Chemistry of 4-hydroxycoumarin

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Manuscript received 22 December 2000

4-Hydroxycoumarin, a highly reactive compound, is reviewed with respect to its synthesis, tautomerism, reactions and structure-activity relationship of its derivatives for anticoagulant property.

Introduction

4-Hydroxycoumarins not only occur in nature but also possess very good physiological activities. Link and coworkers found that cattle feeding on spoiled sweet clover hay suffered from a condition characterized by sharp increase of blood clotting time. The pathogenic haemorrhagic principle of sweet clover hay was found by them to be 3,3’-methylenebis-(4-hydroxycoumarin) (2) popularly called Dicoumarol. It was synthesized by reacting 4-hydroxycoumarin (1) with formaldehyde and found to be a good anticoagulant of blood. Since this discovery and also because of its high reactivity, the chemistry of 4-hydroxycoumarin has assumed great importance.

Methods for the synthesis of 4-hydroxycoumarins

Anschutz first synthesized 4-hydroxycoumarins (1) by treating acetyl salicyloylchloride (3) with sodium salt of malonic ester (4) to form 3-carbethoxy-4-hydroxycoumarin (5) which when heated with alkali gave 1.

Wildi condensed ethyl phenylacetate (6) with 3 in the presence of sodium triphenylmethyl (7) to give ethyl (o-acetylsalicyloyl)phenylacetate (8) which when refluxed with sodium carbonate in acetone furnished 3-phenyl-4-hydroxycoumarin (9). 4-Hydroxy-3-phenoxycoumarin (10) was prepared by condensing 3 with diethyl sodiophenoxymalonate (11) in toluene. Using this procedure, Melchiorre et al. synthesized 8-nitro-4-hydroxycoumarin (12).

Pauley and Lockeman synthesized 1 by intramolecular Claisen condensation of methyl acetyl salicylate (13) by adding metallic sodium to the molten ester. They reported yield of 55% of 1, which was not repeatable. Link and coworkers modified the conditions for the reaction by keeping the temperature at 240–250° and obtained the yield of 22% of pure 1. Sonn and Bauer, and Schoder synthesized 4-hydroxycoumarin derivatives having hydroxyl substituents in the benzene ring by the application of Hoesch synthesis. They condensed resorcinol (14a) and phloroglucinol (14b) with cyanacetic acid or ester (15) in the presence of zinc chloride and hydrochloric acid followed by hydrolysis with sulfuric acid (50%) of the intermediate ketimide (16) to give 4,7-hydroxycoumarin (17a) and 4,5,7-trihydroxy coumarin (17b).

Mentzer and coworkers carried out the thermal condensation of phenols with ethyl monosubstituted malonates by heating the reaction mixture at 200–280° for 2–4 days and obtained 3-substituted-4-hydroxycoumarins in poor yields. It was found by Trivedi that if the above reaction is carried out in high boiling inert solvent, viz. diphenyl ether at its boiling point, the reaction time is reduced to 4 h in the case of reactive phenols and 8 h in the case of less reactive phenols. The yield is greatly improved and the products are cleaner and do not require vacuum sublimation as was found necessary earlier. When resorcinol (14a) was condensed with ethyl methylmalonate (18) in refluxing diphenyl ether it gave 3-methyl-4,7-dihydroxycoumarin (19) as obtained by Mentzer and Vercier. When resorcinol (14a) was condensed with ethyl benzylmalonate (20), it furnished 3-benzyl-4,5-dihydroxycoumarin (21) and not 3-benzyl-4,7-dihydroxycoumarin (22) obtained by Mentzer and Vallet. Thus the course of the reaction was changed by carrying out the reaction in refluxing diphenyl ether.

Ziegler et al. carried out the thermal condensation of 14a with di(2,4-dichlorophenyl)benzyl malonate (23) by heating the reaction mixture at 250° for 15 min and obtained 3-benzyl-4,5-dihydroxycoumarin (21) which when heated with anhydrous aluminium chloride at 215° for 3 min furnished 4,5-dihydroxycoumarin (24). Anand and Venkatraman synthesized 4-hydroxy-7,8-benzocoumarin (25) by internal condensation of o-carboxethoxy-2-acetyl-1-naphthol (26) in the presence of anhydrous potassium carbonate in refluxing toluene. This method has been largely used by different workers2-6 to synthesize naturally occu-
ring 3-phenyl-4-hydroxycoumarin derivatives.

Boyd and Robertson reported that o-hydroxyacetophenones and their o-substituted derivatives 27 readily condensed with diethyl carbonate in the presence of sodium to give 4-hydroxycoumarin derivatives 28 in good yields. This is a very convenient method for synthesizing 4-hydroxycoumarin derivatives and has been explored by a large number of workers 1,4,7-20. Ziegler and Junek prepared 4-hydroxycoumarins in excellent yields by cyclization of diaryl malonates (29) in the presence of anhydrous aluminium chloride using carbon disulfide as solvent. Rao and Sundaramurthy et al. synthesized 6-methoxy-4-hydroxycoumarin (30) by condensing hydroquinone dimethyl ether (31) with malonyl chloride (32) in the presence of anhydrous aluminium chloride using carbon disulfide as solvent. Rao and Sundaramurthy 21 condensed phenyl acetate (33) with malonyl chloride (32) in the presence of anhydrous aluminium chloride using nitrobenzene as the solvent and obtained 3-acetyl-4-hydroxycoumarin (34). Ziegler and Gelfert carried out the condensation of phenol (35) with diethyl malonate (36) in the presence of phosphorus oxychloride to obtain 1. Shah, Bose and Shah prepared 4-hydroxycoumarin derivatives in good yields by the condensation of phenols with malonic acid in the presence of phosphorus oxychloride alone at 65°. Shah et al. 22 extended this method to prepare different alkyl and hydroxy substituted 4-hydroxycoumarins. Re and Sandri prepared 4-hydroxycoumarin 1 by applying modified Kolbe Schmidt reaction on 2-hydroxyacetophenone (37) in poor yield. Resplandy carried out cyclodehydration of (2-hydroxybenzoyl)acetic acid (38) with tetraphosphoric acid to obtain 1.

