

R₁ = H, MeO;
R₂ = H, Cl
R₂ = H, Cl; R₃ = H;
R₂-R₃ = -(CH=CH)₂
3.6. 5-Membered Coumarin Heterocycles with One Oxygen and One Nitrogen Atom, e.g., Oxazoles, Isoxazoles, Oxazines

Reaction of 3-amino-4-hydroxycoumarin 170 either with acetic anhydride or aliphatic aldehydes in nitrobenzene gives 2-methylbenzopyrano [3,4-d]oxazol-4-one 171 [eq 31].

\[
\begin{align*}
\text{R}_1 &= \text{H, COMe; 7-CO}_2\text{Me; 8-Me} \\
&= \text{Ph, 4-HO.C}_6\text{H}_5; 3-\text{NO}_2\text{.C}_6\text{H}_4; \\
&= 2,4-\text{diCl.C}_6\text{H}_3, 3-\text{MeO.C}_6\text{H}_3.(4-\text{HO}) \\
\end{align*}
\]

Heating of 3-ethoxycarbonyl-4-hydroxycoumarins 172 with phenylhydroxyl amine at 150 °C gives a coumarinoisoxazole, namely, 2-N-phenylbenzo-pyrao [3,4-d] isoxazole-3,4-dione 173 [eq 32]. Refluxing substituted 4-chloro-3-formylcoumarins 174 (R = H) with hydroxylamine in NaOAc gives coumarinoisoxoles 175 [eq 33]. Reaction of 3,6-dichloro-4-(2-hydroxyethylamino)-coumarin 176, prepared from 3,4,6-trichlorocoumarin 148 and ethanolamine, in NaH/THF results in intramolecular cyclization yields 2-chlorobenzopyrano[3,4-b][1,4]oxazin-6-one 177 [eq 34].
4-Hydroxycoumarin 41\(^{143,144}\) on heating with hexamethylene tetramine at 180-190 °C or Schiff base in lactic acid\(^{144}\) separately gives 3,4-dihydro-1,3-oxazino[5,6-c][1,2]benzopyran-5-one derivatives 178 and 179, respectively [eq 35].

### 3.7 5-Membered Coumarin Heterocycles with One Oxygen and One Sulphur Atom, e.g., Isothiazoles, Thiazoles

Reaction of 2-methylcoumarino-γ-pyrone 181 with B\(_2\)S\(_3\)/CHCl\(_3\) initially gives 182. Further reaction with P\(_4\)S\(_{10}\)/toluene gives 8-methyl-5,10-dioxa-9,9a-dithia[9a,Siv]pentaleno[2,1-a]naphthalene-6-one 183; compound 181 itself is obtained
from 3-acetyl-4-hydroxycoumain 180. Further hydrolysis of 183 with H2SO4 gives 8-methyl-5,9-dioxa-9a,10-dithia[9a, Siv]pentaleno[2,1-a]naphthalene-6-one 184 as shown in [Scheme XII].

Scheme XII

Reaction of 4-mercaptocoumarin-3-carboxamide 185 with bromine in EtOAc at reflux gives benzopyrano[3,4-d][1,2]isothiazole-3,4-dione 186 [eq 36]. Electrolysis of 3-thioacetamidocoumarin 187 in CH3CN containing Et4N+ClO4- gives 2-methyl benzopyran[3,4-d][1,3]-thiazol-4-one 188 [eq 37].
3.8. 6-Membered Coumarin Heterocycles with One Sulphur and One Nitrogen Atom, e.g., Thiazines

Coumarinothiazines have been prepared starting from 4-hydroxy-41 and 3,4-dichlorocoumarin derivatives.135,147 Thus, reaction of 3,4,6-trichlorocoumarin 148 with 2-mercaptoethyl alcohol in NaOMe gives 3,6-dichloro-4-(2-mercaptoethylamino)-coumarin 189, which cyclizes in NaH/DMF to give 5-oxo[1]benzopyrano[4,3-b][1,4]thiazine 190 [eq 38].135 Heating of 2-mercaptoaniline 191 and 4-hydroxycoumarin 41 in DMSO at 140-145°C gives the coumarinobenzothiazine derivative 192 [eq 39].123 Ullmann-Fetvad Jian-type condensation of 4-hydroxycoumarin 41 with 5-aminobenzothiazole 193 and HCHO gives 12-oxo-chromeno [5,3-b] thiazolo [4,5-f] quinoline 194 [eq 39].147 4-Hydroxycoumarin-3-sulphonic acid 195 gives 2-methyl-5-oxo benzopyrano [4,3-e][1,2,4] thiaadiazine-4,4(3H)-dioxide 197 on reaction with acetamidine hydrochloride 196 [eq 40].
4.0 Naturally Occurring Coumarins

