# CHAPTER I

## GENERAL INTRODUCTION

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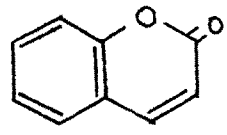
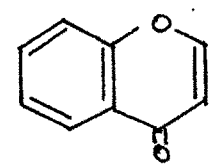
### Substitution in the coumarin ring system.

The fusion of a pyrone ring with a benzene nucleus gives rise to a class of heterocyclic compounds known as benzopyrones of which two distinct types are recognised : benzo-α-pyrones and benzo-γ-pyrones commonly known as coumarins and chromones respectively.



coumarin



chromone

Representatives of these groups of compounds are found to occur in the vegetable kingdom, either in the free or in the combined state. Coumarin, the simplest member of the benzo-α-pyrone group, is the sweet smelling constituent of woodruff, the tonkabean and the new mown hay. Several coumarin derivatives have been found to be widely distributed in the plant kingdom, particularly in the plants belonging to the natural orders of Orchidaceae, Leguminoceae, Rutaceae, Umbelliferae and Labiatae.

The coumarin ring system can give derivatives with substituents in either the benzenoid part or the heterocyclic part of the molecule. This can be realised by starting with

a suitable phenolic compound and building up the α-pyrone ring by one of the many methods available for the synthesis of coumarin derivatives ( See " The Chemistry of Coumarins " Sethna and Shah, Chem. Rev., 1945, 36, 1 - 62 ) or by substitution in the appropriate coumarin derivative. As the present work deals with the application of various substitution reactionson the different coumarin derivatives the previous work on the substitution in the coumarin ring system is briefly reviewed here.

Halogenation of Coumarin Derivatives

(A) Chlorination :

Perkin ( J. Chem. Soc., 1871, 24, 37 ) obtained 3-chlorocoumarin by passing chlorine in a solution of coumarin in chloroform. Halbedel and Heath ( U.S.Patent No. 2,466,657-1949, April 5 ; C.A., 1949, 43, 7513 ) obtained 3-chloro-coumarin by treating coumarin in carbon tetrachloride solution with chlorine at 72° and heating with rapid agitation the dichloride formed at 90° with sodium bicarbonate solution. Fries and Lindemann ( Ann., 1914,, 53, 404 ) chlorinated 7-hydroxy-4-methylcoumarin in acetic acid and assumed the product formed to be the 8-chloro derivative. Dey and Radhabai ( J. Indian Chem. Soc., 1934, 11, 635 ) chlorinated 7-methylcoumarin-4-acetic acid and obtained 7-methylcoumarin-4-chloroacetic acid along with 7-methyl-4-chloromethylcoumarin. 6-Methylcoumarin-4-acetic acid gave similar results. 1,2-Naphtha-α-pyrone-4'-acetic acid however gave the 3'-chloro- derivative. Mentzer and Meunier ( Compt.rend.,

1947, 225, 1329 ; C.A., 1948, 42, 2599 ) chlorinated 4-hydroxycoumarin and obtained the 3-chloro derivative. Seshadri et al. ( J. Sci. Ind. Research India, 1952, 11B, 50 ) chlorinated 7-hydroxy-4-methylcoumarin, its methyl ether and acetyl derivative and obtained the corresponding 3-chloro derivatives. They also obtained 7-hydroxy-3,6,8-trichloro-4-methylcoumarin by using excess of chlorine and heating the reaction mixture on a steam bath.

(B) Bromination :

The bromination of coumarin derivatives has been very extensively studied. Perkin ( J. Chem. Soc., 1870, 23, 368 ) made the first attempt to brominate coumarin and obtained various bromocoumarins to which he did not assign any structures. Simonis and Wenzel ( Ber., 1900, 33, 421 ) prepared 3,6,8-tribromocoumarin by the direct bromination of coumarin. Read and Reid ( J. Chem. Soc., 1928, 745 ) obtained 6-bromocoumarin by the action of bromine water on coumarin. In the course of their investigations on the reactivity of the double bond in coumarin Seshadri and Rao ( Proc. Indian Acad. Sci., 1936, 4A, 162 ) obtained 3,6,8-tribromocoumarin by the action of bromine in acetic acid on 3,6,8-triacetoxymercuri-4-methoxymelilotic anhydride.

Peters and Simonis ( Ber., 1908, 41, 830 ) brominated 4-methylcoumarin and obtained 3-bromo-, 3,6-dibromo- and 3,6,8-tribromo derivatives. Fries and Fickewirth ( Ann., 1908, 362, 49 ) brominated 4,7-dimethylcoumarin and obtained the 3-bromo derivative. Seshadri et al. ( Proc. Indian Acad. Sci.,

1939, 9A, 22 ) obtained the 3,6-dibromo derivative of 4,7-dimethylcoumarin. Jordan and Thorpe ( J. Chem. Soc., 1915, 107, 38 ) brominated 4,5,7-trimethylcoumarin in chloroform and obtained the 3-bromo derivative. Dey and Radhabai ( J. Indian Chem. Soc., 1934, 11, 635 ) studied the action of bromine on 7-methylcoumarin-4-acetic acid. They obtained 7-methylcoumarin-4-bromoacetic acid along with 7-methyl-4-bromomethylcoumarin. A number of other coumarin-3- and 4-acetic acids have been brominated by the same authors and the bromination was found to take place at the methylene group. Only in the case of 2,1-naphtha-α-pyrone-4'-acetic acid it was found that bromination takes place at the ethenoid linkage and not at the active methylene group.

Several hydroxycoumarins have been brominated. Fries and Nohren ( Ber., 1925, 58B, 1027 ) brominated 7-hydroxy-coumarin ethyl carbonate and obtained the 3-bromo derivative. The bromination of 7-methoxycoumarin was carried out by Will and Beck ( Ber., 1886, 19, 1777 ) who obtained the 3-bromo derivative and a dibromo derivative to which they did not assign any structure. Fries and Lindemann ( Ann., 1914, 404, 53 ) brominated 7-hydroxy-4-methylcoumarin and assigned the 8-bromo structure to it as they found it was different from the 6-bromo derivative which they synthesised from 4-bromo-resorcinol. This was later disproved by Dalvi and Sethna ( J. Indian Chem. Soc., 1949, 26, 359, 467 ) who found this compound to be the 3-bromo derivative. Fries and Nohren( loc. cit. ) obtained the 3-bromo derivative from 7-hydroxy-4-

methylcoumarin ethyl carbonate. Masaiti and Yanagita ( Ber., 1938, 71B, 2269 ) brominated 7-hydroxy-4,6-dimethyl-8-ethyl-coumarin and obtained the 3-bromo derivative. Desai et al. ( Proc. Indian Acad. Sci., 1937, 6A, 185 ; 1938, 8A, 194 ) obtained 3-bromo derivatives from 6-acetyl and 6-propionyl-7-hydroxy-4-methylcoumarin and 8-acetyl-6-ethyl-7-hydroxy-4-methylcoumarin. Limaye et al. ( Rasayanam, 1936, 48 ; 1938, 136 ) brominated 7-hydroxy-8-acetyl-4-methylcoumarin and obtained the 3-bromo derivative. They also brominated 7-methoxy-4-methylcoumarin and obtained the 3-bromo derivative and a dibromo derivative to which they did not assign any structure. Pechmann and Graeger ( Ber., 1901, 34, 378 ) brominated ethyl-7-hydroxycoumarin-4-carboxylate in chloroform and assumed the position of the bromine atom to be 8. Dalvi and Sethna ( J. Indian Chem. Soc., 1949, 26, 359, 467 ) studied the bromination of 7-hydroxy-4-methylcoumarin, methyl-7-hydroxy-4-methylcoumarin-6-carboxylate, 7-hydroxy-4-methylcoumarin-6-carboxylic acid and their methyl ethers under different conditions. They found that the first bromine atom in all cases, where the monobromo product could be isolated, entered the 3-position. Further bromination of 7-hydroxy-4-methylcoumarin gave the 3,6-dibromo derivative in preponderating yield along with the 3,8-dibromo isomer in a very small yield. Further bromination of 7-methoxy-4-methyl-coumarin yielded only the 3,6-dibromo isomer.

