SUMMARY

Chromones, chromenes and chromanones belong to the general class of compounds known as benzopyran. They widely occour in nature. Some of the chromones occuring in the nature are Khellin, Visnagin, Eugenin. Similarly Prococene-I Prococene-II. Eupatoriochromene are some simple chromenes occuring in nature. While Xanthyletin and Seslin are naturally occouring coumarins having fused chromene ring system. Furochromenes are pharmacochemical analogues of naturally occouring furocoumarins and they are also potential photosensitizers. Similarly chromanones are also very important compounds which resembles to chromones in pharmacological activity and they are also intermediates in the synthesis of chromenes.

The present work deals with the synthesis of 2,3'-bichromones, furochromenes, benzofuro benzo-γ -pyrones and furochromanones.

CHAPTER - I

Introduction

It describes the natural occourrence, pharmacological activity and spectral datas of chromones, chromenes and chromanones.

CHAPTER - II

Synthesis of 2,3'-Bichromones

o-Hydroxyacetophenones and it's derivtives such as

5-Methyl-2-hydroxyacetophenone, 4-methoxy-2-hydroxyacetophenone and 4,5-Dimethyl-2-hydroxyacetophenones were taken as starting materials which were prepared by the known methods such as Fries migation, Friedel-craft acylation and Alkylation. These o-Hydroxyacetophenones on condensation with ethylformate in the presence of puverized sodium in dry ether furnished 2-hydroxychromanones. It was found that these 2-hydroxychromanones derivatives were thermally unstable, when they were heated above their melting point, they undewent dimerization with elimination of two moles of water to give 1-(2-hydroxybenzoyl)-2-(4-oxo-4H-1-benzopyran-3-yl) ethylene derivatives. These 1-(2-hydroxybenzoyl)-2-(4-oxo-4H-1-benzopyran-3-yl) ethylene derivatives were subjected to oxidative cyclisation by freshly sublimied selenium dioxide in refluxing isoamyl alcohol to obtain 2,3'-bichromones.

CHAPTER - III

Synthesis of furochromenes and furochromene carboxylic acids derivatives

Resacetophenone and 2,4-dihydroxybenzophenone on condensation with Hydroxyisovaleraldehyde dimethylacetal in presence of pyridine at 170°C gave 5-Hydroxy-6-acetyl and 5-hydroxy-6-benzoyl-2,2-dimethyl-2H-1-benzopyran. These chromene derivatives on condensation with ethylbromoacetate followed by

hydrolysis gave 6-acetyl-2,2-dimethyl-5-chromenoxy acetic acid and 6-benzoyl-2,2-dimethyl-5-chromenoxy acetic acid respectively which were cyclized with fused NaOAc and Ac_2O to gave 2,2,7-trimethyl furo [2,3-f]-2H-1-benzopyran and 2,2-dimethyl-7-phenylfuro (2,3-f]-2H-1-benzopyran respectively.

Similarly 5-Hydroxy-6-acetyl ; 5-Hydroxy-6-benzoyl-2,2-dimethyl-2H-1-benzopyran and 7-Hydroxy-6-formyl-2,2,8-trimethyl 2H-1-benzopyran on condensation with ethyl bromomalonate followed by hydrolysis furnished 2,2,7-trimethyl furo-[2,3-f] 2H-1-benzopyran-6-carboxylic acid ; 2,2-Dimethyl-7-phenyl furo-[2,3-f]-2H-1-benzopyran-6-carboxylic acid and Ethyl-2,2-dimethyl-furo-[3,2-g]-2H-1-benzopyran-7-carboxylate (hydro lysis could not be carried out) respectively.

Resacetophenone and 2,4-Dihydroxy-3-methyl acetophenone on BF_3 - catalysed prenylation with 2-Methyl-but-3-en-2-ol in dioxan gave their respective 5-prenyl derivatives which on cyclisation with formicacid provides 7-Hydroxy-6-acetyl-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran and 7-Hydroxy-6-acetyl-2,2,8-trimethyl-3,4-dihydro-2H-1-benzopyran respectively. They were condensed with ethylbromomalonate in dry acetone for 36 hrs. followed by dehydrogenation with 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dry benzene furnished 2,2,6-Trimethyl-furo [3,2-g]-2H-1-benzopyran-7-

carboxylic acid and 2,2,6,9-tetramethyl-furo [3,2-g]-2H-1-benzopyran-7-carboxylic acidrespectively.

