CHAPTER I

GENERAL INTRODUCTION

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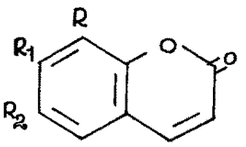
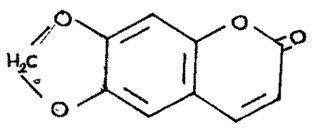
Substitution in the coumarin ring system

Coumarins or benzo-α-pyrones occur in plant kingdom, either in the free or in the combined state. Coumarin, Scopoletin, Aesculetin, Ayapin, Fraxetin and Daphnetin are a few of the simple coumarins found in nature.





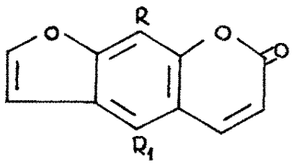
Ayapin

	R	R_1	R_2
Coumarin	H	H	H
Scopoletin	H	OH	OCH_3
Aesculetin	H	OH	OH
Fraxetin	OH	OH	OCH_3
Daphnetin	OH	OH	H

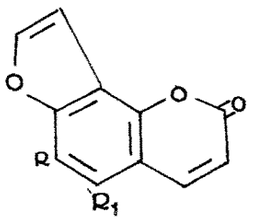
Another group of interesting naturally occuring coumarin derivatives are the furocoumarins. Psoralene, Angelicin, Bergapten, Xanthotoxin, Pimpinellin, Isopimpinellin and Oreoselone are a few members of this group.

The interest in coumarins has been enhanced in recent years by the discovery of their diverse biochemical properties (See review by Bose, J. Indian Chem. Soc., 1958, 35, 367). A few of these may be very briefly described here. Link and co-workers (J. Am. Chem. Soc., 1943, 65, 2285) discovered that 3,3'-methylene bis-4-hydroxycoumarin was the

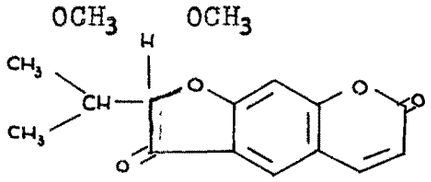
causative factor of the." sweet clover disease " of the cattle and this led to the development of this substance under the name of " Dicumarol " as an anticoagulant of blood.



	R	R_1
Psoralene	H	H
Xanthotoxin	OCH_3	H
Bergapten	H	OCH_3
Isopimpinellin	OCH_3	OCH_3



	R	R_1
Angelicin	H	H
Pimpinellin	OCH_3	OCH_3



Oreoselone

Further synthetic work in this field gave anticoagulants such as Trommexan and Tomorin and rodenticides such as Warfarin. Some of the coumarin derivatives are found to possess the " blastocholine " effect i.e. the property of suppressing the germination of seeds at low concentrations. Some coumarin derivatives such as bergapten, pimpinellin and isopimpinellin are found to be very good fish poisons and others such as psoralene, xanthotoxin, imperatorin and bergapten are found to be photosensitizing agents which can bring about pigmentation of the depigmented skin by hastening the formation of melanin (cf. Pathak and Fellmann Nature, 1960, 185, 382).

Novobiocin, a new antibiotic isolated from Streptomyces Sp., has been found to be a coumarin derivative (Shunk and co-workers. J. Am. Chem. Soc., 1956, 78, 1770 ; Kaczka and co-workers. J. Am. Chem. Soc., 1956, 78, 4125). The antibacterial spectrum of this antibiotic corresponds generally with ~~those~~ that of penicillin and erythromycin.

There are a number of methods available for the synthesis of coumarin derivatives (See " The Chemistry of Coumarins " by Sethna and Shah, Chem. Revs., 1945, 36, 1-62). Considerable work has also been done on substitution in the coumarin ring system. As the bulk of the present work deals with substitution in the coumarin ring system it will not be out of place to briefly review some of the important substitution reactions applied to coumarins to see the pattern of substitution in the coumarin ring system.

Halogenation of coumarin derivatives :

As a part of the present work deals with the iodination of coumarin derivatives the previous work on the halogenation may be described in some detail.