Seshadri et al. ( J. Sci. Ind. Research India, 1952, 11B, 39, 56 ) brominated 7-hydroxy-4-phenylcoumarin and obtained the 3-bromo-,3,6- and 3,8-dibromo- and the 3,6,8-tribromo

derivatives. Its methyl ether yielded the 3-bromo and the 3,6-dibromo derivatives. 7-Hydroxy-3-phenyl- and 7-hydroxy-3-phenyl-4-methylcoumarin on bromination with one mole of bromine gave the 6-bromo derivatives in preponderating yield along with the 8-isomer. With two moles of bromine both yielded the 6,8-dibromo derivatives. With excess of bromine 7-hydroxy-3-phenylcoumarin yielded 7-hydroxy-3-( p-bromophenyl )-6,8-dibromocoumarin.

Borsche ( Ber., 1907, 40, 2731 ) brominated 6-hydroxy-4-methylcoumarin with two moles of bromine and assigned the 5,7-dibromo structure to the product obtained. This has been disproved by Dalvi and Sethna ( loc.cit. ) who found that the first bromine atom entered the 3-position. On further bromination 6-hydroxy-4-methylcoumarin gave the 3,5-dibromo and the 3,7-dibromo compounds while its methyl ether gave only the 3,7-dibromo derivative.

Dey and Kutti ( Proc. Natl. Inst. Sci. India, 1940, 6A, 641 ) brominated 8-hydroxycoumarin and its methyl ether. They found that the first bromine atom exclusively entered the benzene nucleus in 5-position.

Huebner and Link ( J. Am. Chem. Soc., 1945, 67, 99 ) brominated 4-hydroxycoumarin in chloroform solution and obtained 3-bromo-4-hydroxycoumarin. Anschutz et al. ( Ann., 1909, 367, 169, 270 ) obtained 4-chlorocoumarin and 4-bromocoumarin by the action of phosphorus pentachloride and phosphorus pentabromide respectively on 4-hydroxycoumarin. Trivedi and Sethna ( J. Org. Chem., 1960, 25, 1817 ) studied

the bromination of 3-hydroxycoumarin and obtained the 4-bromo derivative.

Sethna et al. ( J. Indian Chem. Soc., 1953, 30, 610 ) systematically studied the bromination of 5-hydroxy-4-methyl- and 5-hydroxy-4,7-dimethylcoumarin and their methyl ethers under different conditions. They found that the first bromine atom entered the 8-position. On further bromination, both the coumarins gave the 6,8-dibromo- and the 3,6,8-tribromo derivatives.

Bauer and Schoder ( Arch. Pharm., 1921, 259, 53 ) brominated 4,7-dihydroxycoumarin and assumed the position of the bromine atom to be 8. Tilden and Burrows ( J. Chem. Soc., 1902, 81, 510 ) obtained a dibromo derivative from 5,7-dimethoxycoumarin with excess of bromine to which they did not assign any structure. By heating the dibromo compound with bromine in a sealed tube they obtained the 3,6,8-tribromo derivative. Sakai and Kato ( J. Pharm. Soc. Japan, 1935, 55, 691 ; C. A., 1935, 29, 7311 ) brominated 7,8-dihydroxy-4-methylcoumarin and its methyl ether and in both cases obtained the 3-bromo derivatives. On further bromination they obtained a dibromo compound to which they arbitrarily assigned the 3,4-dibromo structure. Tilden and Burrows ( loc.cit. ) brominated 5,7-dimethoxy-3-methylcoumarin and arbitrarily assigned the 4-bromo structure. Lele and Sethna ( J. Sci. Ind. Research, India, 1955, 14B, 101 ) in their study of the bromination of some dihydroxycoumarin derivatives found that in the bromination of 4,7-dihydroxy[redacted]coumarin the

3-bromo derivative was obtained thus disproving the 8-bromo structure assigned by Bauer and Schoder ( loc.cit. ). They brominated 7,8-dihydroxy-4-methylcoumarin and its methyl ether and obtained the 3-bromo derivatives. On further bromination they got a dibromo product which they found was the 3,6- and not the 3,4-dibromo compound as reported by Sakai and Kato ( loc.cit. ). They brominated 5,7-dihydroxy-4-methylcoumarin and its methyl ether. From the former they obtained directly the 3,6,8-tribromo derivative while the 3,8-dibromo derivative was obtained from the later.

Dhar ( J. Chem. Soc., 1920, 117, 993 ) found that in the bromination of 6-nitrocoumarin the nitro group was replaced by the halogen atom and further halogenation took place readily with the formation of the tribromo and the tetrabromo derivatives. Dey and Row ( J. Chem. Soc., 1923, 123, 3375 ) brominated 6-nitrocoumarin and obtained directly the 3,8-dibromo-6-nitrocoumarin. They obtained 6-nitro-3-bromocoumarin by nitrating 3-bromocoumarin. 6-Nitro-4,7-dimethylcoumarin on similar bromination gave the 3,8-dibromo derivative. 6-Nitro-4'-methyl-1,2-naphtha-α-pyrone gave the 3'-bromo derivative.

Some work has been carried out using N-bromo-succinimide as the brominating agent and interesting results have been obtained. Molho and Mentzer ( Compt. rend., 1946, 223, 1141 ) obtained 3-( bromomethyl ) coumarin and 7-methoxy-3-bromo-4-methylcoumarin by the action of N-bromosuccinimide on 3-methylcoumarin and 7-methoxy-4-methylcoumarin, respectively. 7-Methoxy-

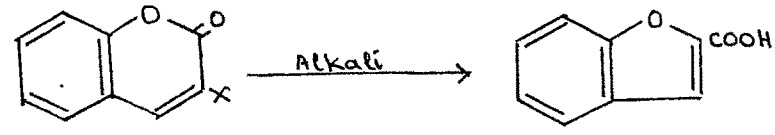
3-ethyl-4-methylcoumarin gave a mixture of 7-methoxy-3-( 1-bromoethyl )-4-methylcoumarin ( 60 % ) and 7-methoxy-6-bromo-3-ethyl-4-methylcoumarin ( 15 % ). Lacocq and Buu-Hoi ( Compt. rend.,1947,224, 937 ) studied the action of N-bromo-succinimide on methylcoumarins and found that it reacts only with methyl groups in the benzene ring and not with the methyl groups in the heterocyclic ring. Thus 6-methyl-, 4,6-dimethyl- and 4,7-dimethylcoumarin gave 6-bromomethyl-, 4-methyl-6-bromomethyl- and 4-methyl-7-bromomethylcoumarin respectively. Lacocq ( Ann.Chim.,1948,3,62 ) obtained 3-bromo-4-methylcoumarin from 4-methylcoumarin and N-bromosuccinimide. Molho and Mentzer ( Compt. rend., 1949, 228,578 ) observed halogen migration in certain brominations. Thus bromination of 3-ethyl- and 3-propyl-4-methyl-7-methoxycoumarin with N-bromosuccinimide gave 3-ethyl-6-bromo-, or 3-propyl-6-bromo-4-methyl-7-methoxycoumarin, the 3-( α-bromoalkyl ) compound being the intermediate.

(C) Iodination :

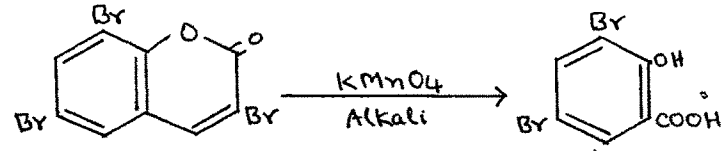
There was no work reported on the iodination of coumarin derivatives prior to the publication of the work described in this thesis.

Methods of proving the structures of halogenatedcoumarins

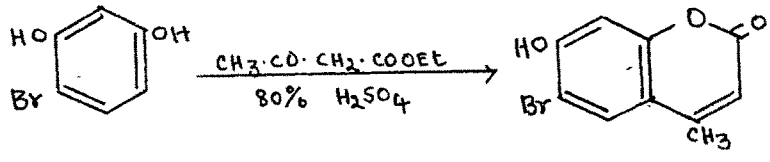
If a halogen atom is present in the 3-position in the coumarin a coumarilic acid is invariably obtained on alkaline hydrolysis.




The halogenated coumarins with halogen in the benzenoid part of the molecule are stable to the action of alkali. In such cases the oxidation of the halocoumarin may prove useful and a simple halogenated phenolic acid may be obtained. Peters and Simonis ( loc.cit. ) oxidised 3,6,8-tribromocoumarin with alkaline potassium permanganate and obtained 3,5-dibromosalicylic acid.




A better course than oxidation however, is to synthesise the halocoumarin required by starting with a suitably substituted halogenated phenolic derivative and building up the α-pyrone ring on the same by an appropriate reaction for the synthesis of coumarin derivative.