CHAPTER - IV

Section - I

Synthesis of Benzofuro benzo-γ -pyrones

7-Hydroxy-2,2-dimethyl-2,3-dihydro-4H-1-benzopyran-4-one ; 7-Hydroxy-2,2,8-trimethyl-2,3-dihydro-4H-1-benzopyran-4-one on condensation with 2-Bromocyclohexanone furnished 7-(cyclohexan-2-enyloxy) ethers which when refluxed with O.1N alcoholic KOH cyclised to give tetrahydrobenzofuro benzo-γ-pyrones which were aromatised to benzofurochromanones with 10% palladised charcol in refluxing diphenyl ether.

Similarly resacetophenone and 2,4-Dihydroxy-3-methyl acetophenone on condensation with 2-bromocyclohexanone gave 4-(cyclohexan-2-onyloxy) ethers which were cyclised to tetrahydro dibenzofuran derivatives. These on condensation with ethyl formate in presence of pulverised sodium metal followed by dehydration with H_2SO_4 (25%) gave tetrahydrobenzofuro benzo-γ-pyrones derivatives which were dehydrogenated to 4H-benzofuro (3,2-g)benzopyran-4-one and 11-Methyl-benzofuro (3,2-g) benzopyran-4-one respectively.

Section - II

Synthesis of Furochromanones and Novel migration of 7-(3',3'-dimethyl-propargyloxy) 2,2,8-trimethyl-2,3-dihydro-4H-1-benzopyran-4-one

7-Hydroxy-2,2-dimethyl-2,3-dihydro-4H-1-benzopyran-4-one and 7-Hydroxy-2,2,8-trimethyl-2,3-dihydro-4H-1-benzopyran-4-one wee condensed with allyl bromide in presence of K_2CO_3 in refluxing acetone gave allyloxy derivatives. These ethers underwent Claisen migration in refluxing N,N-dimethylaniline gave 7-hydroxy-8-allyl and 7-hydroxy-6-allyl chromanones respectively, which were titurated with conc. H_2SO_4 to give 2,5,5-trimethyl-2,3,5,6-tetrahydro-4H-furo (2,3-h)-benzopyran-4-one and 2,7,7,9-tetramethyl-2,3,6,7-tetrahydro-4H-furo (3,2-g)-benzopyran-4-one respectively. Dehydrogenation of these cyclised furochromanones with 10% palladised charcol in refluxing diphenylether failed. In order to get the furo-chromanones, sodium salts of 7-hydroxy-8-allyl-2,2-dimethyl chromanone and 7-hydroxy-6-allyl-2,2,8-trimethylchromanone when treated with dichloro (bisbenzonitrile) palladium complex in dry benzene, gave 2,2,5-trimethyl-5,6-dihydro-4H-furo (2,3-h)benzopyran-4-one and 2,7,7,9-tetramethyl-6,7-dihydro-4H-benzofuro (3,2-g)benzopyran-4-one drespectively.

7-Hydroxy-2,2,8-trimethylchromanone on condensation with prenyl bromide gave 7-prenyloxy-2,2-trimethylchromanone which

underwent Claisen migration in refluxing N,N-dimethylaniline gave 7-hydroxy-6-(1',2'-dimethyl-prop-2-enyl)-2,2,8-trimethyl chromanone which on tituration with 80% H_2SO_4 gave 2,2,3,7,7,9-hexamethyl-2,3,6,7-tetrahydro-4H-furo (3,2-g)-benzopyran-4-one.