(A) Chlorination

Coumarin on chlorination gave 3-chlorocoumarin (Perkin J. Chem. Soc., 1871, 24, 37). 7-Hydroxy-4-methylcoumarin gave 8-chloro derivative (Lindemann, Ann., 1914, 53, 404). 7-Methylcoumarin-4-acetic acid gave two products : 7-methylcoumarin-4-chloroacetic acid and the decarboxylated product 7-methyl-4-chloromethylcoumarin (Dey and Radhabai, J. Indian Chem. Soc., 1934, 11, 635). 6-Methylcoumarin-4-acetic acid yielded similar results,

1,2-naphtha-α-pyrone-4-acetic acid however gave the 3'-chloroderivative. Seshadri and co-workers (J. Sci. Ind. Research, India., 1952, 11B, 50) chlorinated 7-hydroxy-4-methylcoumarin, its methyl ether and its acetoxy derivative and obtained the corresponding 3-chloro derivatives. 7-Hydroxy-3,6,8-trichloro-4-methylcoumarin was also obtained by them. Mentzer and Meunier (Compt. rend., 1947, 225, 1329 ; C.A. 1948, 42, 2599) chlorinated 4-hydroxycoumarin and obtained the 3-chloro derivative.

(B) Bromination

The bromination of coumarin derivatives has been very extensively studied. Perkin (J. Chem. Soc., 1870, 23, 368) brominated 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 from coumarin.

Peters and Simonis (Ber., 1908, 41, 830) obtained 3-bromo, 3,6-dibromo and 3,6,8-tribromo derivatives from 4-methylcoumarin. Fries and Fickewirth (Ann., 1908, 362, 49) brominated 4,7-dimethylcoumarin and obtained the 3-bromo derivative. Seshadri and co-workers (Proc. Indian Acad. Sci., 1939, 9A, 22) obtained the 3,6-dibromo derivative from 4,7-dimethylcoumarin. Jordan and Thorpe (J. Chem. Soc., 1915, 107, 38) brominated 4,5,7-trimethylcoumarin 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 were 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 took place at the ethenoid linkage and not at the active methylene group.

Several hydroxycoumarins have been brominated. Will and Beck (Ber., 1886, 19, 1777) brominated 7-methoxycoumarin and obtained the 3-bromo derivative and a dibromo derivative to which they did not assign any structure. Fries and Lindemann (Ann., 1914, 404, 53) obtained a monobromo derivative from 7-hydroxy-4-methylcoumarin which they considered to be the 8-bromo derivative. 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 (Ber., 1925, 58B, 1027) obtained the 3-bromo derivative from 7-hydroxy- and 7-hydroxy-4-methylcoumarin ethyl carbonate. Masaiti and Yanagita (Ber., 1938, 71B, 2269) obtained the 3-bromo derivative from 7-hydroxy-4,6-dimethyl-8-ethylcoumarin. Desai et al. (Proc. Indian Acad. Sci., 1937, 6A, 185 ; 1938, 8A. 194) obtained the 3-bromo derivatives from 6-acetyl- and 6-propionyl-7-hydroxy-4-methylcoumarin and 8-acetyl-6-ethyl-7-hydroxy-4-methylcoumarin. Pechmann and Graeger (Ber., 1904, 34, 378) brominated ethyl 7-hydroxycoumarin-4-carboxylate and assumed the position of the bromine atom to be 8. Limaye et al.

(Rasayanam, 1936, 48 ; 1938, 136) obtained the 3-bromo derivatives from 7-hydroxy-8-acetyl-4-methylcoumarin and 7-methoxy-4-methylcoumarin.

Seshadri and Varadarajan (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 3,6,8-tribromo derivatives. Its methyl ether yielded the 3-bromo and 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.

Dalvi and Sethna (J. Indian Chem. Soc., 1949,26, 359, 467) studied the bromination of 7-hydroxy-4-methylcoumarin, 7-hydroxy-4-methylcoumarin-6-carboxylic acid and its methyl ester and the methyl ethers of these compounds under different conditions. They found that the first bromine atom in all cases, entered the 3-position. Further bromination of 7-hydroxy-4-methylcoumarin gave the 3,6-dibromo derivative in good yield along with the 3,8-dibromo isomer in a very small yield. Further bromination of 7-methoxy-4-methylcoumarin yielded only the 3,6-dibromo isomer.

Borsche (Ber., 1907, 40, 2731) assigned the 5,7-dibromo structure to the bromination product from 6-hydroxy-4-methylcoumarin. This was 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-and 3,7-dibromo derivative while its methyl ether gave only the 3,7-dibromo derivative.

Hüebner and Link (J. Am. Chem. Soc., 1945, 67, 99) obtained 3-bromo-4-hydroxycoumarin from 4-hydroxycoumarin. Trivedi and Sethna (J. Org. Chem., 1960, 25, 1817) obtained the 4-bromo- derivative in the bromination of 3-hydroxycoumarin. Dey and Kutti (Proc. Natl. Inst. Sci. India., 1940, 6A, 641) obtained the 5-bromo derivative from 8-hydroxycoumarin and its methyl ether.