Nitration :

Morgan ( J. Chem. Soc., 1904, 85, 1233 ) obtained 6-nitrocoumarin by the nitration of coumarin with nitric acid in presence of acetic acid. Dey and Krishnamurty ( J. Indian Chem. Soc., 1927, 4, 197 ) found that in the nitration of coumarin both the 6- and the 8-isomers are formed. Clayton ( J. Chem. Soc., 1910, 97, 1388 ) observed that further nitration of 6-nitrocoumarin and 8-nitrocoumarin yielded first the 3,6-dinitro and 3,8-dinitrocoumarin respectively and then the 3,6,8-trinitrocoumarin. Clayton ( loc.cit. ) also studied the nitration of 7-methyl-,6,7-dimethyl- and 4,6,8-trimethyl-coumarin and obtained various nitro derivatives. The ease of nitration was found to increase with the introduction of alkyl groups. Nitration of coumarin with benzoyl nitrate was reported to give 5-nitrocoumarin ( Francis, Ber., 1906, 39, 3803 ).

Several hydroxycoumarins have also been nitrated. Pechmann and Obermiller ( Ber., 1901, 34, 666 ) nitrated 7-hydroxy-4-methylcoumarin and its methyl ether and obtained the 8-nitro derivative in the case of the former and the 6-nitro derivative in the case of the latter. Dey and Kutti ( Proc. Natl. Inst. Sci. India, 1940, 6A, 641 ) nitrated 8-methoxy- and 8-hydroxycoumarin and obtained the 5- and 7-nitro derivatives respectively. Borsche and Weinheimer ( Chem. Ber., 1952, 85, 198 ) nitrated 8-methoxycoumarin and obtained the 5,7-dinitro derivative. Parekh and Shah ( J. Indian Chem. Soc., 1942, 19, 335 ) nitrated 5-hydroxy-4-methylcoumarin and 5-hydroxy-4-methylcoumarin-6-carboxylic

acid and its methyl ester. From the former they obtained the 8-nitro- and the 6,8-dinitrocoumarin while the acid and the ester yielded the 8-nitro derivatives. Huebner and Link ( J. Am. Chem. Soc., 1945, 67, 99 ) obtained 3-nitro-4-hydroxycoumarin from 4-hydroxycoumarin. Using drastic conditions they obtained 3,6-dinitro-4-hydroxycoumarin.

Naik and Jadhav ( J. Indian Chem. Soc., 1948, 25, 171 ; J. Uni. Bombay, 1948, 16, 46 ) studied the nitration of 7-hydroxy-4-methylcoumarin ( I ), 7-hydroxy-3,4-dimethylcoumarin ( II ) and their methyl ethers and methyl-7-hydroxy-4-methylcoumarin-6-carboxylate ( III ) and its methyl ester. The nitration of ( I ) and its methyl ether yielded both the 6-nitro- and the 3,6,8-trinitro derivatives. The nitration of ( II ) yielded the 6,8-dinitrocoumarin derivative and the methyl ether of ( II ) yielded the 6-nitro derivative. In the nitration of ( III ) they obtained the 8-nitro- and the 3,8-dinitro derivatives. In the case of the methyl ether of ( III ) they obtained the 6-nitro derivative ( the carbomethoxy group having been replaced by the nitro group ) and methyl-7-methoxy-3,8-dinitro-4-methylcoumarin-6-carboxylate. In the nitration of 7-hydroxy-4-methylcoumarin-6-carboxylic acid they obtained 7-hydroxy-6,8-dinitro-4-methylcoumarin and 7-hydroxy-3,6,8-trinitro-4-methylcoumarin, the carboxyl group having been replaced by the nitro group in both the cases. Shah and Mehta ( J. Indian Chem. Soc., 1954, 31, 784 ) have shown that both the 6-nitro and the 8-nitrocoumarin derivatives are obtained in the nitration of 7-hydroxy-4-methylcoumarin.

Shah and Mewada ( Ber., 1956, 89, 2209 ) nitrated 6-hydroxy-4-methylcoumarin and its methyl ether. They obtained a mixture of the 5-nitro- and the 5,7-dinitro derivative from the former and the 5-nitro derivative alone from the latter.

Sulphonation :

Perkin ( J. Chem. Soc.,1873, 24, 37 ) sulphonated coumarin with fuming sulphuric acid and obtained monosulphonic acid at the temperature of steam bath and disulphonic acid at 150° but he did not establish the position of the sulphonic acid groups. Sen and Chakravarti ( J. Indian Chem. Soc., 1928, 5, 433 ) sulphonated coumarin and 6-nitrocoumarin and obtained the 6-sulphonic acid and the 3,6-disulphonic acid derivatives from the former and the 3-sulphonic acid from the latter. The structures were established by oxidation with alkaline permanganate to the known salicylic acid derivatives.Kruger ( Ber., 1923, 56B, 481 ) studied the sulphonation of some methylcoumarins and assumed that the sulphonic acid group entered the 6-position in each case. Rubtsov and Fedosova ( J. Gen. Chem. U.S.S.R.,1944, 14, 848 ; C.A., 1946, 40,1804 ) treated coumarin with chlorosulphonic acid and obtained coumarin-6-sulphonyl chloride. Huebner and Link ( J. Am. Chem. Soc., 1945, 67, 99 ) sulphonated 4-hydroxycoumarin with fuming sulphuric acid and obtained the 3-sulphonic acid derivative.

Merchant and Shah ( J. Indian Chem. Soc., 1957, 34, 35 ; ibid. 1957, 34, 45 ; J. Org. Chem., 1957, 22, 884 ) in an elegant study of the sulphonation of various 7-hydroxy-4-

methylcoumarins with substituents such as alkyl, bromo and carboxy in different positions obtained with chlorosulphonic acid the 6-sulphonic acid derivatives where the 6 position was free. When it was occupied by another substituent sulphonic acid group entered the 8 position. In the case of 6-nitrocoumarin however sulphonic acid group entered the 3 position. Using large amounts of chlorosulphonic acid they obtained the 3,6-disulphonic acid derivatives from coumarin and 7-methoxy-4-methylcoumarin. 7-Hydroxy-4-methylcoumarin and 7-hydroxy-3,4-dimethylcoumarin gave the 6,8-disulphonic acids. 7-Hydroxy-4-methylcoumarin also gave the 3,6,8-trisulphonic acid. The structures of the sulphonic acids were established by oxidation, bromination or nitration to the known compounds. In the case of 5-hydroxycoumarin derivatives they obtained the 8-sulphonic acid-, the 6,8-disulphonic acid- and the 3,6,8-trisulphonic acid derivatives. They observed that the 5-hydroxycoumarin derivatives are sulphonated more readily than the 7-hydroxy-coumarin derivatives. In all these dreactions, the sulphonyl chlorides were also isolated along with the sulphonic acids.

Formylation :

Sen and Chakravarti ( J. Am. Chem. Soc., 1928, 50, 2428 ) prepared 6-aldehydocoumarin by heating coumarin with aqueous potassium hydroxide and chloroform. Spath and Pailer ( Ber., 1935, 68, 940 ) observed that the Gattermann method and the Reimer-Tiemann method of introduction of formyl group in phenols proved unsuccessful in the case of hydroxycoumarins, but by using Duff and Bills hexamethylene tetramine method

( J. Chem. Soc., 1932, 1987 ; 1934, 1305 ) they obtained, in the case of 7-hydroxycoumarin, 7-hydroxy-8-aldehydocoumarin in 10 % yield. Rangaswami and Seshadri ( Proc. Indian Acad. Sci., 1937, 6A, 112 ) applied the same method to formylate 7-hydroxy-4-methylcoumarin and obtained 7-hydroxy-8-formyl-4-methylcoumarin and Sastri et al. ( Proc. Indian Acad. Sci., 1953, 37A, 681 ) formylated 6-hydroxy- and 6-hydroxy-4-methylcoumarin and obtained the corresponding 5-formyl derivatives.