Aurone epoxide (39), obtained by the epoxidation of aurone (40) with m-chloroperbenzoic acid, when reacted with boron trifluoride etherate in benzene undergoes a rearrangement to form 3-phenyl-4-hydroxycoumarin derivative (41) in good yields 23,24. A similar rearrangement was also reported by Seshadri et al. 25,26, when 2-(α-hydroxy-4-methoxybenzyl)-2,4,6-trimethoxycoumaran-3-one (42) obtained by the oxidation of 2'-hydroxy-α,4,6'-tetramethoxy-chalcone (43) with alkaline hydrogen peroxide, was treated with boron trifluoride etherate in benzene to give 3-(4-methoxyphenyl)-4-hydroxy-5,7-dimethoxycoumarin (44). Wolfbeis 27 carried out the thermal condensation of 3-dimethylaminophenol (45) with meldrum acid (46) at 100-130° for 10 min and obtained 7-dimethylamino-4-hydroxycoumarin (47). Knierzingler and Wolfbeis 28 condensed different phenols with malonic acid in the presence of phosphorus oxychloride alone at 105° for 4 h and obtained good yields of 4-hydroxycoumarins. Ogawa et al. 29,30 carried out the selenium assisted c-carbonylation of o-hydroxyacetophenone (37) with carbon monoxide in the presence of a strong base, viz. 1,8-diazabicyclo[5,1,0]undec-7-ene and obtained 4-hydroxycoumarin 1 in quantitative yield. Mizuno et al. 31 also reported a similar sulfur assisted carbonylation of o-hydroxyacetophenone derivatives in the presence of a mixture of DBU or triethylamine and the temperature being kept at 80° and the time reduced to 4 h and obtained 4-hydroxycoumarin derivatives in good to excellent yields.

Appendino et al. 32 synthesized 3-alkyl-4-hydroxycoumarin derivatives (28) in 80% yield by regioselectively alkylationing the diion of ethyl 3-(2-hydroxyphenyl)-3-oxopropanoate (48) with alkyl bromide in the presence of LDA followed by hydrolysis. 3-Phenyl-4-hydroxycoumarins (41) was readily synthesized in two steps by the titanium(III)-mediated reaction of methyl benzoyl formate (49) and substituted salicylaldehydes (50) followed by lactonization under acidic condition of resulting methyl-2,3-dihydroxy-3-(2'-hydroxyphenyl)-2-phenylpropanoates (51) 33.

Tautomerism of 4-hydroxycoumarin derivatives

Anschutz initially recognized 4-hydroxycoumarin 1 as the enol tautomer of 2,4-chromandiol (52). Arndt and coworkers later reported that 4-hydroxycoumarin could also react as 2-hydroxychromone tautomer with diazomethane in ether solution to yield a mixture of 2-methoxychromone (54) and 4-methoxycoumarin (55), the later being the major product (Scheme 1). Similar observations were made by Townsend and Odem 34 and Ahluwalia et al. 35 when warfarin and 3-allyl-4-hydroxy-7-methoxycoumarin was methylated with diazomethane, respectively.

Huebner and Link observed the formation of 2,3,4-trioxochroman-3-arylhydrazone (56) in arylation of 1 with aryl diazonium chloride in alkaline medium indicating the facile conversion of 1 to 52. This is further confirmed by the exchange by vinylic hydrogen at C-3 of 1 with deuterium to form 57 36 (Scheme 2).

Spectroscopic evidence has also been utilized to show the existence in one or other forms of 1. UV spectrum is not helpful in this case but the IR spectrum could easily distin-
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guish between structures 1 and 53. Thus 4-methoxycoumarin (55) showed carbonyl band at 1710 cm⁻¹ (CHCl₃) whereas 2-methoxycoumarin (54) showed the same at 1635 cm⁻¹ (CHCl₃)³⁷. IR spectra of 4-hydroxycoumarin (I) in solid state showed weak bands at 3000, 2720 and 2500 cm⁻¹ (OH) and a strong carbonyl band at 1704 cm⁻¹, however, the carbonyl band shifted to 1730 cm⁻¹ in dioxane solution indicating the presence of intramolecular hydrogen bond-

Porter et al.³⁸,³⁹ studied the IR spectra of 4-hydroxycoumarins by isotopic replacement of carbonyl carbon with ¹³C and also by replacement of hydrogen atoms at 3 and 4 positions by deuterium and identified the C=O stretching frequency. Thus carbonyl frequency of I at 1700 cm⁻¹ (s, br) shifted to 1658 cm⁻¹ (m, sh) in the case of I 2-¹³C ; while it shifted to 1690 cm⁻¹ (s, br) in the case of I 3,4-d₂, and identified the primary carbonyl band. In the case of 3-substituted-4-hydroxycoumarin and 3-substituted-4-alkoxy-
coumarin, the replacement of carbonyl carbon by ¹³C, the carbonyl stretching frequency was identified as the highest frequency strongly absorbing in 1550–1750 cm⁻¹ region. The carbonyl band varied from 1664 cm⁻¹ in inter- or intramolecularly hydrogen bonded derivative to 1718 cm⁻¹. No evidence for existence of 2-hydroxycromone tautomer was found except in the case of anhydrous 4-hydroxycoumarin in solid state as it showed two bands at 1700 (α-pyronyl group) and 1670 cm⁻¹ (γ-pyronyl group).

¹H NMR spectra of I (DMSO-d₆) exhibited signals at δ 5.66 (1H, s, C-2-H), 7.20–8.0 (4H, m, ArH) and 12.48 (1H, bs, C₄-OH). ¹H NMR of dicoumarol (CDCl₃) showed signals at δ 3.54 (2H, s, CH₂), 7.8–7.0 (6H, m, ArH), 8.2–8.0 (2H, m, aromatic C-5 and C-5'), 11.7 (2H, s, 2×OH). The last signal is independent of concentration and can also be removed by deuterium exchange. This indicates the presence of intramolecular hydrogen bonds and suggests the structure 58 for dicoumarol (Scheme 3). In the dicoumarol 58 (R = H), the two hydrogen bonded protons give rise to single resonance at δ 11.7; however, when the bridge methylene group bears an alkyl or an aryl group each proton gives rise to separate singlets, viz. when R = CH₃, the two protons appear at δ 11.44 and 12.14. This is because the alkyl or aryl group lies close to one of the hydroxyl protons accounting for their difference in magnetic moments.⁴³

Cussans and Huckbery⁴⁰ studied ¹³C NMR spectra of I and established that it has benzo-α-pyronyl structure and not 53 as its chemical shift of C-2 is almost near C-2 of coumarin. C-2 of I is at δ 162 and the C-2 of coumarin at δ 159.6 while the C-4 of chromone occurs at δ 177.

