SUMMAIRY

S U M M A R Y

Benzopyran-2-ones generally known as coumarins are widely occuring natural products. Some naturally occuring coumarins are Umbelliferon, Aesculetin, ayapin, daphentin and scopoletin.

Coumarin derivatives have anticoagulent, antifungal, insecticidal, photochemotherapeutic properties. They also inhibit seed germination and subsequent root growth of plants.

The present work deals with the synthesis of furobenzopyrans, difuranobenzopyrans, pyranobenzopyrans, benzofurobenzopyrans, coumestans and isocoumestans.

CHAPTER - II

Synthesis of Furobenzopyrans

Some of the linear furocoumarins (psoralene) and angular furocoumarins are photochemotherapeutic agents in the treatment of psoriasis, vitiligo, leucoderma and micosis fungoids. The present work deals with the synthesis of linear as well as angular furo coumarins.

Pyrogallol on condensation with ethyl 2-cyclohexanonecarboxylate in presence of conc. H_2SO_4 gave 3,4-dihydroxy-7,8,9,10-tetrahydro-dibenzo-(b,d)-pyran-6(H)-one, which on

acetate and acetic anhydride gave its acetoxy derivative which on bromination with N-bromosuccinimide gave 7-acetoxy-8-bromomethyl-4-methyl coumarin. This on condensation with triphenyl phosphine gave corresponding bromonium salt which on Witting reaction gave 2,7-dimethyl-furo-(2,3-h)-benzopyran-5(H)-one.

Using similar procedure, synthesis of 2-phenyl-7-methyl-furo-(2,3-h)-benzopyran-5(H)-one, 2,5-dimethyl-furo (3,2-g)-benzopyran-7(H)-one, 2-phenyl-5-methyl-furo-(3,2-g)-benzopyran 7(H)-one, 2,8-dimethyl-furo-(2,3-g)-benzopyran-6(H)-one and 2 2-phenyl-8-methyl-furo-(2,3-g)-benzopyran-6(H)-one was also achieved.

CHAPTER - III

Synthesis of Isocoumestan and Coumestan derivatives

Coumestans are class of compounds which show antifungal, estrogenic and insecticidal properties. Therefore, it was thought of interest to synthesize different furo and pyrano-isocoumestans, difurocoumestans and benzofuro coumestans.

Resorcinol on condensation with 2-carbethoxy-3-2(H)-benzofuranone gave 3-hydroxy-benzofuro-(2,3-c)-benzopyran-6(H)-one, which on allylation followed by Claisen rearrangement

gave 3-hydroxy-4-allyl-benzofuro-(2,3-c)-benzopyran-6(H)-one. This on cyclisation followed by dehydrogenation with palladised charcoal gave 2-methyl-furo-(2,3-h)-benzofuro(2,3-c) benzopyran-5(H)-one.

Similar series of reactions were carried out on 3-hydroxy-4-methyl-benzofuro-(2,3-c)-benzopyran-6(H)-one to obtain 2,4-dimethyl-furo (3,2-g)-benzofuro (2,3-c)-benzopyran-6(H)-one.

Synthesis of 2-methyl-furo-(3,2-g)-benzofuro-(2,3-c)-benzopyran-6(H)-one by intramolecular Wittig reaction of triphenylphosphonium salt of 7-acetoxy-6-bromomethyl-benzofuro-(2,3-c)-benzopyran-6(H)-one and furo-(3,2-g)-benzofuro-(2,3-c) benzopyran-6(H)-one from 6-acetoxy coumaran were also achieved.

To synthesise pyranoisocoumestan, 3-hydroxy-benzofuro-(2,3-c)-benzopyran-6(H)-one was condensed with 3-chloro-3-methyl-but-1-yne, followed by Claisen rearrangement in N,N-dimethylaniline to give 2,2-dimethyl-pyrano-(2,3-h)-benzofuro-(2,3-c)-benzopyran-6(H)-one.

Similar series of reactions were carried out on 3-hydroxy-4-methyl-benzofuro-(2,3-c)-benzopyran-6(H)-one to obtain 3,3-dimethyl-(3,2-g)-pyrano-benzofuro-(2,3-c)-benzopyran-7(H)-one. The structures of all these compounds were proved by their PMR spectra.