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 coumarin derivatives 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 the dibromo derivative from 5,7-dimethoxycoumarin to which they did not assign any structure. 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 derivative. 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. and Ind. Research, India,, 1955, 14B, 101) in their study of the bromination of some dihydroxycoumarin derivatives found that in the bromination of 4,7-dihydroxycoumarin the 3-bromo derivative was obtained and thus the 8-bromo structure assigned by Bauer and Schoder (loc. cit.) was incurrect. They brominated 7,8-dihydroxy-4-methylcoumarin and its methyl ether and obtained the 3-bromo derivatives. On further bromination they obtained a dibromo derivative which they found was the 3,6 and not the 3,4-dibromo derivative as reported by Sakai and Kato (loc. cit.). They also brominated 5,7-dihydroxy-4-methylcoumarin and its methyl ether. From the former they obtained directly the 3,6,8-tribromo derivative and from the latter the 3,8-dibromo 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-bromomethylcoumarin and 7-methoxy-3-bromo-4-methylcoumarin by the action of N-bromo succinimide on 3-methylcoumarin and 7-methoxy-4-methylcoumarin. 7-Methoxy-3-ethyl-4-methylcoumarin gave a mixture of 7-methoxy-3-(1-bromoethyl)-4-methylcoumarin in good yield and 7-methoxy-6-bromo-3-ethyl-4-methylcoumarin in poor yield. Lecocq 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. Lecocq (Ann. Chim., 1948, 3, 62) obtained 3-bromo-4-methylcoumarin from 4-methylcoumarin on reaction with N-bromo succinimide. 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-bromo succinimide gave 3-ethyl-6-bromo- and 3-propyl-6-bromo-4-methyl-7-methoxycoumarin, the 3-(α-bromo alkyl) compound being the intermediate.

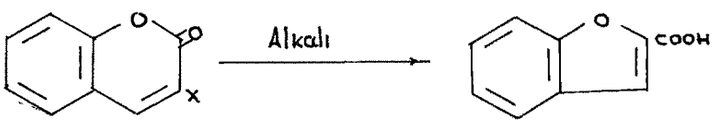
Dhar (J. Chem. Soc., 1920, 117, 993) found that in the bromination of 6-nitrocoumarin the nitro group was replaced by the halogen atom and further halogenation took place readily with the formation of the tribromo and the tetrabromo derivatives. Dey and Row (J. Chem. Soc., 1923, 123, 3375) brominated 6-nitrocoumarin and obtained directly the 3,8-dibromo-6-nitrocoumarin. 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.

(C) Iodination

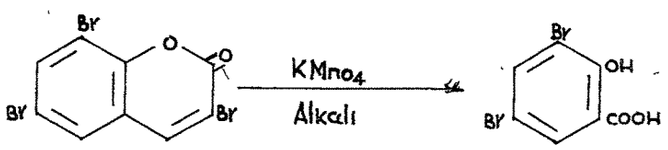
No work on the iodination of coumarins has been reported other than the work carried out in our laboratory.

Methods of proving the structures of halogenated coumarins

If a halogen atom is present in the 3-position in the coumarin a coumarilic acid is invariably obtained on heating with alkali.

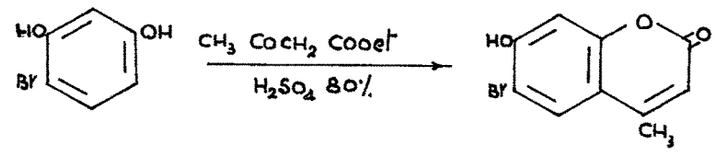


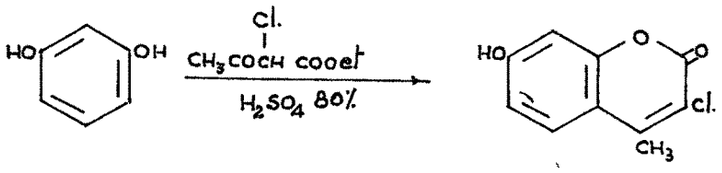
A halogenated coumarin with halogen in the benzenoid part of the molecule is not affected by alkali. In such cases the oxidation of the halocoumarin may be useful and a simple halogenated phenolic acid may be obtained. For example Peters and Simonis (loc. cit.) oxidised 3,6,8-tribromocoumarin with alkaline potassium permanganate and obtained 3,5-dibromo salicylic acid.