X-Ray studies of 4-hydroxycoumarin monohydrate reveal that it crystallizes with four molecules of I and four molecules of water in an orthorhombic unit cell. Each water molecule is hydrogen bonded to carbonyl oxygen of two adjacent 4-hydroxycoumarin molecules with inter-oxygen distance 2.59 and 2.73 Å. The oxygen of each water molecules is in turn hydrogen bonded to enolic hydroxyl of a third 4-hydroxycoumarin molecule with an inter-oxygen distance of 2.8 Å⁴¹. X-Ray studies of all other 4-hydroxycoumarin derivatives confirm that they always crystallize as 4-hydroxycoumarin and not as 2-hydroxycromone⁴².

In the mass spectral studies of 4-hydroxycoumarin, the fragmentation occurs completely in a different manner. CO expulsion from the molecular ion is virtually suppressed, while the base peak at m/z 120 corresponds to the loss of ketene (C₂H₂O) fragment from the molecular ion. It was proposed that the fission of the heterocyclic ring occurs by retero-Diels-Alder reaction, a mode which has been rationalized by assuming the participation of tautomeric chromandione molecular ion. The ion at m/z 121 arises from H transfer reaction in the course of retero-Diels-Alder cleavage. An intense fragment at m/z 92 arises by the loss of CO from [RDA]⁺ ion arised from 4-hydroxycoumarin. This observation supports the enol structure which is obtained from deuterium labeling experiment. The mass spectral studies of I, its acetyl derivative and deuterium labeled derivatives on the above lines clearly establishes the enolic structure of I⁴³.

The controversy of the tautomerism of 2,3,4-trioxo-
chronan-3-arylhydrazone (56)⁴⁴ and 3-arylazo-4-hydroxy-
coumarin (59)⁴⁵,⁴⁶ is finally settled in the favor of structure 56 by IR and ¹H NMR studies⁴⁷ and also confirmed by ¹H NMR of ¹⁵N-phenylhydrazone derivative of 2,3,4-trioxochroman⁴⁸.

Reactions of 4-hydroxycoumarin

Cyclocondensation:

Dholakia and Trivedi⁴⁹,⁵⁰ carried out the Pechmann condensation of I with malic acid in the presence of conc. sul-
furfuric acid and obtained 2,5-dioxo-2\(H\),5\(H\)-pyrano[3,2-c][1] benzopyran (60). Woods condensed I with ethyl acetoacetate in the presence of trifluoroacetic acid and claimed to have obtained 2-methyl-4,5-dioxo-4\(H\),5\(H\)-pyrano[3,2-c][1] benzopyran (61), m.p. 252\(^\circ\), principle IR bands at 3344, 1727, 1631, 1613 cm\(^{-1}\). Mustafa et al. synthesized 61 (yellow crystals, m.p. 246\(^\circ\), C=O stretching frequency at 1754 and 1667 cm\(^{-1}\)) by a different route and claimed identical with the compound prepared by Woods. Trivedi et al. repeated the work of Woods and found that 4-methyl-2,5-dioxo-2\(H\),5\(H\)-pyrano[3,2-c][1]benzopyran (62), colourless crystals, m.p. 243\(^\circ\), C=O stretching frequency at 1740 cm\(^{-1}\)) is the only isolable product when the condensation is carried out in the presence of trifluoroacetic acid. M.m.p. with authentic sample of 62 prepared by using either conc. H\(_2\)SO\(_4\) or anhydrous aluminium chloride was not depressed but the m.m.p. with authentic sample of 61 (C=O stretching frequency at 1760, 1670 cm\(^{-1}\)) prepared according to Mustafa et al. was depressed by 20\(^\circ\). The above condensation was also carried out in the presence of basic condensing agents such as ammonium acetate\(^{28,52,53}\), potassium carbonate\(^{54,55}\) and sodium bicarbonate\(^{56}\).

Compound I, refluxed with malonic acid in the presence of phosphorus oxychloride or thionyl chloride in tetrachloroethane gave 2\(H\),5\(H\)-4-hydroxypyranol[3,2-c][1] benzopyran-2,5-dione (63). Compound 63 was also prepared when 1 was refluxed with diphenyl malonate and phenol at 220\(^\circ\) for 20 min and also when 1 was refluxed with malonyl chloride in tetrachloroethane at 130\(^\circ\) for 30 min (Scheme 4).

\(1 + \text{CH}_2(\text{COOH})_2 \xrightarrow{\text{POCl}_3 \text{ or SOCl}_2} 63\)

**Scheme 4**

Subba Rao et al.\(^{57,58}\) condensed 1 with o-bromobenzoic acid (64) under the catalytic influence of aqueous copper sulfate in alkaline medium and obtained 2\(H\),7\(H\)-benzopyran[3,2-c][1]benzopyran-2,7-dione (65) in good yields (Scheme 5). When the above condensation was carried out in the presence of pyridine and anhydrous cupric chloride 2\(H\),3\(H\)-benzopyranol[3,2-c][1] benzopyran-2,3-dione (66) was obtained\(^{59}\). Reisch\(^{60}\) condensed 1 with acetylene derivative 67 in the presence of acetic acid and sulfuric acid and obtained 68, while the same condensation when carried out in the presence of phosphorus oxychloride in chloroform gave 69 (Scheme 6). Secondary alcohol 70 when condensed with 1 in the presence of hydrochloric acid followed by treatment with phosphorus oxychloride gave 71 (Scheme 7).

\(1 + \text{C}_6\text{H}_5-\text{COOH} \xrightarrow{(i) \text{H}_2\text{SO}_4, (ii) \text{POCl}_3} 71\)

**Scheme 7**

Compound 1, when condensed with o-hydroxyphenolic Mannich bases by heating at 180\(^\circ\) for 3 h followed by treatment with phosphorus oxychloride furnished benzopyranol[4,3-b][1] benzopyran-6-(7\(H\))-one (72). 1, when condensed with benzyldiene malononitrile in the presence of pyridine followed by acidic hydrolysis and cyclization with acetic anhydride gave 3,4-dihydro-2\(H\),5\(H\)-4-phenylpyranol[3,2-c][1]benzopyran-2,5-dione (73). 1, when condensed with crotonyl chloride in the presence of pyridine gave 3,4-dihydro-2\(H\),5\(H\)-4-methyl pyrano[3,2-c][1]benzopyran-2,5-dione (74)\(^{61}\).