Synthesis of difurano coumestan was carried out by first condensing 4-hydroxy coumarin with catechol using potassium periodate and sodium acetate in aq. acetone to give dihydroxy-coumestan derivative which was allylated and the diallyloxy derivative obtained was subjected to Claisen rearrangement. Here in this case one allyl group migrated while the other allyl group got cyclised. The product obtained was cyclised with Conc. H_2SO_4 and then dehydrogenated with palladised charcoal to give 8,11-dimethyl-difurano-(2,3-e : 2',3'-g)-benzofuro (3,2-c)-benzopyran-6(H)-one.

Synthesis of benzofurocoumestans was carried out by condensing 2-bromocyclohexanone with resacetophenone followed by cyclisation in O.1N alc. KOH solution. The benzofuro acetophenone was condensed with diethylcarbonate in presence of sodium metal to give 10-hydroxy-1,2,3,4-tetrahydro-benzofuro-benzopyran-8(H)-one. This was condensed with catechol using potassium periodate and sodium acetate in aq. acetone to obtain corresponding dihydroxy coumestan, which was methylated with dimethylsulfate followed by dehydrogenation with palladised charcoal to obtain 10,11-dimethoxy-dibenzofuro (3,2-c : 3',2'-g)-benzopyran-8(H)-one.

Similar series of reactions were carried out on 2-methyl resacetophenone to obtain 10,11-dimethoxy-6-methyl-dibenzofuro-(3,2-c : 3',2'-g)-benzopyran-8(H)-one. similarly dibenzofuro-

(3,2-c : 3',2'-g) benzopyran-8(H)-one was synthesised by condensing 6,7,8,9-tetrahydro-benzofuro-4-hydroxy coumarin with 2-bromo-cyclohexanone followed by cyclisation and then dehydrogenation.

CHAPTER - IV

Synthesis of benzofurobenzopyrans ayapin and Dioxo-Benzo-Dipyran

This chapter describes the synthesis of different benzofurobenzopyrans.

6,7,8,9-Tetrahydrobenzofuro-4-hydroxy-benzopyran-2(H)-one was condensed with p-toluenesulfonylchloride to give corresponding 4-tosyloxy derivative. This on reductive detosyloxylation with zinc dust and HCl gave 6,7,8,9-tetrahydrobenzo-furo-2-oxo-2H-benzopyran. This was dehydrogenated with palladised charcoal to give (3,2-g)-benzofuro-2-oxo-2H-benzopyran.

Ayapin and 4-chloroayapin were synthesised from 6,7-methylene-dioxy-4-hydroxy-benzopyran-2-one by using same technique of tosylation and reductive detosyloxylation using zinc dust and HCl. The structures of these compounds were proved by its PMR spectra.

2,10-dioxo-4-methyl-2H-10H-benzo (1,2-b : 5,6-b')-dipyran-8-carboxylic acid was synthesised from 7-hydroxy-4-methyl coumarin by condensing it with dimethylacetylene-dicarboxylate. The adduct obtained was hydrolysed with 4% aq. KOH and then cyclised with conc. H_2SO_4 to give 2,10-dioxo-4-methyl-2H-10H-benzo-(1,2-b : 5,6-b') dipyran-8-carboxylic acid. The methyl ester of this acid was obtained by condensing it with dimethylsulfate using sodium bi carbonate and dry acetone.

Similar series of reactions were carried out on 7-hydroxy-4,8-dimethyl coumarin and 6-hydroxy-4-methyl coumarin to obtain 2,6-dioxo-4,10-dimethyl-2H-6H-benzo (1,2-b : 4,5-b')-dipyran-8-carboxylic acid and 2,5-dioxo-4-methyl-2H-5H-benzo (1,2-b : 3,4-b')-dipyran-7-carboxylic acid respectively. The structures of all these compounds were proved by IR spectra.