It is often advantageous to try the synthetic approach by starting with a suitably substituted phenolic derivative and building up the α-pyrone ring on the same by an appropriate reaction for the synthesis of a coumarin

derivative as shown below.·





Sethna and his co-workers (J. Indian Chem. Soc., 1950, 27, 369 ; 1951, 28, 213, 366) have used the Elbs Persulphate Oxidation as a diagnostic test to find out whether the halogen has entered the 6-position or not (See p. 19).

Sulphonation

Perkin (J. Chem. Soc., 1873, 24, 37) sulphonated coumarin with fuming sulphuric acid and obtained a monosulphonic acid at the temperature of steam bath and a disulphonic acid at 150° but he did not establish the structures of the sulphonic acids. 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. 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. 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-sulphonylchloride.

Huebner and Link (J. Am. Chem. Soc., 1945, 67, 99) obtained the 3-sulphonic acid derivative from 4-hydroxycoumarin and fuming sulphuric acid.

Merchant and Shah (J. Indian Chem. Soc., 1957, 34, 35, 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 carboxyl 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 the sulphonic acid group entered the 8-position. In the case of 6-nitrocoumarin however the 3-substituted compound was obtained. 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 derivative. 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 5-hydroxy-4-methylcoumarin derivatives were sulphonated more readily than the 7-hydroxycoumarin derivatives. In all these cases the sulphonyl chlorides were also isolated along with the sulphonic acid derivatives.

Nitration

Morgan (J. Chem. Soc., 1904, 85, 1233) reported the formation of 6-nitrocoumarin in the nitration of coumarin. Dey and Krishnamurthi (J. Indian Chem. Soc., 1927, 4, 197) found that in the nitration of coumarin both the 6- and the 8-isomers were 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 the 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-trimethylcoumarin and obtained various nitro derivatives. The ease of nitration was found to increase with the introduction of alkyl groups.

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 later. 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-dinitro derivatives while the acid and the ester yielded the 8-nitro derivatives. Naik and Jadhav (J. Indian Chem. Soc., 1948, 25, 171 ; J. Uni. Bombay, 1948, 16, 46) nitrated 7-hydroxy-4-methylcoumarin and its methyl ether and obtained the 6-nitro and the 3,6,8-trinitro derivatives. Shah and Mehta (J. Indian Chem. Soc., 1954, 31, 784) later showed that both the 6-nitro and the 8-nitrocoumarin derivatives are obtained in the nitration of 7-hydroxy-4-methylcoumarin. Further Naik and Jadhav (loc.cit.) found that 7-hydroxy-3,4-dimethylcoumarin gave the 6,8-dinitro derivative while its methyl ether yielded the 6-nitro derivative. Methyl-7-hydroxy-4-methylcoumarin-6-carboxylate gave the 8-nitro and the 3,8-dinitro derivatives while its methyl ether gave the 6-nitro derivative (the carbomethoxy group having been replaced by the nitro group) and 7-methoxy-3,6-dinitro-4-methylcoumarin. 7-Hydroxy-4-methylcoumarin-6-carboxylic acid gave the 6,8-dinitro and the 3,6,8-trinitro derivatives, the carboxyl group having been replaced by the nitro group in both the cases.

Dey and Kutti (Proc. Natl. Inst. Sci. India, 1940, 6A, 641) nitrated 8-hydroxycoumarin and its methyl ether and obtained 7-nitro and 5-nitro derivatives respectively. Borsche and Hahn Weinheimer (Ber., 1952, 85, 198) obtained the 5,7-dinitro derivative from 8-methoxycoumarin.

Huebner and Link (J. Am. Chem. Soc., 1945, 67, 99) obtained 3-nitro- and 3,6-dinitro-4-hydroxycoumarin from 4-hydrocycoumarin.

Shah and Mewada (Ber., 1956, 89, 2209) obtained a mixture of 5-nitro and 5,7-dinitro derivatives in the nitration of 6-hydroxy-4-methylcoumarin. Its methyl ether however gave only the 5-nitro derivative.

Fries migration and Friedel-Crafts reaction

Limaye (Ber., 1932, 65, 375 ; 1934, 67, 12 and 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. The same 8-acyl derivatives were also obtained in the Friedel-Crafts reaction on 7-hydroxycoumarin. Shah and Shah (J. Chem. Soc.,1938, 228, 1424 ; 1939, 1250) studied the Fries migration of 5-acetoxy-, 5-benzoyloxy-, 5-propionoxy- and 5-butyroxy-4-methylcoumarin and obtained the corresponding 6-acyl derivatives.