Aflatoxins (B1, B2, G1, G2, M1, M2) \(^{148-151}\) form a group of acutely toxic and extremely carcinogenic, hepatotoxic metabolites produced by some strains of *Aspergillus flavus*. Aflatoxin B1 has been synthesized, \(^{152}\) starting from 5-benzyloxy-4-methyl-7-methoxy coumarin 198, via the corresponding 4-formyl derivative [eq 41].
One of the yellow pigments isolated from the scent glands of beaver has been identified as urolithin-A \textbf{200} and urolithin-B \textbf{201}. Alternariol \textbf{202} is the first 3:4-benzocoumarin antibacterial agent of fungal origin isolated from \textit{Alternaria tenuis}.\textsuperscript{155,156} Benzocoumarins autumnariol \textbf{203} and autunnarriniol \textbf{204} isolated from bulbs\textsuperscript{157} constitute the flavored components of Shilajit. A furocoumarin glapalol \textbf{205}\textsuperscript{158,159} and a coumastan, namely coumasterol \textbf{206}, have been isolated, also. The accumulation of compounds known as phytoalexins (rotenonones, stemonone \textbf{207} and stemonal \textbf{208}) and the concomitant shifts in metabolism are believed to be the mechanism for disease resistance in plants.

\begin{equation}
\begin{align*}
\textbf{200} & \quad X = Y = HO; Z = H; R_1 = R_2 = R_3 = H \\
\textbf{201} & \quad X = Y = H; Z = HO; R_1 = R_2 = H; R_3 = HO \\
\textbf{202} & \quad X = Z = H; Y = H; R_1 = Me; R_2 = R_3 = H \\
\textbf{203} & \quad X = Z = HO; Y = H; R_1 = Me; R_2 = R_3 = H \\
\textbf{204} & \quad X = Z = HO; Y = H; R_1 = Me; R_2 = OMe; R_3 = H
\end{align*}
\end{equation}

5.0 Biologically Active Coumarins

Several pharmacologically active coumarin derivatives have been invented and tested for various activities. Cyclocoumarol \textbf{209} is one of the most active anti-coagulants among the 106 synthetic compounds tested for the activity.\textsuperscript{160} Cyclocoumarol has 60% of the activity of dicoumarol \textbf{210}. 4-Methyl-2,5-dioxo-3-phenyl-2H-5H-pyrano[3,2-c][1]benzopyran \textbf{211} exhibited considerable anti-coagulant activity.\textsuperscript{161} Many aromatic coumarin glycosides \textbf{212} bearing C-2 and C-3-alkoxy substituents were reported as anti-diabetic agents\textsuperscript{162} and bactericides.\textsuperscript{163} 7-(Bromomethyl)-4-(furan-3-yl) coumarin \textbf{213} was studied as an inhibitor of leukotriene biosynthesis for treatment of angina in preventing formation of atherosclerotic plagues,\textsuperscript{164} and as an anti-allergy compound.\textsuperscript{165}
4-Methoxy-coumarin derivatives 214 were reported as therapeutic agents for fibrosis, and 3-acyl-7-nitro-6,8-dialkyl coumarins 215 as plant growth regulating agents. 4-Methylcoumarins, bearing 7-\(O\)-alkyl- and/or aminoalkyl, hydroxyl alkyl, and 7-amino halo alkyl groups, were cited as cardiovascular agents; and 3-benzazolyl-7-aminoalkyl coumarins 216 have been reported as diagnostic probes for amyloid accumulation disease. 7-(2-Piperizinyl) coumarin derivatives were studied for treatment of pain, as were furo[3,2-g]4-hydroxy-9-alkenyl coumarin 217 derivatives as antibacterial agents.

In a study, 6,7-dihydroxy-8-(sulfoxyl)-coumarins were examined for treatment of oxidative stress, and \(\text{bis}\)-4-hydroxy coumarins for anticoagulant activity. \(\text{3,3}'-(4-\text{Chlorophenylmethylene})\text{bis}\)-4-hydroxycoumarin 218 was the most prospective compound in the study. 6-Hydroxy-3,4-dihydrocoumarin 219 derivatives were studied for control of anti-ageing and their prospects as skin-lightening compounds.

### 6.0 Photosensitive Coumarins

Several coumarins were found to have the property of fluorescence. Notable among them are 2-chromone for skin composition, and 3-[4-bromoethyl] phenyl-7-(diethylamino)-
coumarins as fluorescent derivatization reagents for carboxylic acid in High Pressure Liquid Chromatography. Coumarins fused to naphthopyrans were reported as fluorescent brighteners; novel hetarylazo coumarins made from 4-hydroxycoumarins provided disperse dyes, and the derivatives from the reaction of 3-aryl-7-diethylamino coumarins with isatin served as fluorescent materials. 7-Amino-4-hydroxymethyl coumarins were used for making caged γ-Amino Butyric Acid (GABA) to investigate neuronal circuits in tissues and coumarins having tertiary amino group as photosensitive resins for PCBs. Chiral N-(coumarin-3-yl carbonyl)-α-amino acids have been prepared as fluorescent markers for amino acids and dipeptides.

7.0 Summary
A brief outline of chemistry done in the area of coumarins, almost for more than a century, has been reviewed to benefit the community of chemists and manufacturers of various commercial products.

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