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Studies in Synthesis of Furocoumarins : Part XXVIII†—Synthesis of Difuranocoumarins

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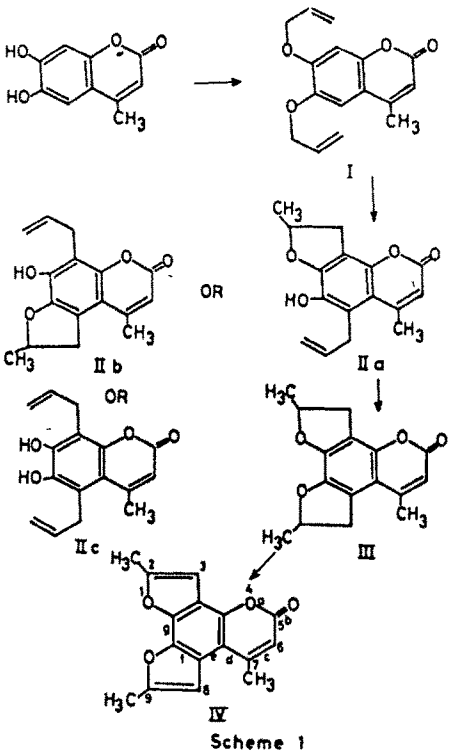
6,7-Diallyloxy-4-methylcoumarin(I) on Claisen migration gives 8-allyl-9-hydroxy-2,7-dimethyldihydrofurano[2,3-*h*] [1]-benzopyran-5(*H*)-one (IIa). The structure of IIa has been confirmed by spectral data (UV, PMR) and IIa is found to be identical (m.m p., co-TLC) with a product synthesised unambiguously starting from 6,7-diacetoxy-4-methylcoumarin. Product (IIa) on cyclisation with H_2SO_4 gives a tetrahydrodifurano derivative (III) which on dehydrogenation over 10 % Pd/C furnishes the difurano derivative (IV). Structures of all these compounds have been confirmed by their PMR spectra

For sometime we have been interested in the synthesis of various difurocoumarins[1,2]. Presently we have synthesised some diallyloxycoumarins and studied their Claisen rearrangement.

6,7-Diallyloxy-4-methylcoumarin (I), prepared by allylation of 6,7-dihydroxy-4-methylcoumarin, on Claisen rearrangement in N,N-dimethylaniline gave a product which could have either structure IIa or IIb. The possibility of structure (IIc) was ruled out on the basis of PMR spectrum which indicated the presence of dihydrofurano ring system and free allyl group. It also did not develop green colouration with neutral ferric chloride solution. The identity of IIa (Scheme 1) was finally confirmed by an unambiguous synthesis as follows:

6,7-Diacetoxy-4-methylcoumarin (V), obtained by acetylation of 6,7-dihydroxy-4-methylcoumarin, on condensation with one mol of allyl bromide (K_2CO_3-acetone method) gave 6-acetoxy-7-allyloxy-4-methylcoumarin (VI). The structure of VI was assigned on the basis of analogy of allylation of 6,7-diacetoxycoumarin[3]. VI on Claisen rearrangement in boiling N,N-dimethylamiline gave 8-allyl-6,7-dihydroxy-4-methylcoumarin (VII), which on cyclisation with 80 % sulphuric acid furnished 9-hydroxy-2,7-dimethyldihydrofurano[2,3-*h*][1]-benzopyran-5(*H*)-one (VIII). Compound (VIII) on condensation with allyl bromide led to 2,7-dimethyl-9-allyloxy-dihydrofurano [2,3-*h*] [1]-benzopyran-5(*H*)-one (IX), which on Claisen rearrangement in boiling N,N-dimethylaniline gave the product which was identical (m.m.p., co-TLC) with IIa (Scheme 2). Product (IIa) on cyclisation with 80% sulphuric acid gave 2,7,9-trimethyl-2,3,8,9-tetrahydrodifurano [2,3-*h*: 2',3'-*f*][1]-benzopyran-5(*H*)-one (III), which on dehydrogenation with palladised charcoal afforded 2,7,9-trimethyldifurano [2,3-*h*: 2',3'-*f*][1]-benzopyran-5(*H*)-one (IV).