Naik and Thakor ( J. Org. Chem., 1957, 22, 1626 , 1630 ) using this method obtained from 5-hydroxy-4-methyl- and 5-hydroxy-4,7-dimethylcoumarin the 6,8-diformyl derivatives. 7,8-Dihydroxy-4-methylcoumarin gave the 6-formyl derivative while 7,8-dimethoxy-6-hydroxy-4-methylcoumarin gave the 5-formyl derivative. Reactions with 5,7-dihydroxy-, 5,6,7-trihydroxy- and 7,8-dihydroxy-5-methoxy-4-methylcoumarin met with failures. They also studied the formylation of hydroxycoumarins with N-methylformanilide in presence of phosphorus oxychloride. 5,7-Dihydroxy-4-methylcoumarin gave the 8-formyl derivative while 5,7-dimethoxy-4-methylcoumarin gave both the 8-formyl as well as the 6-formyl derivatives. The formylation of 5,6,7-trihydroxy-4-methylcoumarin did not succeed but its trimethyl ether gave the 8-formyl derivative. The N-methylformanilide reaction with 5-hydroxy-4-methylcoumarin furnished the 6-formyl derivative while 5-hydroxy-4,7-dimethylcoumarin gave both the 6-formyl and the 8-formyl derivatives.

Zeigler and Maier ( Monatsh, 1958, 89, 787 )

formylated 4-hydroxycoumarin in chlorobenzene with N-methylformanilide in presence of phosphorus oxychloride and obtained the 3-formyl derivative.

o-Hydroxy formyl derivatives are of synthetical importance and various coumarino-α-pyrones have been prepared from them by the Knoevenagel reaction. The formyl group has also been replaced by the hydroxyl group by the action of hydrogen peroxide ( Naik and Thakor loc.cit. ).

Fries migration and Friedel-Crafts reaction :

Limaye ( Ber., 1932, 65, 375 ; 1934, 67, 12 ; Rasayanam, 1936, 20 ) carried out the Fries migration of various esters of 7-hydroxycoumarin derivatives and in all cases obtained the 8-acylcoumarin derivatives accompanied in some cases with traces of the 6-acyl isomer. Shah et al. ( J. Chem. Soc., 1938, 228, 1424 ; 1939, 1250 ) studied Fries rearrangement of 5-acetoxy-, 5-benzoyloxy-, 5-propionoxy- and 5-butyroxy-4-methylcoumarin and obtained the corresponding 6-acyl derivatives. Shah and Shah ( J. Indian Chem. Soc., 1942, 19, 481 ) studied the Fries migration of ethyl-7-acetoxy-4-methylcoumarin-3-acetate and obtained 7-hydroxy-8-acetyl-4-methylcoumarin-3-acetic acid.

Thakor and Shah ( J. Indian Chem. Soc., 1946, 23, 199, 234 ) investigated the Fries migration of 7-acetoxy- and 7-benzoyloxy-4-methylcoumarin with a view to investigate the effect of various factors on the migration. They observed that : 3 moles of aluminium chloride are necessary to effect the migration ; nitrobenzene as solvent faciliates the

reaction ; the acyl group predominantly occupies the 8-position in the nucleus and only traces of the 6-isomer are obtained ; the benzoyl group requires higher temperature for migration. They also studied the Fries migration of esters of 7-hydroxy-3-alkyl-4-methyl-6-ethylcoumarins and obtained the corresponding 8-acyl derivatives. Thakor ( Current Sci. India, 1951, 20, 234 ) studied the Fries rearrangement of 6-acetoxy- and 6-benzoyloxycoumarin and obtained the corresponding 5-acyl derivatives. Esters of 6-hydroxy-4-methylcoumarin did not rearrange. Friedel-Crafts acetylation and benzoylation of 6-hydroxycoumarin however proceeded readily to give 5-acyl derivatives.

Bhavsar and Desai ( J. Indian Chem. Soc., 1954, 31, 141 ) studied the Fries migration of 4-methylcoumarinyl-7-p-toluenesulphonate and obtained 8- and 6-p-toluenesulphonyl-4-methyl-7-hydroxycoumarin. The Fries migration of 4,7-dimethyl-5-coumarinyl-p-toluenesulphonate yielded the 6-p-toluene-sulphonyl derivative. Setalwad and Shah ( J. Indian Chem. Soc., 1954, 31, 600 ) studied Fries isomerisation of the acetyl and the benzoyl esters of 7-hydroxy-6-bromo- ( and -6-chloro )-4-methylcoumarin. They obtained the corresponding 8-acyl derivatives. Aleykutty and Balish ( J. Indian Chem. Soc., 1955, 32, 773 ) studied Fries rearrangement of 4-methyl-7-coumarinyl benzenesulphonate and obtained the corresponding 8-phenylsulphonyl derivative. When the isomerisation was effected in nitrobenzene the 6-isomer was also obtained along with the 8-isomer.

Evans and Robertson ( J. Chem. Soc., 1954, 4565 ) carried out Fries rearrangement of 5,7-diacetoxy-3-chloro-4-methylcoumarin using boron trifluoride and that of 5,7-diacetoxy-3-chloro-4,8-dimethylcoumarin using aluminium chloride and obtained the 8-acetyl derivative in the former and the 6-acetyl derivative in the later. Klosa ( Arch. Pharm., 1956, 289, 71 ; C.A., 1957, 51, 386 ) studied the Fries rearrangement of 4-acetoxy-,4-propionoxy and 4-butyroxycoumarin using several metal halides and obtained the corresponding 3-acyl derivatives. Sethna and Trivedi ( J. Org. Chem., 1960, 25, 1817 ) carried out Fries rearrangement of 3-acetoxycoumarin and obtained 3-hydroxy-4-acetylcoumarin. Friedel and Crafts reaction on 3-hydroxy-coumarin gave the same product.

Limaye ( loc. cit. ) obtained 7-hydroxy-4-methyl-8-benzoylcoumarin on Friedel-Crafts benzoylation of 7-hydroxy-4-methylcoumarin. Desai and Hamid ( Proc. Indian Acad. Sci., 1937, 6A, 257 ) failed to introduce the acyl group in 7-hydroxy-4-methylcoumarin by the Friedel-Crafts method using acetyl chloride in presence of aluminium chloride. Borsche and Hahn-Weinheimer ( Chem. Ber., 1952, 85, 198 ) prepared the 6-acetyl derivative from 8-methoxycoumarin by Friedel-Crafts acetylation. Parikh and Thakor ( J. Indian Chem. Soc., 1954, 31, 137 ) studied the Friedel-Crafts acetylation and benzoylation of 7-hydroxy-4-methyl-(I), 5-hydroxy-4-methyl-(II), 5-hydroxy-4,7-dimethyl-(III) and 5,7-dihydroxy-4-methylcoumarin (IV). In both acetylation and

benzoylation ( I ) gave the 8-acyl derivatives while ( II ) and ( III ) gave the 6-acyl derivatives. On acetylation ( IV ) yielded the 6-acetyl as well as the 6,8-diacetyl derivatives. In the case of benzoylation it gave the 6,8-dibenzoyl derivative only.

Robertson et al. ( J. Chem. Soc., 1950, 903 ) found that 4-hydroxycoumarins on treatment with acetic anhydride and boron trifluoride give rise to C-acetylated coumarins the acetyl group entering the 3-position. Klosa ( Arch. Pharm., 1956, 289, 104 ) prepared a number of 3-acyl-4-hydroxycoumarins by carrying out the condensation of 4-hydroxycoumarin with various organic acids in the presence of phosphorus oxychloride. Similar results were obtained on treating 4-hydroxycoumarin with aliphatic acid chlorides and pyridine or pyridine and piperidine ( Iguchi, J. Pharm. Soc., Japan, 1952, 72, 122 ; Ukita, Nojima and Matsumoto, J. Am. Chem. Soc., 1950, 72, 5143 ; Eisenhauer and Link, J. Am. Chem. Soc., 1953, 75, 2044 ).

The acyl coumarins are substances of synthetical importance and they have been used for the synthesis of coumarino-α-and coumarino-γ-pyrones and 2-acylresorcinols.

Claisen rearrangement :

Baker and Lothian ( J. Chem. Soc., 1935, 628 ) studied the Claisen rearrangement of 7-allyloxy-4-methyl-coumarin and obtained 7-hydroxy-8-allyl-4-methylcoumarin. Krishnaswami and Seshadri ( Proc. Indian Acad. Sci., 1941, 13A, 43 ) applied this reaction to 7-allyloxycoumarin and

obtained 8-allyl-7-hydroxycoumarin. Rao and Seshadri ( Proc. Indian Acad. Sci., 1944, 19A, 5 ) carried out Claisen migration of 5-allyloxy-4,7-dimethylcoumarin and found that it gave the 8-allyl or the 6-allyl derivative depending on the temperature of the reaction. Claisen migration of 7-allyloxy-5-methylcoumarin yielded only the 8-allyl derivative. Shamshurin ( J. Gen. Chem. U.S.S.R., 1944, 14, 881 ; C.A., 1945, 39, 3789 ) found that 7-allyloxy-4-methylcoumarin in boiling decalin solution rearranged to the 8-allyl derivative.