In order to synthesize pyranochromanones 7-Hydroxy-2,2-dimethyl chromanone was condensed with propargyl bromide and 3-methyl-3-chloro-but-1-yne, the respective ethers underwent cyclisation in refluxing N,N-dimethylaniline gave 6,6-dimethyl-6,7-dihydro-4H-pyrano (2,3-h)benzopyran-4-one and 2,2,6,6-tetrahydro-6,7-dihydro-4H-pyrano (2,3-h)benzopyran-4-one respectively.

Similarly 7-hydroxy-2,2,8-trimethylchromanone on condensation with 3-chloro-3-methyl-but-1-yne gave 7-(3',3'-propargyloxy)-2,2,8-trimethylchromanone. This ether on refluxing with N,N-dimethylaniline for 6 hrs. furnished the novel product 1,2,3,5,6,7-hexahydro-1,1,3,5,5-pentamethyl-cyclopenta (2,3-h) [2H,7H]-benzopyran-2,7-dione. The structure of which was assigned by IR, PMR and C^{13}NMR spectral datas.

Mechanism of this novel migration is also discussed.

Indian Journal of Chemistry
Vol 27B, September 1988, pp. 811-813

Thermal Dimerization of 2-Hydroxychromanones to 1-(2-Hydroxybenzoyl)-2-(4-oxo-4*H*-1-benzopyran-3-yl)ethylene Derivatives: An Unusual Observation

R R SONI & K N TRIVEDI*
Department of Chemistry, Faculty of Science,
M S. University of Baroda, Baroda 390002

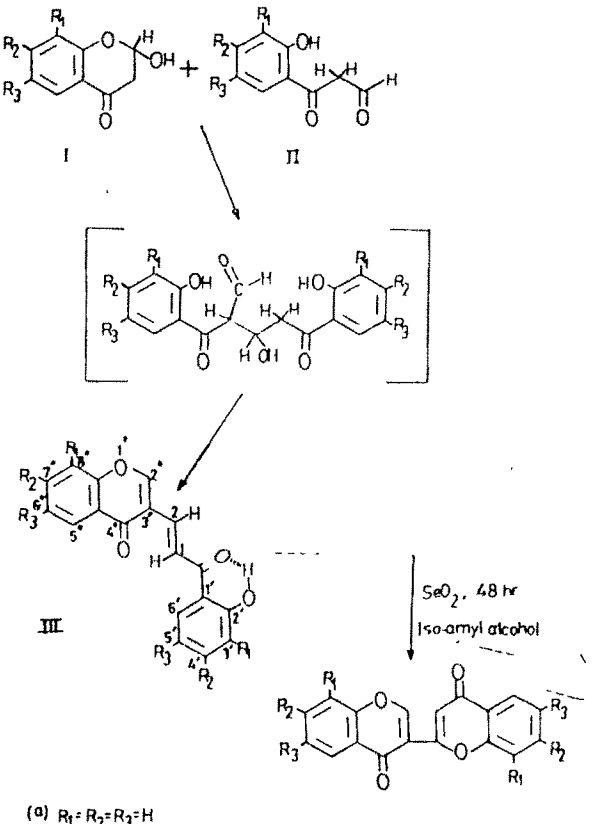
Received 21 *August* 1987, *revised and accepted* 7 *March* 1988

o-Hydroxyacetophenone derivatives on condensation with ethyl formate in the presence of sodium give the corresponding 2-hydroxychromanones (I), which when heated above their melting points afford 1-(2-hydroxybenzoyl)-2-(4-oxo-4*H*-1-benzopyran-3-yl)ethylene derivatives (III) These ethylene derivatives (III) are cyclized to [2, 3'-bi-4*H*-1-benzopyran]-4, 4'-dione derivatives (IV) by selenium dioxide in refluxing isoamyl alcohol

Shah[1] has reported the synthesis of 2,2'-dimethyl-7,7'-dimethoxy-[6,6'-bi-4*H*-1-benzopyran]-4,4'-diones and 2,2'-dimethyl-7,7'-dimethoxy-[8,8'-bi-4*H*-1-benzopyran]-4,4'-diones by the Ullaman reaction from the corresponding iodochromones. The present work deals with the synthesis of [2,3'-bi-4*H*-1-benzopyran-4,4'-diones (IV)