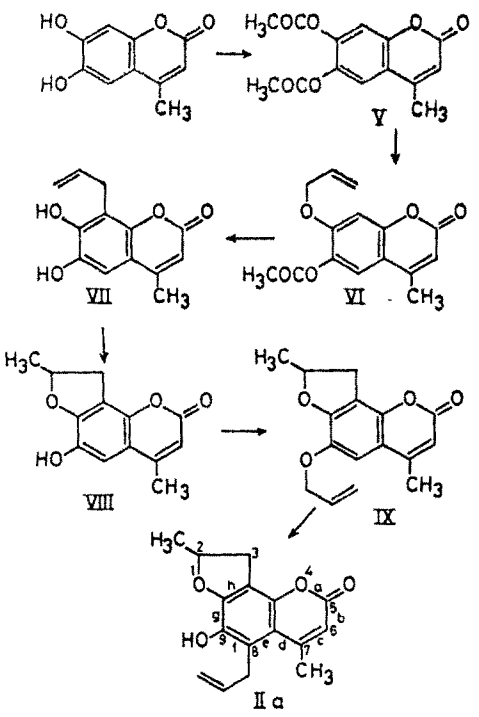
Scheme 1

Experimental Procedure

6,7-*Diallyloxy*-4-*methylcoumarin* (*I*)[3]

A mixture of 6,7-dihydroxy-4-methylcoumarin (4.0g), allyl bromide (4 2 ml) and anhydrous potassium carbonate (16g) in dry acetone (200 ml) was

†Part XXVII Desai S M & Trivedi K N, *Indian J Chem*, **24B** (1985) 47



Scheme 2

refluxed for 10 hr on a water-bath, concentrated and poured into water. The solid obtained was filtered, washed with aq sodium hydroxide and crystallised from benzene, m.p. 102°, yield 3.4 g (Found : C, 71.0; H, 6.2. $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.8 %).

8-Allyl-9-hydroxy-2,7-dimethyl-dihydrofurano [2,3-h] (1) - benzopyran-5(H)-one (IIa)

Compound (I, 2g) was refluxed with N,N-dimethylaniline (10 ml) for 5 hr and poured into concentrated hydrochloric acid containing crushed ice. The reaction mixture was extracted with ether, etheral layer shaken with aq. sodium hydroxide, the alkaline layer separated and acidified with conc. hydrochloric acid. The separated product was purified by column chromatography using benzene as an eluent and recrystallised from benzene, m p. 144°; yield 1.0 g (Found : C, 70.2; H, 5.8. $C_{16}H_{16}O_4$ requires C, 70.6; H, 5 8 %); PMR ($CDCl_3$/TMS) : δ 1.5 (3H, *d*, J= 7Hz,C_2-CH_3), 2.8(3H, *s*, C_7-CH_3), 3.0 (1H, *dd*, J= 18, 8Hz, C_3-H), 3.4 (1H, *dd*, J= 18, 8 Hz, C_3-H), 3.75 (2H, *m*, $-CH_2$-CH=CH_2), 5.0 (3H, *m*, $-CH_2$-CH=CH_3) and C_2-H), 5.6 (1H, *m*, $-CH_2$-CH=CH_2), 6 0(1H, *s*, C_6-H), UV(MeOH)[4] : λ_{max} 340 nm (log ε 5 2), 1 *M* NaOH · λ_{max} 400 nm (log ε 2 4)

2,7,9-Trimethyl-2,3,8,9-tetrahydrodifurano[2,3,-h : 2',3'- f][1]-benzopyran-5(H)-one (III)

Compound (IIa, 1g) was triturated with conc. sulphuric acid (5 ml) and then heated on a water-bath for 10 min. The mixture was poured onto crushed ice, the separated product filtered off and washed with aq. sodium hydroxide. It was purified by column chromatography using benzene as an eluent and then recrystallised from benzene, m.p. 182°, yield 0.7g (Found : C, 70.4; H, 6.0. $C_{26}H_{16}O_4$ requires C, 70.6; H, 5.8 %); PMR ($CDCl_3$/TMS) : δ 1.5(6H, *d*, J= 7Hz, C_2-CH_3 and C_3-CH_3), 2.4(3H, *s*, C_7-CH_3), 2 8-3.8 (4H, *m*, C_3-CH_2- and C_8-CH_2-), 5.1 (2H, *m*, C_2-H and C_9-H), 6.0 (1H, *s*, C_6-H).