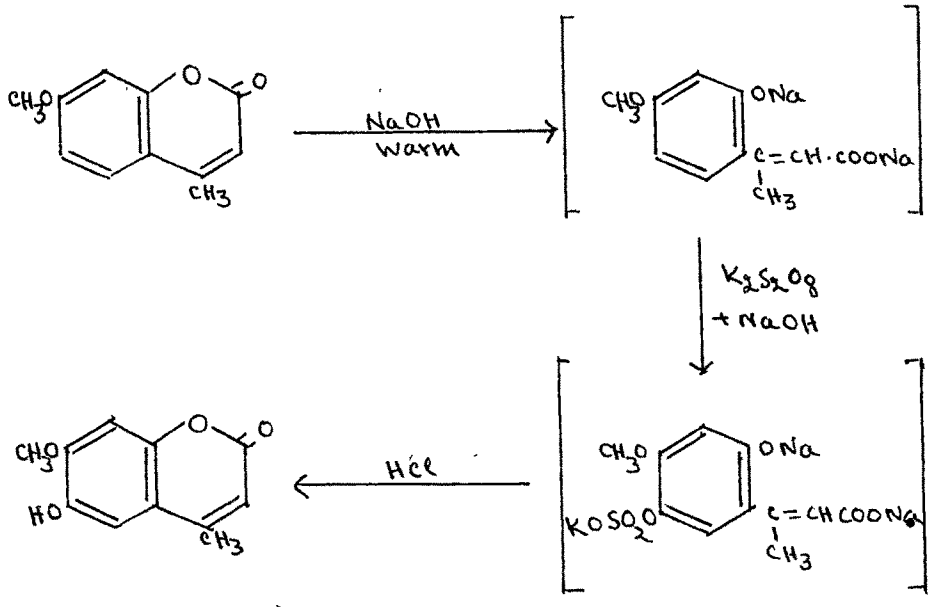
Sulphination :

Usgaonkar and Jadhav ( J. Indian Chem. Soc., 1958, 35, 251, 775 ; 1959, 36, 176,346 ) studied the action of thionyl chloride on some 7-hydroxy-4-methylcoumarin derivatives with and without alkyl substituent in 6-position in presence of anhydrous aluminium chloride and obtained the corresponding 8-sulphinic acid derivatives in good yield. 7-Hydroxy-4-methyl-8-ethylcoumarin gave the 6-sulphinic acid derivative. 5-Hydroxy-4-methyl- and 5-hydroxy-4,7-dimethylcoumarin gave the corresponding 6-sulphinic acid derivatives. 6-Hydroxycoumarin gave the 5-sulphinic acid derivative. Attempts to sulphinate methyl-7-hydroxy-4-methylcoumarin-6-carboxylate and 6-hydroxy-4-methylcoumarin with thionyl chloride did not succeed.

Elbs Persulphate Oxidation :

This reaction has been successfully applied to a number of coumarin derivatives. 6-Hydroxycoumarins are

invariably obtained in this reaction if that position is free. If it is occupied then the reaction usually does not take place. Bargellini and Monti ( Gazzetta, 1915, 45, 90 ) oxidised coumarin and 7-methoxycoumarin. Wessely and Demmer ( Ber., 1929, 62, 120 ) oxidised 7,8-dimethoxycoumarin and 7-methoxy-8-ethoxycoumarin. Mauthner ( J. prakt. Chem., 1939, 152, 23 ) oxidised 8-methoxycoumarin. Sethna et al. ( J. Indian Chem. Soc., 1950, 27, 369 ; 1951, 28, 213, 366 ) applied this reaction to 4-methyl-, 7-methoxy-4-methyl-, 5-methoxy-4-methyl-, 5-methoxy-4,7-dimethyl-, 5,7-dimethoxy-4-methyl- and 7,8-dimethoxy-4-methylcoumarin. In all these cases the corresponding 6-hydroxycoumarin derivatives were obtained.




The oxidation is usually carried out with completely methylated coumarins because hydroxycoumarins give generally pasty uncrystallisable products. The completely methylated

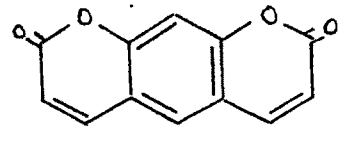
coumarins are dissolved in alkali by warming on a steam bath, their dissolution being presumably due to the opening of the α-pyrone ring and the formation of an o-hydroxy-cinnamic acid derivative. The position para to the hydroxyl group formed by the opening of the ring is the 6-position in the original coumarin and therefore oxidation takes place in this position. The coumarin ring is formed again when the reaction mixture is acidified.

Bhavsar and Desai ( J. Indian Chem. Soc., 1954, 31, 141 ) applied this reaction to several coumarins after protecting the hydroxyl group by p-toluenesulfonyl group. They could prepare isomeric methoxyhydroxycoumarins by this method. Seshadri et al. ( Proc. Indian Acad. Sci., 1951, 33A, 11, 21 ; 1959, 49A, 104 ) oxidised several coumarins and obtained the corresponding 6-hydroxy derivatives. Schiavello and Sebastiani ( Ricerca. Sci., 1950, 20, 1304 ; C.A., 1951, 45, 5684 ) oxidised 5-hydroxy-6-acetyl-4-methylcoumarin and obtained 5,8-dihydroxy-6-acetyl-4-methylcoumarin. They also oxidised 5,7-dimethoxy-4-phenylcoumarin and obtained the corresponding 6-hydroxy derivative. Sebastiani et al. ( Gazz. Chin. ital., 1953, 83, 647 ) oxidised several 3-methylcoumarin derivatives and obtained the corresponding 6-hydroxy derivatives.

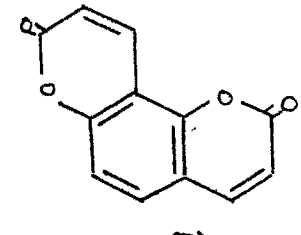
Pechmann reaction on some hydroxycoumarins :

Sen and Chakravarti ( J. Indian Chem. Soc., 1929, 6, 793 ) observed that hydroxycoumarins react under proper conditions with a second molecule of acetoacetic ester or

malic acid producing coumarino-a-pyrones in good yields. They condensed 7-hydroxy-, 7-hydroxy-4-methyl-, 5-hydroxy-7-methyl-, 5-hydroxy-4,7-dimethyl-, 5,7-dihydroxy-, 5,7-dihydroxy-4-methyl-, 7,8-dihydroxy- and 7,8-dihydroxy-4-methylcoumarin with acetoacetic ester and malic acid and obtained various coumarino-a-pyrones. They observed that the hydroxycoumarins reacted more readily with malic acid than with acetoacetic ester. 7,8-Dihydroxy- and 7,8-dihydroxy-4-methylcoumarins did not react with acetoacetic ester. Seshadri and Rangaswami ( Proc. Indian Acad. Sci., 1937, 6A, 112 ) found that the angular compound, coumarino-7,8-a-pyrone ( I ) was formed in 95 % yield and the linear compound, coumarino-7,6-a-pyrone ( II ) was formed only in 5 % yield when 7-hydroxycoumarin reacted with malic acid. 7-Hydroxy-4-methylcoumarin gave only the angular compound.