Schonberg and Sina[2] condensed *o*-hydroxyacetophenones with ethyl formate in the presence of sodium metal and claimed to have obtained ω-formyl derivatives (II) of the ketones. Their structure assignment was carried out by their strong ferric reaction and conversion into chromones by ethanolic sulphuric acid Narsimhachari *et al.*[3] carried out the condensation of phloroacetophenone dimethyl ether with ethyl formate in the presence of sodium and obtained a product which on the basis of colour reaction and change in melting point, on recrystallization was considered to be a tautomeric mixture of ω-formyl derivative and the cyclic product 2,3-dihydro-2-hydroxy-5, 7-dimethoxychromone

Recently Ahluwalia and Prakash[4] made a detailed study of the above reaction and confirmed the cyclic 2-hydroxychromanone structure. In the present work, the *o*-hydroxyacetophenone when condensed with ethyl formate and sodium gave 2-hydroxychromanone (Ia). Its structure was confirmed by PMR spectrum in $CDCl_3$ showing signals at δ 2.85-3.15 (*m*, 2H, 3-CH_2), 5.92 (*t*, *J*=5Hz, 1H, H-2), 6.9-7.5 (*m*, 3H, H-6, H-7 and H-8), 7.8 (*dd*, *J*=8 Hz, 2Hz, 1H, H-5) and 4.3 (*bs*, 1H, C_2-OH). There was no signal for the aldehydic proton around δ 9.0. This compound was unexpectedly unstable around it's melting point (105°) and underwent a rapid transformation to a yellow compound (m.p. 178-79°). This thermal reaction appears to be a bimolecular condensation between I and II to give 1-(2-hydroxybenzoyl)-2-(4-oxo-4*H*-1-benzopyran-3yl) ethylene (IIIa; m.p. 178-79°). This is



a novel observation of thermal dimerisation taking place at the m.p. of the substance. The change in m p observed by earlier workers may be due to this type of thermal dimerisation.

The stucture of IIIa was established by its spectral data. Its PMR ($CDCl_3$) spectrum showed signals at δ 12 7 (1H, *s*, bonded OH), 8.75 (*d*, *J*=16Hz, H-1), 7.45 (*d*, *J*=16Hz, H-2, *trans*-alkene), 8 2 (*dd*, *J*=9, 2Hz,

H-5″), 8.14 (*s*, 1H, H-2″), 7.95 (*dd*, *J*=9, 2Hz, 1H, H-6′), 6.85-6.94 (*m*, 2H, H-5′ and H-3′) and 7.4-7.7 (*m*, 4H, Ar-*H*). The Mass spectrum of IIIa exhibited peaks at *m/z* 292 (M^+), 171 (**a**), 121 (**b**).

Similarly 6-methyl-2-hydroxychromanone (Ib), 7-methoxy-8-methyl-2-hydroxychromanone (Ic) and 6, 7-dimethyl-2-hydroxychromanone (Id) were prepared from the corresponding *o*-hydroxyacetophenone derivatives. These compounds when heated above their melting points gave 1-(2-hydroxy-5-methylbenzoyl)-2-(6-methyl-4-oxo-4*H*-1benzopyran-3-yl)ethylene (IIIb), 1-(2-hydroxy-4-methoxy-3-methylbenzoyl)-2-(7-methoxy-8-methyl-oxo-4*H*-1-benzopyran 3-yl)ethylene (IIIc) and 1-(2-hydroxy-4,5-dimethylbenzoyl)-2-(6, 7-dimethyl-4-oxo-4*H*-1-benzopyran-3-yl-)ethylene (IIId), respectively.