Cyclocondensation of 1 with crotonyl chloride in the presence of titanium tetrachloride in tetrachloroethane gave 2,3-dihydro-4\(H\),5\(H\)-2-methylpyranol[3,2-c][1] benzopyran-4,5-dione (75) which on reaction with lead tetraacetate furnished 4\(H\),5\(H\)-2-methylpyranol[3,2-c][1]benzopyran-4,5-dione (76)\(^{62}\) (Scheme 8). 1, when condensed with hexachloropropene in the presence of anhydrous aluminium chloride in carbondisulphide gave 3,4-dichloro-2\(H\),5\(H\)-pyranol[3,2-c][1] benzopyran-2,5-dione (77)\(^{63}\). 1, when condensed with \(\alpha,\beta\)-unsaturated acids in the presence of polyphosphoric...
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Condensation of 1 with (2-chloro-2-nitroethenyl)benzene (79) in the presence of potassium fluoride gave 2,3-dihydro-2-nitro-3-phenyl-4H-furo[3,2-c][1]benzopyran-4-one (80). Using the same starting materials and by replacing potassium fluoride with triethyl-amine, 3-phenyl-4H-furo[3,2-c][1]benzopyran-4-one was obtained.

Soliman and Kappe carried out thermal condensation of 1 with β-aminocrotononitrile (82) and obtained tricyclic compound 2-amino-4-methyl-5H-[1]benzopyranyl[4,3-b]pyridin-5-one (83). Buu Hoi et al. condensed 1 with aniline in the presence of formaldehyde at 240° and obtained 6-oxo-6H-[1]benzopyranyl[4,3-b]quinoline (84). Tavakovic et al. condensed ethanolic solution of α-aminobenzaldehyde (85) in the presence of piperidine and obtained 6H-[1]benzopyrano[4,3-b]quinolin-6-one (84). They further condensed 2-mercaptoaniline with 1 in dimethylsulfoxide at 140–145° and obtained 6,8-dioxo-6H,7H,8H,9H,10H,11H,12H,13H,14H-5,8-dioxa-6,7,8,9-tetrahydrobenzo[a]naphthacene (93) (Scheme 10). I, when condensed with 2-arylidene naphthylamine underwent Hofmann-Mauritius type rearrangement to give benzopyranooxazine derivative (96) (Scheme 12). Checchi et al. condensed 1 with hexamethylen-tetramine at 180–190° and obtained 3,4-dihydro-1,3-oxazino[5,6-c][1,2]benzo-

![Scheme 8](image)

Acid gave 2,3-dihydro-4H,5H-pyrazo[3,2-c][1]benzopyran-4,5-dione (78). Condensation of 1 with (2-chloro-2-nitroethenyl)benzene (79) in the presence of potassium fluoride gave 2,3-dihydro-2-nitro-3-phenyl-4H-furo[3,2-c][1]benzopyran-4-one (80). Using the same starting materials and by replacing potassium fluoride with triethyl-amine, 3-phenyl-4H-furo[3,2-c][1]benzopyran-4-one was obtained.

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![Scheme 9](image)

![Scheme 10](image)

![Scheme 11](image)

![Scheme 12](image)

![Scheme 13](image)
Condensed 1 with benzoin (103) in the presence of p-toluene sulfonic acid and obtained 2,3-diphenyl-4H-furo[3,2-c]benzopyran-4-one (104).

Fucik et al. condensed two moles of 1 with α-chloroacetaldehyde diethyl acetal (112) and obtained 3-(4-hydroxycoumarin-3-yl)-2H-2,3-dihydrofuro[3,2-c][1]benzopyran-2-one (113) (Scheme 17). Eckstein and Pazidro condensed 1 with glyceraldehyde in aqueous medium and obtained 114, while condensation in dioxane gave 115 (Scheme 18). Link et al. condensed 1 with o-hydroxybenzaldehydes under different conditions and obtained different products.

When the condensation of molar ratio of 1 with o-hydroxybenzaldehyde was carried out in ethanol, 3-(o-hydroxybenzal)-2,4-diketochroman (116) was obtained. When the molar ratio was increased to two-to-one and the time of heating was increased, it gave 3-[6-oxo-[1]benzopyrano[4,3-b][1]benzopyranyl]-4-hydroxycoumarin (117). The product 117 was also obtained when 116 and 1 was refluxed in ethanol (Scheme 19). Similar results were also
Recently, Sanchez-Ferrando et al.\textsuperscript{82} have established that the structure of the product obtained by the condensation of one mole of 1 with one mole of $o$-hydroxybenzaldehyde is \(3\text{-}(2\text{-hydroxybenzoyl})\text{-}2H\text{-chromen-2-one (118)}\) and not 116. The structure of 118 was established by \(^1\)H NMR spectra (40 MHz) using 2D-COSY experiment and HETONE technique. The key feature of the spectrum of 118 is an intramolecularly bonded OH proton at \(\delta\ 11.72\) and a long range coupled double doublet at \(\delta\ 7.95\) assigned to C4-H.

Appendino et al.\textsuperscript{83} synthesized the natural product ferprenin (119) by the condensation of farnesal (120) with 1 using ethylene diammonium diacetate as catalyst (Scheme 20). They made a systematic study of the condensation of 1 with different types of enals. They observed that in the case of $\beta$-unsubstituted enals, viz. propenal, 2-ethylpropenal and 2-phenylpropenal, conjugate addition followed by hemiacetal formation between enolic OH and HC=O took place to give 121a, 121b and 121c respectively. Eckstein and Pazdro\textsuperscript{84} condensed propenal with 1 and claimed to have obtained the dimer 122 but Appendino et al.\textsuperscript{83} reported that this dimer could not be obtained on repeating the work. They also reported that in the presence of $\alpha$-substituent, the resulting hemiacetalic pyranocoumarins 121b and 121c were isolated as a mixture of diastereoisomers that could be separated in the case of 121c after methylation. In the case of $\beta$-alkyl substituted enals, 2H-pyran[3,2-c]coumarins (123) were isolated as the only reaction products. In the case of $\beta$-arylsubstituted enals, viz. 4-methoxycinnamaldehyde and 4,4-dimethylaminocinnamaldehyde gave the corresponding alkylidene chroman-2,4-diones 124a and 124b, while cinnamaldehyde gave a dimer 125 and a mixture of 123c and 124c. Talapatra et al.\textsuperscript{85} reported that compound 126 is formed when 1 is condensed with cinnamaldehyde (Scheme 21).