Thakor (Current Sci. India, 1951, 20, 234) studied the Fries migration of 6-acetoxy and 6-benzoyloxy-coumarin and obtained the corresponding 5-acyl derivatives. These were also obtained in the Friedel-Crafts acetylation and benzoylation of 6-hydroxycoumarin. Esters of 6-hydroxy-4-methylcoumarin did not rearrange.

Bhavsar and Desai (J. Indian Chem. Soc.,1954, 31, 141) studied the Fries migration of 4-methylcoumarinyl-7-p-toluene sulphonate and obtained the 8- and the 6-p-toluene sulphonyl derivatives. The Fries migration of 4,7-dimethyl-5-coumarinyl-p-toluene sulphonate yielded the 6-p-toluene

sulphonyl derivative. Setalwad and Shah (J. Indian Chem. Soc., 1954, 31, 600) studied Fries isomerization of the acetyl and benzoyl esters of 7-hydroxy-6-bromo (and 6-chloro)-4-methylcoumarin. They obtained the corresponding 8-acyl derivatives. Thakor and Shah (J. Indian Chem. Soc., 1946, 23, 199, 234) obtained the corresponding 8-acyl derivatives from 7-acetoxy- and 7-benzoyloxy-4-methylcoumarin. Only traces of the 6-isomers were also obtained.

Aleykutty and Baliah (J. Indian Chem. Soc., 1955, 32, 773) studied the Fries rearrangement of 4-methyl-7-coumarinyl-benzene sulphonate and obtained the corresponding 8-phenyl sulphonyl derivative. When the isomerization was effected in nitrobenzene the 6-isomer was also obtained along with the 8-isomer.

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. 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 from the former and the 6-acetyl derivative from the later. Sethna and Trivedi (J. Org. Chem., 1960, 25, 1817) carried out Fries rearrangement of 3-acetoxycoumarin and obtained the 4-acetyl derivative. The same product was also obtained on acetylation of ~~reaction on~~ 3-hydroxycoumarin.

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 (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 derivative while (II) and (III) gave the 6-acyl derivative. On acetylation (IV) yielded the 6-acetyl as well as the 6,8-diacetyl derivatives. In the case of benzoylation it gave only the 6,8-dibenzoyl derivative. 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. Robertson and co-workers (J. Chem. Soc., 1950, 903) found that 4-hydroxycoumarins on treatment with acetic anhydride and boron trifluoride give rise to 3-acetyl derivatives. Similar results were obtained on heating 4-hydroxycoumarin with aliphatic acid chlorides and pyridine or pyridine and piperidine (Iguchi, J. Pharm. Soc., Japan, 1952, 72, 122 ; Ukita, Nojima and Matsumota, J. Am. Chem. Soc., 1950, 72, 5143 ; Eisenhauer and Link, J. Am. Chem. Soc., 1953, 75, 2044).

Formylation

Sen and Chakravarti (J. Am. Chem. Soc., 1928, 50, 2428) prepared 6-formylcoumarin by heating coumarin with aqueous potassium hydroxide and chloroform. Spath and Pailer (J. Chem. Soc., 1932, 1987 ; 1934, 1305) obtained the 8-formyl derivative from 7-hydroxycoumarin by using the hexamethylene tetramine method of Duff and Bills. They also observed that the Gattermann method and the Reimer-Tiemann method of introduction of formyl group in phenols proved unsuccessful in the case of hydroxycoumarins. Rangaswami and Seshadri (Proc. Indian Acad. Sci., 1937, 6A, 112) similarly obtained the 8-formyl derivative from 7-hydroxy-4-methylcoumarin. 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) similarly 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. Reaction with 5,7-dihydroxy-,5,6,7-trihydroxy- and 7,8-dihydroxy-5-methoxy-4-methylcoumarin met with failure. They also studied the formylation of hydroxycoumarins with N-methylformanilide in the 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-methyl formanilide 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. 6-Hydroxy coumarin and 6-hydroxy-4-methylcoumarin yielded the corresponding 5-formyl derivatives. Ziegler and Maier (Monatsh, 1958, 89, 787) formylated 4-hydroxycoumarin in chlorobenzene with N-methyl formanilide in the presence of phosphorus oxychloride and obtained the 3-formyl derivative.