(II)

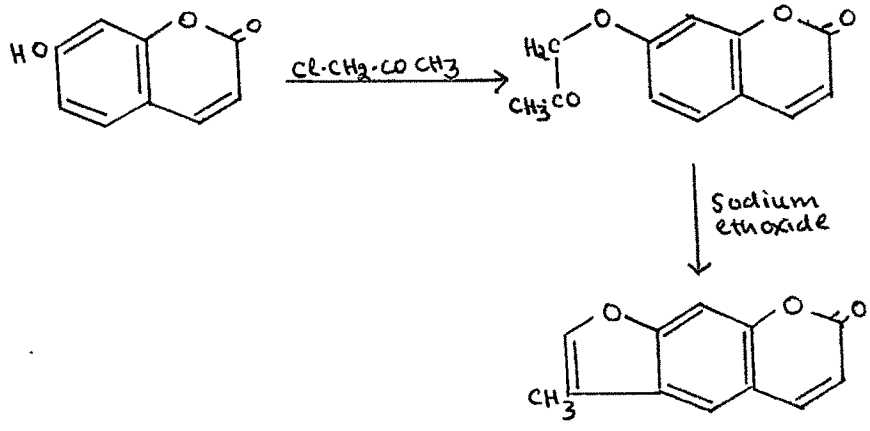


(I)

Furocoumarins :

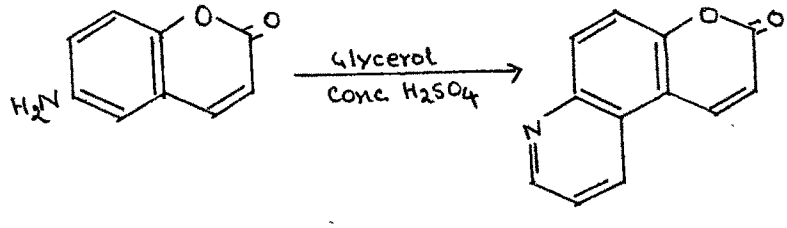
A large number of furocoumarins have been synthesised by other methods such as from o-hydroxyformyl and o-hydroxyacyl-coumarins but their discussion is outside the scope of this chapter as no direct substitution in the coumarin ring system is involved. Only the method of Ray( J. Chem.Soc., 1935, 812 ) may be discussed here. He found that 7-hydroxycoumarin condensed with chloroacetone and bromoacetophenone in alkaline solution and the resulting acetonyl and phenacyl derivatives readily cyclised with $C_2H_5ONa$ to give the linear compounds, 3'-methyl-, and 3'-phenyl-7,6-furocoumarin respectively. Similar reactions with

7-hydroxy-4-methylcoumarin were also studied and the corresponding furanocoumarins obtained.




Quinolino-α-pyrones :

Dey and Goswami ( J. Chem. Soc., 1919, 115, 531 ) obtained quinolino-6,5-α-pyrones from 6-aminocoumarin and 6-amino-1,2-naphtha-α-pyrone through Skraup synthesis. Dey and Seshadri ( J. Indian Chem. Soc., 1926, 3, 166 ) used the same method and obtained quinolino-6,5-α-3-bromopyrone from 3-bromo-6-aminocoumarin. Dey and Kutti ( Proc. Natl. Inst. Sci. India, 1940, 6, 641 ) obtained quinolino-α-pyrones from 5-amino-8-methoxy and 6-amino-8-methoxycoumarin by the same method.

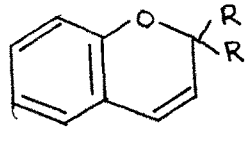


Petrow and Rewald ( J. Chem. Soc., 1949, 769 ) prepared quinolino-α-pyrone by the same method. Siddiqui et al. ( J. Sci. Ind. Research, India, 1950, 9B, 165 ; 1952, 11B, 81 ) obtained several quinolino-α-pyrones from 6-aminocoumarin by the Conrad-Limpach method.

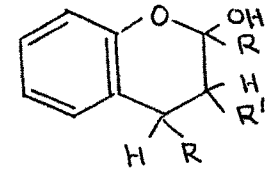
Grignard reaction :

Coumarins with Grignard reagents give products the nature of which is dependent upon the position of the substituents. They may be chromylium salts, dialkyl or diaryl chromenes, chromanols or open chain carbinols.

Shriner and Sharp ( J. Org. Chem., 1939, 4, 575 ) and Smith and Ruoff ( J. Am. Chem. Soc., 1940, 62, 145 ) observed that coumarins with excess of n-alkyl magnesium halides give 2,2-dialkyl-1,2-benzopyrans (I) . Heilbron and Hill ( J. Chem. Soc., 1927, 2005 ), Bridge et al. ( J. Chem. Soc., 1937, 1530 ; 1938, 1375 ) and Kartha and Menon ( Proc. Indian Acad. Sci., 1943, 18A, 28 ) observed that 4-substituted coumarins behaved similarly and gave 2,2-dialkyl-1,2-benzopyrans. Lowenbein and Rosenbaum ( Ann., 1926, 448, 223 ), Heilbron and Hill ( loc.cit. ) and Geissman and Baumgarten ( J. Am. Chem. Soc., 1943, 65, 2135 ) observed that with 3-substituted coumarins the final product was 2,3,4-substituted chromanol-2 ( II ).

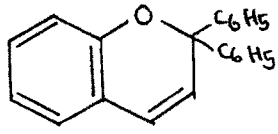



I

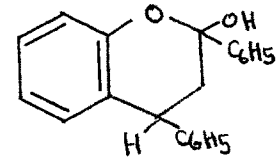



II

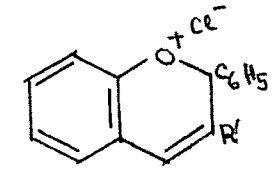
Lowenbein and Rosenbaum ( loc. cit. ) observed that with phenyl magnesium bromide coumarin gave a mixture of products ( III and IV ) , 3-substituted coumarins gave 2-phenyl benzopyrilium salts ( V ) whereas 4-substituted coumarins do not react.



III

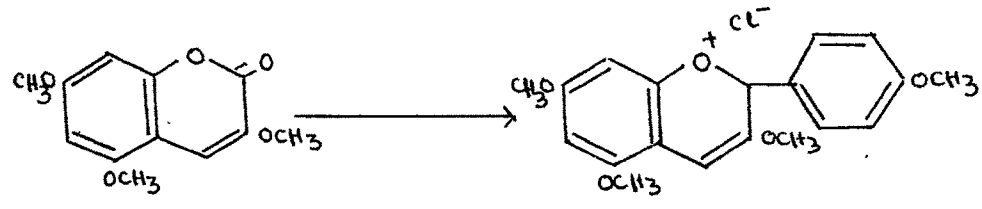


IV



V

Decker and Fellenberg ( Ber., 1907, 40, 3815 ) observed that in the presence of excess of coumarin addition of one mole of Grignard reagent occurs. This reaction has been used for the preparation of anthocyanins. Willstatter et al. ( Ber., 1924, 57, 1938 ) prepared pelargonidin chloride starting ~~from~~ with 3,5,7-trimethoxycoumarin and p-bromoanisolmagnesium.



Wawzonek et al. ( J. Am. Chem. Soc., 1954, 76, 1080 ) studied the action of ~~N-magnesium halides~~ Grignard reagents on 4-hydroxy- and 4-ethoxycoumarin. 4-Ethoxycoumarin was found to react with phenyl magnesium bromide and methyl magnesium

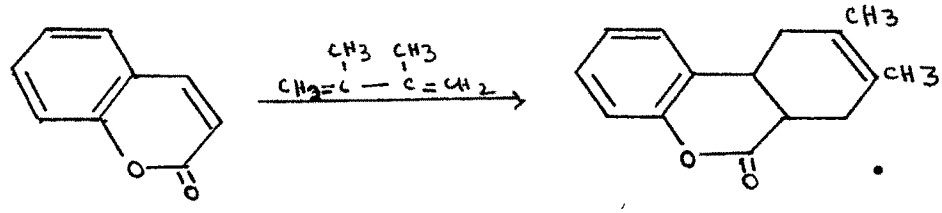
iodide and gave 2,2'-diphenyl- and 2,2'-dimethyl-4-chromanone respectively if the intermediate carbinol was decomposed with acid. 4-Hydroxycoumarin was found to be resistant to the addition reaction of Grignard reagents.

Mannich reaction :

Robertson and Link ( J. Am. Chem. Soc., 1953, 75, 1883 ) synthesised various 3-substituted aminoalkyl 4-hydroxycoumarins by the application of Mannich reaction to 4-hydroxycoumarins. These Mannich bases were assigned the 3-aminoalkyl structures because of the known reactivity of the 3-position in 4-hydroxycoumarins. The reaction with primary amines proceeded very rapidly but with secondary amines it was slow.