Appendino et al.\textsuperscript{83} carried out the condensation of citral (127) with 1 in the presence of ethylene diammonium diacetate and obtained 2-methyl-2-(4-methylpent-3-enyl)-2H,5H-pyran[3,2-c][2]benzopyran-5-one (128) in 68% yield. Dike and Merchant\textsuperscript{86} carried out the condensation of citral (127) with 1 in the presence of pyridine at 140° for 8 h and obtained a mixture of tetracyclic compounds 129 and 130 as viscous oil. Appendino et al.\textsuperscript{83} carried the condensation of 127 with 1 in presence of pyridine at 50° and obtained 128 as the only product; when the reaction was carried out at 120° using 2 moles of pyridine, pure tetracyclic compound 129 (m.p. 120°) was obtained in 18% yield. Compound 128 was the only product when the reaction was carried out with large excess of pyridine (Scheme 22).

Link et al. carried out the condensation of 1 with benzalacetone (131) in the presence of pyridine and obtained warfarin (132), a powerful anticoagulant drug, which when
treated with methanolic dry hydrogen chloride gave the cyclic ketal (133) (Scheme 23).

\[
\begin{align*}
1 + \text{C}_6\text{H}_5-\text{CH;CH-CH-CH}_3 & \xrightarrow{\text{Pyridine}} \text{MeOH + HCl} \xrightarrow{(\text{CH}_3)_2\text{CO+5N HCl}} 132 \\
131 & \xrightarrow{133}
\end{align*}
\]

Scheme 23

Bush and Trager\(^8\) condensed 1 with 131 in refluxing methanol without catalyst for 20 h and obtained 133, which on treatment with acetone and 5 \(N\) hydrochloric acid gave warfarin (132) in 93% yield. Joshi and Bose\(^8\) condensed 1 with 131 in aqueous medium using different basic condensing agents and obtained excellent yields of 132. Ivanov \textit{et al.}\(^8\) used NaF, KF and phase transfer catalysts in the above condensation and obtained good yields of 132. Link \textit{et al.}\(^9\) also condensed mesityl oxide (134) with 1 in the presence of pyridine and obtained two products, normal product 135 and alkali-insoluble product 136. Hutchinson and Tomlinson\(^9\) revised the structure of 136 as 137 on the basis of \(^1\)H NMR spectra of its hydrogenated product. Talapatra \textit{et al.}\(^5\) revised the structure of 135 as 138 on the basis of its \(^1\)H NMR spectra (Scheme 24).

\[
\begin{align*}
1 + \text{H}_2\text{C=CH-O} & \xrightarrow{\text{Pyridine}} 135 + 136 \\
134 & \xrightarrow{137 138}
\end{align*}
\]

Scheme 24

Oxidative cyclization of 4-hydroxycoumarin to coumestans:

Coumestans are naturally occurring compounds which are readily synthesized by oxidative cyclization of 4-hydroxycoumarins. Wenzlick \textit{et al.}\(^\) carried out the oxidative cyclization of 1a with catechol in the presence of potassium iodate and sodium acetate and obtained 8,9-dihydroxycoumestan (139a). They also synthesized wedelolactone (139b), a naturally occurring coumestan by the oxidative cyclization of 4,5-dihydroxy-7-methoxycoumarin with catechol using potassium ferricyanide as oxidizing agent (Scheme 25). Trivedi \textit{et al.}\(^9\) synthesized different substituted coumestan derivatives (140), furocoumestan derivatives (141, 142), 2,2-dimethylpyranocoumestan derivatives (143), benzofurocoumestan derivatives (144) and difurocoumestan derivatives (145) by condensing different 4-hydroxycoumarins with catechol using potassium iodate as oxidizing agent (Scheme 26).

\[
\begin{align*}
a: R_1=R_2=H; R_3=\text{CH}_3 \\
b: R_1=\text{OH}, R_3=\text{OCH}_3 \\
c: R_1=\text{CH}_3; R_2=\text{OCH}_3; R_3=\text{R}_4=\text{H} \\
d: R_1=\text{R}_2=\text{H}; R_3=\text{OCH}_3 \\
e: R_1=\text{R}_2=\text{OCH}_3; R_3=\text{R}_4=\text{H}
\end{align*}
\]

Scheme 25

\[
\begin{align*}
a: R_1=R_2=H; R_3=\text{CH}_3 \\
b: R_1=\text{OH}, R_3=\text{OCH}_3 \\
c: R_1=\text{CH}_3; R_2=\text{OCH}_3; R_3=\text{R}_4=\text{H} \\
d: R_1=\text{R}_2=\text{H}; R_3=\text{OCH}_3 \\
e: R_1=\text{R}_2=\text{OCH}_3; R_3=\text{R}_4=\text{H}
\end{align*}
\]

Scheme 26

Trikovnik \textit{et al.}\(^5\) synthesized 8,9-dihydroxycoumestan (139a) in high yields by anodic oxidation of catechol in the presence of 1. Wagh and Usagai\(^9\) synthesized 8-hydroxycoumestan (146) by first condensing 1 with p-benzoquinone followed by reduction with ascorbic acid and cyclohydration with methanolic hydrochloric acid gas at 0\(^\circ\). Rani and Darbarwar\(^7\) synthesized 8,9-dihydroxycoumestan derivatives by first condensing 4,5-dihydroxycoumarin with p-benzoquinone followed by Thiele's acety-
ation and cyclodehydration with methanolic hydrochloric acid gas to obtain 1,8,9-trihydroxycoumestan (147). Kappe and Brandner\textsuperscript{98} synthesized coumestrol (148), an estrogen, by first condensing resorcinol monomethyl ether with 4-methoxyphenylmalonic acid-bis-2,4,6-trichlorophenyl ester (149) at 210\textdegree to obtain 4-hydroxy-3-(4'-methoxyphenyl)-7-methoxycoumarin (150). 150, when refluxed with palladium on charcoal in diphenyl ether gave 3,9-dimethoxy-6H-benzo[furo][3,2-c][1]benzopyran-6-one (151) which when refluxed with hydrobromic acid in acetic acid gave 148. Shrihari and Sundermurty\textsuperscript{99} condensed 1 with \( o \)-benzoxquinone and obtained 3-aryl-4-hydroxycoumarin which underwent cyclocondensation upon treatment with potassium ferricyanide and sodium acetate to give 8,9-dihydroxy-3-arylbenzofuran (152) which upon irradiation with UV-light furnished coumestan (153, m.p. 190-191\textdegree), Kappe\textsuperscript{90} dehydrogenation of which with DDQ gave tetrahydrocoumestan (153, m.p. 187-188\textdegree) in 90\% yield. Kappe\textsuperscript{90} treated 177 with palladized charcoal (10\%) in diphenyl ether to obtain 4-allyloxycoumarin (178) which was directly subjected to Heck reaction in the presence of palladium chloride and triethylamine to coumestan (179) and 2,3-dihydro-2,3-cyclohexo-2,3-dimethylallyloxy-3-(1',2'-dimethylallyl)coumarin (180). They refluxed the ether 174 in diphenyl ether for 6 h and obtained 2,3,4,5-tetrahydrobenzofuro[3,2-c][1]benzopyran-6[H]-one (181) which upon irradiation with UV-light furnished coumestan (182) which upon irradiation with UV-light furnished coumestan (182) which upon irradiation with UV-light furnished coumestan (182) which upon irradiation with UV-light furnished coumestan (182).