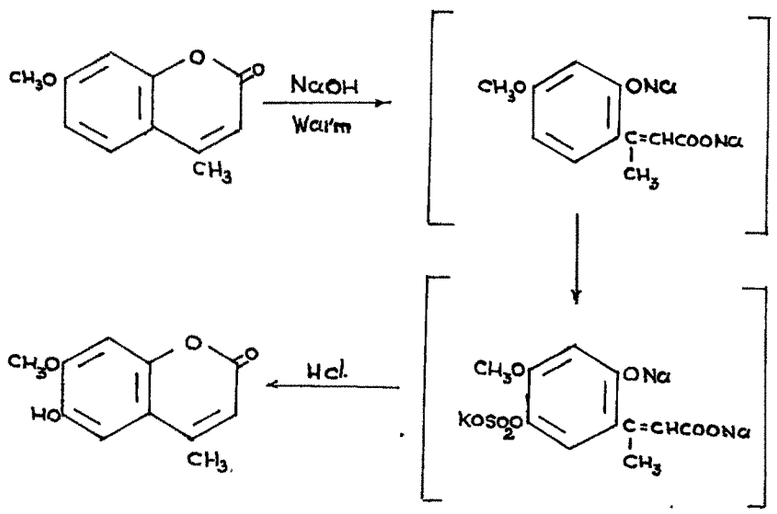
Claisen Rearrangement

Baker and Lothian (J. Chem. Soc., 1935, 628) studied the Claisen rearrangement of 7-allyloxy-4-methylcoumarin and obtained 7-hydroxy-8-allyl-4-methylcoumarin. Krishnaswami and Seshadri (Proc. Indian Acad. of Sci., 1941, 13A, 43) applied this reaction to 7-allyloxycoumarin and obtained 7-hydroxy-8-allylcoumarin. Rao and Seshadri (Proc. Indian Acad. Sci., 1944, 19A, 5-13) carried out Claisen migration of 5-allyloxy-4,7-dimethylcoumarin and found that it gave the 8-allyl or 6-allyl derivative depending on the temperature of the reaction. Claisen migration of 7-allyloxy-5-methylcoumarin yielded only the 8-allyl derivative.

Elbs Persulfate 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 (Gazz. Chim. ital., 1915, 45, 90) oxidised coumarin and 7-methoxycoumarin. Wessely and Demmer (Ber., 1929, 62, 120) oxidised 7,8-dimethoxy and 7-methoxy-8-ethoxycoumarin. Mauthner (J. Prakt.Chem., 1939, 152, 23) oxidised 8-methoxycoumarin. Sethna and co-workers (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.

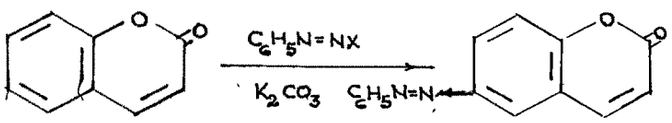


Bhavsar and Desai (J. Indian Chem. Soc., 1954, 31, 141) applied this reaction to several coumarins after protecting the hydroxy group by p-toluenesulfonyl group. They could prepare isomeric methoxy hydroxycoumarins by this method. Seshadri and co-workers (Proc. Indian Acad. Sci.,1951, 33A,

11, 21 ; 1959, 49A, 104) oxidised several coumarins and obtained the corresponding 6-hydroxy derivatives. Schiavello and Sebastiani (Ricercia. 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.

Coupling reaction

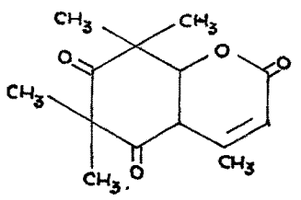
Borsche (Ber., 1904, 37, 346) observed that when coumarin is coupled with diazonium salts the coupling takes place at 6-position.



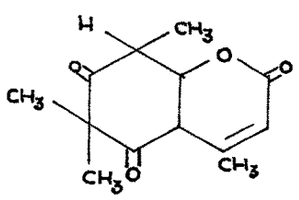
Rangaswami and Seshadri (Proc. Indian Acad. Sci., 1939, 9A, 526) condensed diazotized p-nitroaniline with 7-hydroxy- and 7-hydroxy-4-methylcoumarin. They observed that when caustic soda was employed the formation of the disazo dyes took place but when sodium carbonate was used monoazo dyes alone were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

Nuclear methylation

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.