Diels-Alder reaction :

Adams et al. ( J. Am. Chem. Soc., 1943, 65, 356 ) treated coumarin with 2,3-dimethylbutadiene at 260° and obtained 8,9-dimethyl-6a-7,10,10a-tetrahydrodibenzopyrone in poor yield

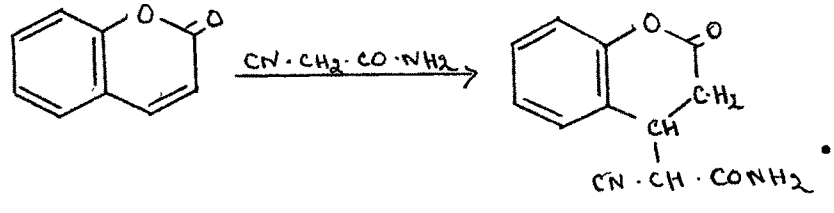



Mustafa and Kamal ( J. Am. Chem. Soc., 1955, 77, 1828 ) obtained various additive products from 4-styryl-

coumarins and 4-styryl-7,8-benzocoumarins with maleic anhydride and N-phenyl and N-p-tolylmaleimide by Diels-Alder reaction.

Michael reaction :

Seshadri et al. ( J. Chem. Soc., 1928, 166 ; Proc. Indian Acad. Sci., 1942, 15A, 424 ; 16A, 29 ) observed that coumarin (A) undergoes Michael reaction and adds cyanacetamide giving 3,4-dihydrocoumarin-4-cyanoacetamide (B). He found that alkyl and halogen substituents in the pyrone ring, as in 4,7-dimethylcoumarin, 3-methylcoumarin and 3-bromocoumarin, completely inhibited the addition, but, their presence in benzenoid part offered no hindrance. Thus 7-methyl-, 6-amino- and 6-nitrocoumarin gave additive compounds with cyanacetamide. Further, 7-hydroxy and 7-methoxycoumarin gave 7-hydroxy- and 7-methoxy-3,4-dihydrocoumarin-4-cyanacetamide. Acyl or negative substituents in the 3-position were found to increase the reactivity of the double bond and also the rate of reaction ; thus cyanacetamide and ethyl cyanacetate added to 3-acetyl-, 3-benzoyl- and 3-cyanocoumarin.

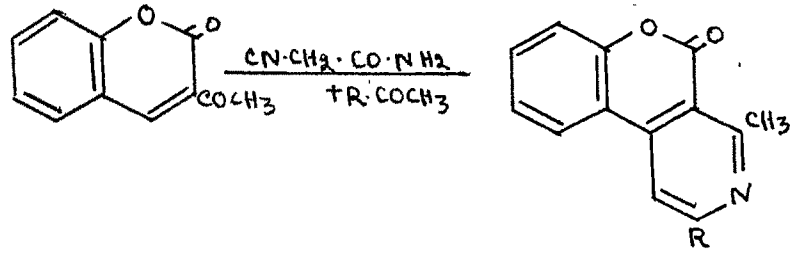



( A ) ( B )

Connor and McClellan ( J. Org. Chem., 1938, 3, 570 ) condensed coumarin with malonic ester and ethyl phenylacetate and obtained the corresponding 3,4-dihydrocoumarins. They

also observed that the methyl group in the 3-position inhibits the reaction thus 3-methylcoumarin did not give any condensation products. Ikawa, Stahmann and Link ( J. Am. Chem. Soc., 1944, 66, 902 ) condensed α,β-unsaturated ketones with 4-hydroxycoumarin and obtained corresponding addition products.

Koelsch and Sundet ( J. Am. Chem. Soc., 1950, 72, 1681 ) observed that 3-acetocoumarin reacts with certain ketones in the presence of amides forming derivatives of 5-keto-4-methyl ( 1 ) benzopyrano ( 3,4-c ) pyridine. The condensation involves a Michael reaction.



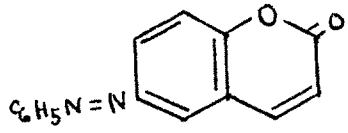

Trivedi ( J. Sci. Ind. Research, India, 1959, 18B, 397 ) condensed cyanacetamide with coumarin, 3-benzoylcoumarin and 3-cyanocoumarin ; ethyl cyanacetate with 3-cyanocoumarin and diethyl malonate with coumarin, using Amberlite IRA-400 as catalyst and obtained the corresponding 3,4-dihydro-coumarin derivatives.

Coupling reaction :

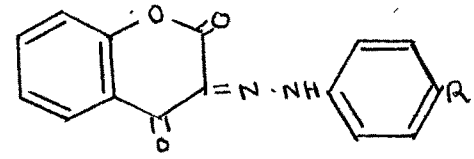
Borsche ( Ber., 1904, 37, 346 ) observed that in the case of coumarin, diazonium salts couple in 6-position (I) . Rangaswami and Seshadri ( Proc. Indian Acad. Sci.,

1939, 9A, 526 ) condensed diazotised p-nitroaniline with 7-hydroxy- and 7-hydroxy-4-methylcoumarin. They observed that when caustic soda was employed the formation of the disazo dyes took place but when sodium carbonate was used monoazo dyes alone were produced. Rangaswami and Rao ( Proc. Indian Acad. Sci., 1944, 19A, 14 ) condensed 5-hydroxy-7-methyl-, 5-hydroxy-4,7-dimethyl- and 7-hydroxy-5-methylcoumarin with diazotised p-nitroaniline at 0° and obtained monoazo as well as disazo dyes.

Huebner and Link ( J. Am. Chem. Soc., 1945, 67, 99 ) observed that 4-hydroxycoumarin coupled with diazotised amines in sodium carbonate solution. Soon after coupling, an insoluble product separated without acidification to which the hydrazone structure ( II ) was assigned.




I

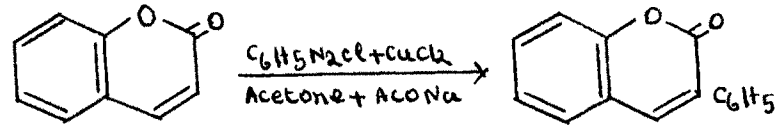



II

Meerwein reaction :

Meerwein et al. ( J. prakt. Chem., 1939, 152, 237 ) observed that α,β-unsaturated compounds and their derivatives react under suitable conditions with aromatic diazo compound during which nitrogen is split off and in most cases the aryl group of the diazo compound replaces the hydrogen of the α-C-atom. He obtained 26 % yield of 3-phenylcoumarin and 50 %

yield of 3-p-nitrophenylcoumarin from the corresponding diazonium salts in acetone solvent. With 7-hydroxycoumarin and diazotized p-chloroaniline he obtained 48 % yield of the 3-p-chlorophenyl derivative.

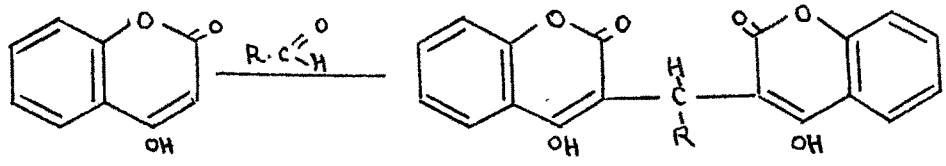



Freund ( J. Chem. Soc., 1951, 1943 ) used this method for the preparation of 3-( p-arsonophenyl ) coumarin. Siddiqui et al. ( J. Sci. Ind. Research India, 1952, 11B, 81 ) obtained 4'- and 3'-nitro-3-phenylcoumarins by the condensation of p- and m-nitrobenzenediazonium chlorides with coumarins. Sawhney and Seshadri ( J. Sci. Ind. Research India, 1954, 13B, 316 ) obtained a number of 3-phenyl-coumarins by this method.

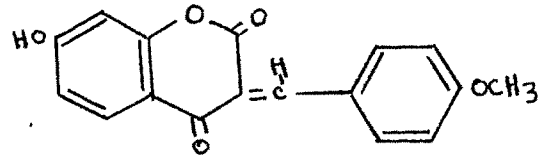
Condensation of aldehydes with 4-hydroxycoumarins and 3-hydroxycoumarin :

Anschutz ( Ann. 1909, 367, 217 ) reported the condensation of 4-hydroxycoumarin with formaldehyde and acetaldehyde in aqueous solution, This reaction has assumed importance since the discovery that 3,3'-methylene bis-( 4-hydroxycoumarin ) ( dicoumarol ) is an anticoagulant of blood. Link et al. ( J. Am. Chem. Soc., 1943, 65, 2288 ) prepared compounds containing substituent groups on the methylene carbon atom of 3,3'-methylene bis- ( 4-hydroxy-

coumarin ) by condensing 4-hydroxycoumarin with various aldehydes.