\begin{equation}
\text{Scheme 27}
\end{equation}

I with 2-bromocyclohexanone in the presence of potassium carbonate in acetone and obtained the corresponding ether 155 instead of 153. Compound 155 when heated with polyphosphoric acid at 95-100\textdegree gave tetrahydrocoumestan (153, m.p. 190-191\textdegree), dehydrogenation of which with DDQ in benzene furnished coumestan (154, m.p. 187-188\textdegree) in 90\% yield. Kappe et al.\textsuperscript{102} condensed 1 with iodosylacetophenone (156) to obtain iodinium ylides (157) which upon heating gave 3-iodo-4-aryloxycoumarin (158). The latter deiodinated with zinc and acetic acid to give 4-aryloxycoumarin (159) which upon irradiation with uv-light furnished coumestan (154, m.p. 181-182\textdegree). Lasheober and Kappe\textsuperscript{103} modified this route for the synthesis of 154. 158 was directly subjected to Heck reaction in the presence of palladium chloride and triethylamine to coumestan (154, m.p. 182-183\textdegree) in 95\% yield.

Claissen rearrangement of allyl, prenyl and propargyl derivatives of 4-hydroxycoumarin:

Dholakia and Trivedi\textsuperscript{104} condensed 1 with allyl bromide in the presence of potassium carbonate in acetone and obtained 4-allyloxycoumarin (160), which on Claisen rearrangement at 210-220\textdegree gave 2-methyl-2,3-dihydro-4-oxo-4H-furo[3,2-c][1]benzopyran (161). The latter on heating with palladized charcoal (10\%) in diphenyl ether gave 2-methyl-4-oxo-4H-furo[3,2-c][1]benzopyran (162). The intermediate 3-allyl-4-hydroxycoumarin (163) which could not be isolated in the above reaction was prepared by Ahluwalia et al.\textsuperscript{105} by heating 160 with acetic anhydride and sodium acetate to give 4-acetoxy-3-allylcoumarin (164) followed by hydrolysis with ethanolic hydrochloric acid.

When 1 was condensed with 2,3-dichloropropene (165) in the presence of potassium carbonate in acetone, 4-(2'-chloroprop-2'-enyl)coumarin (166) was obtained. 166 on Claisen rearrangement in refluxing chlorobenzene gave 3-(2'-chloroprop-2'-enyl)-4-hydroxycoumarin (167) which when refluxed in \( N,N \)-dimethylaniline underwent cyclization to give 162. Shah and Trivedi\textsuperscript{107} condensed 1 with 1-chloro-3-methyl-2-butene (168) and obtained 4-(3,3'-dimethylallyl)coumarin (169) which on Claisen rearrangement in \( N,N \)-dimethylaniline gave the abnormal product 2,3-dihydro-4-oxo-4H-2,2,3-trimethylfuro[3,2-c][1]benzopyran (170). The intermediate 3-(1,1'-dimethylallyl)-4-hydroxycoumarin (171a) was prepared by Ahluwalia et al.\textsuperscript{108} by carrying out the reaction with acetic anhydride and sodium acetate followed by hydrolysis. Luis et al.\textsuperscript{109} also reported the Claisen rearrangement of 169 at 130\textdegree under 0.2 mm pressure gave 170; but when the rearrangement was carried out in \( N,N \)-dimethylaniline in the presence of acetic anhydride, it gave 170 and 4-acetoxy-3-(1',2'-dimethylallyl)coumarin (172). When the rearrangement was carried out in acetic anhydride only, it gave 4-acetoxy-3-(1',1'-dimethylallyl)coumarin (171b) and 4-acetoxy-3-(1',2'-dimethylallyl)coumarin (172).

Mitra et al.\textsuperscript{110} carried out the Claisen rearrangement of 4-(2-methylallyl)coumarin (173) and 4-(cyclohex-2'-enyl)coumarin (174) under reduced pressure and obtained 4-hydroxy-3-(2-methylallyl)coumarin (175) and 3-(cyclohex-2'-enyl)-4-hydroxycoumarin (176). 176 on treatment with cold conc. sulfuric acid gave a mixture of 2,3-cyclohex-2,3-dihydrofuro[3,2-c][1]benzopyran-2[H]-one (177) and 2,3-dihydro-2,3-cyclohexofuro[2,3-b][1]benzopyran-4[H]-one (178). Majumdar et al.\textsuperscript{111} treated 176 with mercury acetate in methanol and obtained 179 which when refluxed with palladized charcoal in diphenyl ether furnished benzofuro[3,2-c][1]benzopyran-6[[H]-one (180). They refluxed the ether 174 in diphenyl ether for 6 h and obtained 2,3,4,5-tetrahydrobenzofuro[3,2-c][1]benzopyran-6[H]-one (181).
(181), which on dehydrogenation with palladized charcoal in refluxing diphenyl ether gave 180. They also treated 176 with conc. sulfuric acid and obtained 177 and 182. 177 when refluxed with palladized charcoal in diphenyl ether under the similar reaction condition gave 180, while 182 remain unchanged (Scheme 28).