I



II

5,7-Dihydroxy-4-methylcoumarin underwent substitution in the 6-position 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 (I) and 4,6,6,8-tetramethyl-5,7-diketo-5,6,7,8-tetrahydrocoumarin (II).

Chloromethylation

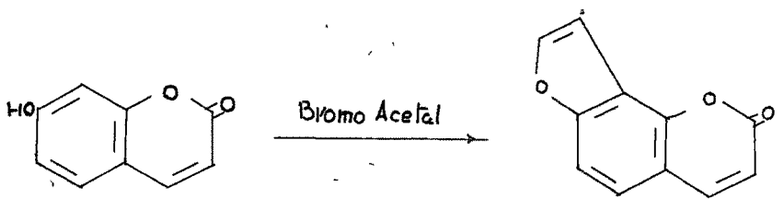
Lele, Sawant and Sethna (J. Org. Chem., 1960, 25, 1713) have recently reported the chloromethylation of a number of coumarin derivatives. They obtained various chloromethyl derivatives and established their structures by reduction to the corresponding methyl derivatives and comparing them with authentic specimens synthesised by unambiguous methods. Coumarin, 4-methylcoumarin, 4'-methyl-1,2-naphtha-α-pyrone and 7,8-dimethoxy-4-methylcoumarin yielded the corresponding 3-chloromethyl derivatives. No higher chloromethyl

derivatives were obtained. 7-Methoxy-4-methylcoumarin gave 6-chloromethyl-,6,8- and 3,8-dichloromethyl and 3,6,8-trichloromethylcoumarin derivatives.

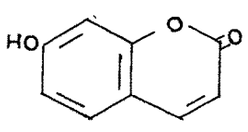
7-Hydroxy-4-methylcoumarin-6-carboxylic acid yielded the 3,8-dichloromethyl derivative, while methyl-7-methoxy-4-methylcoumarin-6-carboxylate yielded 7-methoxy-3-chloromethyl-4-methylcoumarin-6-carboxylic acid.

Coumarins have been subjected to a number of other reactions such as Diels-Alder reaction and Michael reaction in which the double bond in the heterocylic ring is attacked (Seshadri et al. J. Chem. Soc., 1928, 166 ; Proc. Indian Acad. Sci., 1942, 15A, 424 ; 16A, 29 ; Ikawa and co-workers J. Am. Chem. Soc., 1944, 66, 902 ; Connor and McClellan J. Org. Chem., 1938, 3, 570 ; Adams and co-workers J. Am. Chem. Soc., 1943, 65, 356 ; Mustafa and Kamal J. Am. Chem. Soc., 1955, 77, 1828) and the Grignard reaction in which the Co group is usually attacked (Shriner and Shah, J. Org. Chem., 1939, 4, 575 ; Smith and Ruoff J. Am. Chem. Soc., 1940, 62, 145 ; Bridge and co-workers J. Chem. Soc., 1937, 1530 ; 1938 , 1375) have been studied. Further, the coumarins have been subjected to reactions in which another heterocyclic ring such as the α- or γ-pyrone ring or furan ring is built up on the benzenoid part of the coumarin ring (Sen and Chakravarti, J. Indian Chem. Soc., 1929, 6, 793 ; Seshadri and Rangaswami, Proc. Indian Acad. Sci., 1937, 6A, 112 ; Ray, J. Chem. Soc., 1935, 812 ; Spath and Pailer, Ber., 1934, 67, 1212).

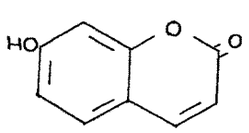
Rangaswami and Seshadri (Proc. Indian Acad. Sci., 1941, 14A, 547) explained the reactivity of 7-hydroxycoumarin derivatives on the theory of the fixation of the double bond. They state that though in coumarin itself substitution invariably takes place in the 6-position, in the 7-hydroxy-coumarins it is exclusively in the 8-position. When attempts are made to build up a fresh ring starting with 7-hydroxy-coumarin, it is the 8-position that is involved in the ring formation. Thus employing 7-hydroxycoumarin and bromoacetal Spath and Pailor (Ber., 1934, 67, 1212) obtained the angular compound angelicin.



Again attempts to introduce a formyl group into 7-hydroxycoumarin gave the 8-formylcoumarins. All these show that 7-hydroxycoumarins react in the form (A).



A



B

Further evidence for this structure comes from the work of Baker and Lothian (J. Chem.Soc., 1935, 628 ; 1936, 275) who found that 7-allyloxy-4-methylcoumarin undergoes Claisen transformation to 7-hydroxy-8-allyl-4-methylcoumarin thus proving conclusively that there exists a double bond between the 7 and 8 positions.