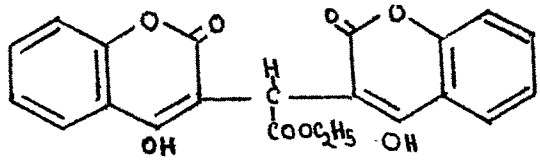
Sonn ( Ber., 1917, 50, 1292 ) condensed anisaldehyde with 4,7-dihydroxy- and 4,5,7-trihydroxycoumarin and obtained 3-( p-methoxybenzal )-2,4-diketochroman.



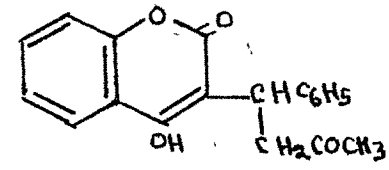
Klosa ( Arch. Pharm., 1955, 288, 545 ; C.A., 1956, 50, 12038 ) carried out the condensation of 4-hydroxycoumarins with heterocyclic and unsaturated aldehydes and obtained the corresponding 3-substituted products. Ikawa and Link ( J. Am. Chem. Soc., 1950, 72, 4373 ) proposed a general mechanism for the condensation of aldehydes with 4-hydroxycoumarins.

Such condensations are numerous and cannot be all listed here. Other compounds which have so far been found to be comparable or in some respects superior to dicoumarol are ethyl bis-( 4-hydroxy-3-coumarinyl ) acetate ( Tromexan ) ( I ) and warfarin ( II ). The latter is synthesised by a Michael

addition of 4-hydroxycoumarin to benzalacetone.



I

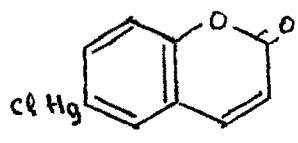


II

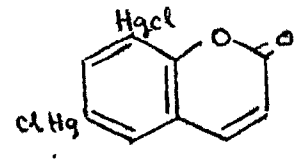
Trivedi and Sethna ( J. Org. Chem., 1960, 25, 1817 ) observed that formaldehyde condenses with 3-hydroxycoumarin derivatives giving 4,4'-methylene bis-( 3-hydroxycoumarin ) derivatives.

Mercuration :

Sen and Chakravarti ( J. Indian Chem. Soc., 1929, 6, 847 ) mercurated coumarin by boiling with yellow mercuric oxide in alkaline solution and obtained the 6-chloromercuri (i) and the 6,8-dichloromercuri (ii) derivatives. If the 6-position was occupied, no mercury compound was formed. They also carried out mercuration with mercuric acetate. Coumarin did not react but 7-hydroxy-4-methylcoumarin gave the 6,8-diacetoxymercuri derivative while the 7,8-dihydroxy-4-methylcoumarin gave the 7,8-diacetoxymercurioxy derivative.



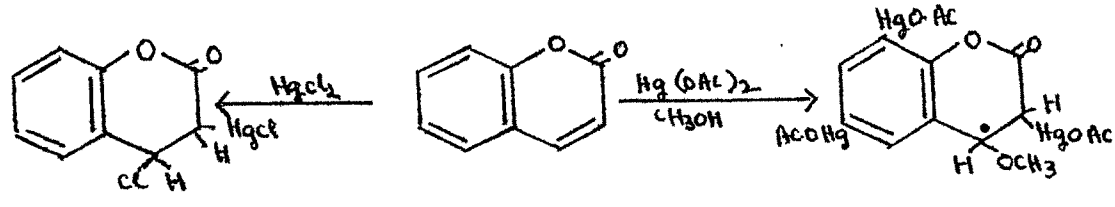
(i)



(ii)

Naik and Patel ( J. Chem. Soc., 1934, 1043 ) studied the mercuration of various substituted coumarin derivatives with mercury acetamide and found that the 6- and the 8-substituted mercury derivatives were obtained. Desai and Ahmad ( Proc. Indian Acad. Sci., 1937, 5A, 277 ) mercurated coumarins obtained from cyclic β-ketonic esters using the method of Sen and Chakravarti. Coumarins from resorcinol, orcinol and phloroglucinol gave diacetoxymercuri derivatives. The coumarins from α-naphthol did not undergo mercuration.

Seshadri and Rao ( Proc. Indian Acad. Sci., 1936, 4A, 163, 630 ) found that coumarin reacted with mercuric acetate in methanol to give 3,6,8-triacetoxymercuri-4-methoxy-dihydrocoumarin.(A) When the 6 position was blocked only the 3,8-diacetoxymercuri-4-methoxydihydrocoumarin was formed. In the case of coumarin and 7-methylcoumarin mercuric chloride only added to the double bond. 6-Nitrocoumarin did not react. In compounds with amino and phenolic groups NH.Hg.X and O.Hg.OH compounds were formed.




(A)

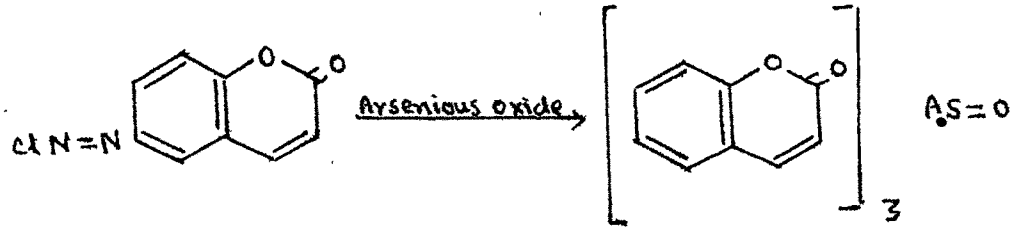
Nuclear methylation of coumarins :

Gupta and Seshadri ( J. Sci. Ind. Research India, 1957, 16B, 257 ) studied the nuclear methylation of typical

hydroxycoumarins. 7-Hydroxy- and 7-hydroxy-4-methylcoumarin did not undergo any change at 0° but in boiling methanolic solution they underwent substitution in the 8-position. 5,7-Dihydroxy-4-methylcoumarin underwent substitution in position 6 at 0° and on prolonged reaction in boiling methanolic solution it gave a mixture of 4,6,6,8,8-pentamethyl-5,7-diketo-5,6,7,8-tetrahydrocoumarin and 4,6,6,8-tetramethyl-5,7-diketo-5,6,7,8-tetrahydrocoumarin.

Arsonation :

Goswami and Das Gupta ( J. Indian Chem. Soc., 1931, 8, 417 ; 1932, 9, 91 ) treated diazotised solution of 6-aminocoumarin with arsenious oxide in sodium carbonate solution ( Bart's method ) and obtained tricoumarylarsenic oxide.[8] They also applied this reaction to 7-methyl-6-aminocoumarin, 4,7-dimethyl-6-aminocoumarin, 6-amino-1,2-naphtha-α-pyrone and 4'-methyl-6-amino-1,2-naphtha-α-pyrone and obtained the corresponding 6-arsinic acid derivatives. This reaction did not succeed with 7-hydroxy-6-amino-4-methylcoumarin and its methyl ether.




(A) (B)

## PRESENT WORK

A perusal of the literature on the substitution in the coumarin ring system reveals that coumarins have been subjected to various reactions such as bromination, nitration, sulphonation, formylation etc. but the iodination and the chloromethylation of coumarins has not been studied at all. Both, the iodocoumarins and the chloromethylcoumarins are compounds of synthetical importance. Iodo compounds are of interest because they can be converted readily into the cyano compounds which can then be hydrolysed to the amides or the acids. The iodo compounds can also be subjected to the Ullmann and crossed Ullmann reaction. Chloromethyl compounds can be converted to methyl derivatives through reduction or to aldehydes through Sommelet reaction. In view of these potentialities it was thought of interest to study the iodination and chloromethylation of some typical coumarin derivatives.

In chapter I the work done so far on substitution in the coumarin ring system is reviewed.

In chapter II the iodination of some typical coumarin derivatives using three different iodinating agents : iodine monochloride, iodine and iodic acid and iodine and ammonia and the determination of the structures of the iodocoumarins is described.

In chapter III the synthesis of various bicoumarinyl and 8-phenylcoumarin derivatives by the Ullmann and crossed Ullmann reaction on iodocoumarins is described.

In chapter IV, the synthesis of cyanocoumarins by the Rosenmund-von Braun reaction on iodocoumarins is described. Further, the hydrolysis of the cyanocoumarins with alkali and acid is discussed.

In chapter V the chloromethylation of various coumarin derivatives, the determination of the structures of the chloromethylcoumarins and the utilisation of some of the chloromethyl derivatives for the synthesis of other compounds is described.