The isomeric structure 2,3-dihydro-4-oxo-4H-2,3,3-trimethylfuro[3,2-c][1]benzopyran (183) of 170 was also synthesized by Shah and Trivedi112. I on condensation with 3-chloro-3-methylbut-1-yne (184) in the presence of potassium carbonate in acetone gave directly 2,3-dihydro-4-oxo-4H-2-methylene-3,3-dimethylfuro[3,2-c][1]benzopyran (185) which on catalytic hydrogenation furnished 183. 185 on ozonolysis gave the lactone 2,3-dihydro-2,4-dioxo-4H-3,3-dimethylfuro[3,2-c][1]benzopyran (186) (Scheme 29). The first step of the above series of reactions was also reported by Chenevert et al.113, Patra et al.114 and Sawhney and Mathur44. Reisch and Dharmaratne115 carried out the above condensation of I and 184 and also with 3-chlorobut-1-yne (187) under phase transfer catalyst tetrabutyl ammonium bromide and obtained 2,2-dimethyl-5H-pyran[3,2-c][1]benzopyran-5-one (188) and 2,3-dihydro-4-oxo-4H-2-methylene-3-methylfuro[3,2-c][1]benzopyran-4-one (189). Majumdar et al.116 condensed I with propargylbromide (190) in the presence of potassium carbonate in acetone and obtained 4-(2-propynlyoxy)coumarin (191, m.p. 156°), which when heated in chlorobenzene gave 2H,5H-pyran[3,2-c][1]benzopyran-5-one (192, m.p. 152°) in 60% yield. Rao and Shrimannarayan117 reported Claisen rearrangement of 191 (m.p. 160°) in refluxing toluene and obtained 192 in 56% yield. Both of them reported identical spectral data. Majumdar et al.118 with 1-aryloxy-4-chlorobut-2-ynes (193) in the presence of potassium carbonate in acetone and obtained 1-aryloxy-4-(4'-coumarinylxyloxy)but-2-ynes (194). The ether 194 on Claisen rearrangement in chlorobenzene gave 4-aryloxymethyl-2H-pyran[3,2-c][1]benzopyran-5[H]-one (195) (Scheme 30).

Miscellaneous reactions of 4-hydroxycoumarin:

Compound I on bromination in chloroform gave 3-bromo-4-hydroxycoumarin (196a). Nitration of I with nitric acid in acetic acid gave 3-nitro-4-hydroxycoumarin (196b) which on hydrogenation gave 3-amino-4-hydroxycoumarin (196c). Sulfonation of I with fuming sulfuric acid gave 4-hydroxycoumarin-3-sulfonic acid (196d). 1 when reacted with acetylchloride in the presence of pyridine and piperidine gave 3-acetyl-4-hydroxycoumarin (196e). When 1 with aromatic acid chlorides, it gave the corresponding esters 197. Treatment of I with acetic anhydride gave 4-acetoxycoumarin (197a) below 155° and 3-acetyl-4-hydroxycoumarin (196e) above 180°. 197a on heating above 180°
rearranges to 196. When reacted with acetic anhydride in the presence of pyridine gave 4-acetoxy-3-(N-acetyl-1',2'-dihydro-2'-pyridyl)coumarin (198). 4-Benzoyloxy-coumarin (197b) on Fries rearrangement in the presence of anhydrous aluminium chloride gave 3-benzoyl-4-hydroxy-coumarin (196g). When the rearrangement to 197b was carried out in refluxing trifluoroacetic acid for 15 h, an abnormal product 5-benzoyl-4-hydroxycoumarin (199) was obtained (Scheme 31).

Ahluwalia et al. 128 reacted 1 with cinnamyl bromide in dioxane and obtained 4-hydroxy-3-(1-phenyl-2-propen-1-yl)coumarin (213) and 3-cinnamyl-4-hydroxycoumarin (214). Majumdar et al. 129 reacted 1 with 3-chlorocyclopentene (215) in the presence of potassium carbonate in acetone and obtained 3-(2'-cyclopenteny)-4-hydroxycoumarin (216). 1 when boiled with anisole in trioxymethylene in propionic acid gave 3-(4-methoxybenzyl)-4-hydroxycoumarin (217). Wolfrum and Bohlman 130 synthesized naturally occurring pyran[3,2-c]coumarins by Diels-Alder trapping of 3-methylene-2,4-chromandione (218a). Thus 5-methyl-4-hydroxycoumarin (219a), paraformaldehyde, cyclopentadiene (218b) when refluxed in dioxane for 4 h gave rac-norbornaphalin (221a) in 67% yield. Appendino et al. 131,132 explored this method extensively for the synthesis of substituted pyran[3,2-c]coumarins. They carried out the Diels-Alder trapping of 3-methylene-2,4-chromandione (218b), generated in situ from 1 and paraformaldehyde, with large number of dienes and acetylenes. They also synthesized (±)isoferprenin (222), a naturally occurring coumarin (Scheme 33). They found this reaction to be highly chemo-

and regioselective. Chauhan and Mathur 133 reacted 1 with benzoyl peroxide (223) with 1 and obtained 3-phenyl-4-hydroxycoumarin (214) 1 when refluxed with phosphorus oxychloride, 4-chlorocoumarin (225) and 4-chloro-3,4',3',4''-tercoumarin (226) were obtained 134,135 (Scheme 34). Mustafa et al. 136 refluxed 1 with aniline and obtained

Paraskar and Ladwa 127 prepared the Mannich base 210 by condensing (-)-menthone with paraformaldehyde and dimethylamine hydrochloride. The methiodide (221) of Mannich base reacted smoothly with 1 in the presence of triethylamine in acetonitrile to furnish (+)-4-hydroxy-3-(3-oxo-2-p-methylmethyl)coumarin (212) (Scheme 32).
Robertson and Link carried out the Mannich reaction on 1 and obtained 3-substituted-aminomethyl-4-hydroxycoumarin derivatives 235. Compounds 235 were prepared by first reacting the amines with formaldehyde in ethanol and then solution of 1 in ethanol was added to it. Trkovnik et al.142 reacted first paraformaldehyde in absolute ethanol with primary amines, and to this solution, a solution of 1 in absolute ethanol was added, when N,N-bis-(4-hydroxycoumarin-3-ylmethyl)arylamine (236) was obtained. Hismat and Khalil143 condensed different N-hydroxymethylcarboxamide (prepared by the condensation of formaldehyde with amides) with 1 in the presence of conc. sulfuric acid and obtained 3-acylamino-4-hydroxycoumarin (237). Trkovnik et al.144 condensed 1 with epibromohydrine and obtained 4-(2,3-epoxypropoxy)coumarin (238), which on treatment with hydrobromic acid gave 4-(2-hydroxy-3-bromopropoxy)coumarin (239). 239 when reacted with diethyl amine gave 4-(2-hydroxy-3-N,N-diethylaminopropoxy)coumarin (240).