Evidence which does not fall into line with the above was first obtained by Limaye and Gangal (Rasayanam, 1936, 15) who found that when 7-acetoxy-4-methylcoumarin was subjected to Fries migration, the 8-acetyl derivative was the major product but it was accompanied by a small quantity of the 6-acetyl isomer. The simultaneous formation of the angular coumarino-α-pyrone and the linear isomer from the Pechmann condensation between 7-hydroxycoumarin and malic acid (Rangaswami and Seshadri, Proc. Indian Acad. Sci.,1937, 6A, 112) corroborates the above observation and shows the slight but significant reactivity of the 6-position in this compound. These authors applied Fieser's technique to the coumarin ring system and obtained unequivocal evidence on the distribution of the single and double bonds. They (Proc. Indian Acad. Sci., 1944, 19A, 14) found that 7-hydroxy-4,8-dimethylcoumarin coupled with diazotised p-nitraniline and formed with mercuric acetate a mercury derivative which contained 2-acetoxymercuri group's replacable by bromine atoms. The allyl ether and the acetyl derivative also smoothly underwent the Claisen transformation and Fries migration respectively. In structure (A) the carbon atom 7 which

carried the hydroxyl group is attached by means of a double bond to the carbon atom 8. Therefore, the position 8 will be more reactive than the position 6. In structure (B) for the same reason the position 6 will be more reactive than the position 8. All these reactions can be explained only on the assumption of a reactive 6-position which is possible only if the bonds can take up positions as depicted in structure (B). Thus in coumarins while the normal structure corresponds to (A) the other is not precluded. Thus the double bond fixation theory does not satisfactorily account for all the recorded observations, if this fixation is taken to be rigid.

The Theory of Resonance (Pauling and Sherman, J. Chem. Phys., 1933, 1, 605 ; Pauling, Brockway and Beach, J. Am. Chem. Soc., 1935, 57, 2705) seems to eliminate this difficulty. According to this theory, the actual structure of coumarin can neither be (A) nor (B), but some intermediate between the two. If (A) is of materially lower energy than (B), the actual structure will resemble more closely to the structure of the lower energy (A). Since the structure with a double bond common to both the rings possesses lower energy (due to less distortion of valency bonds) the actual structure will resemble more the structure (A) and hence the reactivity will be manifested according to the structure (A) and the 6-position will be less reactive than the 8-position.

An obvious exception to the above is the bromination of coumarin, which is found to occur in many cases in the

3-position of the coumarin nucleus as already stated. Perkin (J. Chem. Soc., 1870, 23, 368 ; 1871, 24, 37) suggested that bromination of coumarin is essentially an addition reaction. It produces the 3,4-dibromo product, which then loses hydrobromic acid, giving 3-bromocoumarin. In some cases however, this is not the case and the first bromine atom enters the benzene ring.

PRESENT WORK

A persual 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 of coumarins has not been studied at all. Further, there is only one reference in the literature on the application of Mannich reaction to coumarins. The iodocoumarins are compounds of synthetical importance. They can be converted into the cyano compounds which can then be hydrolysed to the amides or the acids. They can also be subjected to the Ullmann and Crossed Ullmann reaction and bicoumarinyls and aryl coumarins synthesised. The present work deals with these aspects of coumarin chemistry.

The iodination of some typical coumarin derivatives using three different iodinating agents such as iodine monochloride, iodine and iodic acid and iodine and ammonia has been studied and the structures of the iodocoumarins obtained have been established.

The monoiodocoumarins have been subjected to Ullmann reaction and various bicoumarinyl derivatives synthesised. Crossed Ullmann reaction between the iodocoumarins and iodo benzene has been carried out and a number of phenylcoumarins have been synthesised.

The iodocoumarins have been subjected to the Rosenmund-von Braun reaction and various cyanocoumarins

have been synthesised. Further, the hydrolysis of the cyanocoumarins with alkali and acid is studied.

Several coumarins have been subjected to Mannich reaction with primary and secondary amines such as aniline, benzylamine and dimethylamine in presence of different quantities of formaldehyde and the structures of the Mannich bases and oxazino derivatives obtained established.

Lastly, the pattern of substitution in 6,7-dihydroxy-4-methylcoumarin and its methyl ether has been investigated by subjecting them to various reactions such as bromination, nitration, chloromethylation, formylation, Friedel-Crafts and Fries reaction and iodination.