2,7,9-Trimethyl-difurano[2,3-h; 2',3'-f][1]-benzopyran-5(H)-one (IV)

A mixture of III (0.5g) and 10 % pd/C (1g) was refluxed in diphenyl ether (5-6 ml) for 24 hr. The reaction mixture was filtered hot and the solvent removed by steam distillation. The product was purified by preparative TLC and crystallised from benzene, m.p 212°; yield 0.2g (Found : C, 71.2; H, 4.2. $C_{16}H_{12}O_4$ requires C, 71.6; H, 4.4 %). It showed yellow fluoroscence in UV light; PMR ($CDCl_3$/TMS): δ 2.5 (6H,*s*, C_2-CH_3 and C_9-CH_3), 2.6(3H, *s*, C_7-CH_3), 6.2(1H, *s*, C_6-H), 6.8(2H, *s*, C_3-H and C_8-H).

6,7-Diacetoxy-4-methyl coumarin (V)

6,7-Dihydroxy-4-methylcoumarin (4g) was acetylated (anhydrous sodium acetate/Ac_2O). Usual work-up afforded V, which was crystallised from benzene, m.p. 154°; yield 4.2g (Found : C, 60.7; H, 4.1. $C_{14}H_{12}O_6$ requires C, 60.8; H, 4.2 %).

7-Allyloxy-6-acetoxy-4-methylcoumarin (VI)

Allylation of V (2.7g) with allyl bromide (1.2 ml) by anhydrous K_2CO_3-acetone method afforded VI, after usual work-up VI was crystallised from benzene, m p. 142°, yield 2 9g (Found : C, 65.2, H, 5 0 $C_{15}H_{14}O_5$ requires C, 65.6; H, 5.1 %).

8-Allyl-6,7-dihydroxy-4-methylcoumarin (VII)

Compound (VI, 2g) was refluxed with dimethylaniline (10 ml) for 5 hr and poured into concentrated hydrochloric acid containing crushed ice. The reaction mixture was extracted with ether, the ethereal layer shaken with aq. sodium hydroxide, the alkaline layer separated and acidified with conc. hydrochloric acid to yield VII. The separated product was purified by column chromatography using benzene as an eluent and recrystallised from benzene, m.p. 225°, yield 1g (Found : C, 66.8; H, 5 0 $C_{13}H_{12}O_4$ requires C, 67.2; H, 5.1 %).

9-Hydroxy-2,7-dimethyl-dihydrofurano[2,3-h][1]-benzopyran-5(H)-one (VIII)

Compound (VII, 1g) was triturated with conc.

sulphuric acid (5 ml) and then heated for 10 min in a water-bath. The mixture was poured onto crushed ice, the separated product filtered and crystallised from benzene, m.p. 201°, yield 0.6g (Found : C, 67.6; H, 5.3. $C_{13}H_{12}O_4$ requires C, 67.2; H, 5.1 %); PMR (DMSO-d_6/TMS) : δ 1.4(3H, *d*, *H*=7Hz, C_2-CH_3), 2.4(3H, *s*, C_7-CH_3), 2.8-3.2 (2H, *m*, C_3-H_2), 5.1 (1H, *m*, C_2-H), 6.1(1H, *s*, C_6-H), 6.95 (1H, *s*, C_8-H).

9-Allyloxy-2,7-dimethyl-dihydrofurano[2,3-h]-(1) benzopyran-5(H)-one (IX)

A mixture of VIII (2.5g), anhydrous K_2CO_3 (8g) and allyl bromide (1.2 ml) was refluxed for 8 hr in dry acetone (150 ml); usual work-up afforded IX which was washed with aq. NaOH and crystallised from benzene, m.p. 130°, yield 1.5 g (Found : C, 70.9; H, 5.7. $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.8 %).

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