Checchi et al.145 condensed 1 with ethyl orthoformate at 105° and obtained triscoumarin (241) which on hydrolysis with aqueous sodium acetate gave 3-formyl-4-hydroxycoumarin (242). The structure of 241 was revised as 3-[(4-hydroxy-3-coumarinyl)methyl]-2,4-chromandione (243) by Checchi et al.146 on the basis of 1H NMR spectra. Khan et al.147 modified the Checchi's method by condensing 1 with ethyl orthoformate in the presence of p-toluene sulfonic acid and obtained 242 in 67% yield. Zeigler and Mair prepared 242 in 19% yield by condensing 1 with N-methylformanilide in the presence of phosphorus oxychloride. Moorty et al.148 condensed 1 with dimethylformamide and phosphorus oxychloride and obtained 4-chloro-3-formylcoumarin (244) in 50% yield. Steinfuhrer et al.149 and Haber et al.150 modified the experimented conditions to obtain 244 in 85% yield (Scheme 37).

3-Ureidomethylene coumarin (245) were synthesized by the condensation of substituted ureas with 1 in the presence of ethyl orthoformate151. N-(Methylene-4-oxocoumarinyl) amino acids (246) were prepared by the condensation of 1 with α-amino acids in the presence of ethyl orthoformate152. N-(Methylene-4-oxocoumarinyl)carbamates (247) were prepared by the condensation of 1 with carbamates in the presence of ethyl orthoformate153.

Khan et al.154 condensed 1 with acetic anhydride in dimethyl sulfoxide at 120°, and obtained the ylide 3-dimethyl sulfoniochroman-2,4-dionate (248). At 160°, the reaction afforded dicoumarol (2), 2,3-dihydro-2-(2-hydroxybenzoyl)-4H-furo[3,2-c][1]benzopyran-4-one (249), 2-(2-hydroxybenzoyl)-4H-furo[3,2-c][1]benzopyran-4-one (250), 3-(2,3-dihydro-2-hydroxymethyl-1-3-oxobenz[b]furan-2-ylme-
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thyl)-4-hydroxycoumarin (251) and 2,3-dihydro-2-(2-hydroxybenzoyl-2-hydroxymethyl-4H-furo[3,2-c][1]benzopyran-4-one (252) (Scheme 38).

When 1 was refluxed with phenyl isocyanate in dimethyl sulfoxide in the presence of triethylamine, 3-phenylcarbamoyl-4-hydroxycoumarin (253) was obtained. The use of pyridine as solvent yielded urethanes (254)\(^\text{155}\) Junek carried out the addition reaction of 1 with tetracyanoethylene (255) and obtained the adduct 256. Reid et al.\(^\text{156,157}\) carried out the photochemical addition of 1 with cyclohexene in methanol by irradiation of the reaction mixture through a silica filter with a medium pressure mercury lamp and obtained 257 which readily formed acetate 258 by treatment with acetic anhydride and boron trifluoride etherate. Pyrolysis of 258 gave 259 (Scheme 39). Haywood and Reid\(^\text{58}\) carried out the intramolecular photoaddition of 4-(but-3-enyloxy)coumarin (260) as above and obtained 261. The product 262 was obtained when 4-(pent-4-enyloxy)coumarin was used (Scheme 40).

Suginome et al.\(^\text{159}\) carried out the photolysis of hypoiiodites generated by the cyclobutanol obtained by the (2+2)-photocycloaddition of 1 and (a) three cycloalkenes, (b) two acyclic alkenes, (c) vinyl ethyl ether and (d) isopropenyl acetate with mercury(II) oxide and obtained furocoumarins and furochromones. Thus 257 gave 263; when a cyclic alkene was used in the above reaction, it gave a mixture of furocoumarins (264) and furochromones (266) and a mixture of 265 and 267 (Scheme 41).

Kirkiacharian and Mentzer\(^\text{160}\) reported the total synthesis of the natural bicoumarindephnoretin (268). In the last
step of the synthesis, they carried out the reductive detosyloxylation of 4-tosyloxydephnoretin (269) with zinc and hydrochloric acid to obtain 268. This facile elimination of 4-hydroxy group to get 4-unsubstituted coumarins was utilized by Ahluwalia et al.\textsuperscript{161–163} and also by Soman and Trivedi\textsuperscript{164} to synthesize the natural coumarin-Ayapin.

**Structure and anticoagulant activity of 4-hydroxycoumarin derivatives**

Since the discovery of dicoumarol (2), which is the only bis type of 4-hydroxycoumarin used in the medicine today, many attempts have been to establish the structure-activity relationship of 4-hydroxycoumarin derivatives. The correlation of chemical structure with anticoagulant activity of 4-hydroxycoumarin derivatives has been studied by Link et al., Mentzer et al. and Chmielewska and Cieslak. These studies have clearly pointed out that minimum structural requirement is 4-hydroxycoumarin unit with a substituent in position-3 bearing a suitably placed carbonyl group and a phenyl ring separated from the 4-hydroxycoumarin by one carbon atom. For maximum activity, a bis arrangement as in dicoumarol (2) was considered to be necessary. Seshadri et al.\textsuperscript{165} have synthesized many bridge substituted dicoumarols and found them to be much less active than dicoumarol. Thus any alteration in the structure of dicoumarol results in decrease in activity. Compounds with an alkyl or aryl group in 3-position showed diminished activity. 3-Benzyl-4-hydroxycoumarin (270a) has slight anticoagulant activity but the acetylonyl derivative warfarin (132) is a powerful anticoagulant and rodenticide which is marketed. Warfarin and phenprocoumon (270b) have an asymmetric carbon atom in them. Both (+)R and (−)S enantiomers of warfarin have been tested for anticoagulant activity in rats and the (−)S isomer is 5–8 times potent than (+)R. Commercially available warfarin for use in man, however, is a racemic mixture. Other compounds which are related to warfarin and possess anticoagulant activity are coumarchlor (270c), sintron (270d). Chmielewska and Cieslak analysed the structural requirement for anticoagulant activity from the viewpoint of their vitamin K antagonism. They postulated that the active form of vitamin K can be represented by formulae 271 and 272. On the other hand, an anticoagulant which is antivitamin K should have the structure 273 and 274 which is cyclic hemiacetal obtained from appropriate 3-substituted-4-hydroxycoumarin. For such acetal formation, the carbon chain in position-3 should carry a carbonyl group in position 2′ or 3′. Link et al. synthesized cyclocoumarol, a cyclic ketal and found that it possesses greater activity than dicoumarol (Scheme 42).

**Acknowledgement**

The authors are very much grateful to Prof. A. K. Rakshit and Prof. Surekha Devi for their keen interest and moral support.

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