The ethylene derivatives IIIa-d when refluxed with selenium dioxide in isoamyl alcohol furnished (2, 3′-bi-4*H*-1-benzopyran)-4, 4′-dione (IVa), 6, 6′-dimethyl-(2, 3′-bi-4*H*-1-benzopyran)-4,4′-dione (IVb), 7, 7′-dimethoxy-8, 8′dimethyl-(2, 3′-bi-4*H*-1-benzopyran)-4, 4′-dione (IVc) and 6, 6′, 7, 7′-tetramethyl- (2, 3′-bi-4*H*-1-benzopyran)-4, 4′-dione (IVd), respectively. The structural assignments of IV were based on elemental analyses and mass spectral data (Table 1). Due to insolubility of these compounds in common PMR solvents, their PMR spectra could not be recorded.

Experimental Procedure

Melting points are uncorrected PMR spectra were recorded on Perkin-Elmer R-32 90MHz and 220 MHz spectrophotometers and mass spectra on a Kratrs MS 30 instrument fitted with a DS 55 data system.

The required *o*-hydroxyacetophenones were prepared by known methods.

2-Hydroxychromanone (I)

To *o*-hydroxyacetophenone (0.05 mol) in warm ethyl formate (30 ml) in a flask fitted with a reflux condenser, was added pulverized sodium (3.0 g) suspended in dry ether, and the vigorous reaction regulated by external cooling whenever necessary. After the reaction subsided, ethyl formate (6.0 ml) was added followed by sodium (1.0 g) and the reaction mixture refluxed for 10 min and left overnight. Ice and water were then added carefully and the resulting solution was extracted twice with ether. The aq. layer was acidified with dil. acetic acid. An oil separated out which solidified quickly into a crystalline solid. It was filtered, dried and crystallised from a 1:1 mixture of benzene and ether (40-60°) to give I as colourless crystals, m.p. 105°

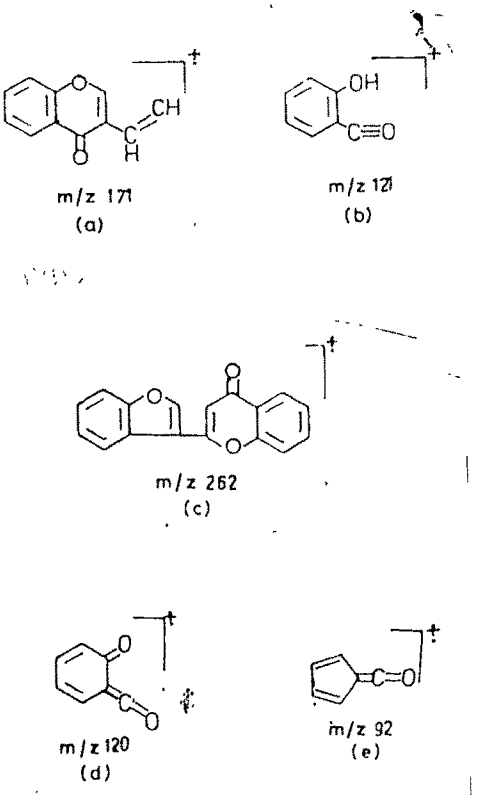


Table 1 - Physical Data of 2-Hydroxychromanones (I), Hydroxybenzoyl)-2-(4-oxo-4*H*-1-benzopyran-3-yl) ethyl (III) and [2,3′-Bi-4*H*-1-benzopyran]-4,4′-diones (IV

	I		III		IV		
	m.p. °C	Yield (%)	m.p. °C	Yield (%)	m.p. °C	Yield (%)	MS (*m/z*)
a	105	75	178-79	51	238	20	290, 262(120 (d) 92 (e)
b	132	74	196	50	258	17	318, 290, 134, 106
c	155	74	252	53	318	22	378, 363, 335, 215
d	138	73	233	51	276	20	--

All the compounds gave satisfactory C and H analyses

Melting points and % yields of 2-hydrochrom ones (I), thus prepared, are given in Table. I

1-(2-hydroxybenzoyl)-2-(4-oxo-4H-1-benzopyran yl) ethylenes (III; Table 1)

An appropriate 2-hydroxychromanone (I, 0.01 m was taken in a dry test tube and immersed in an bath having temperature slightly higher than melting point. The substance first melted and t resolidified at the same temperature. It was crystal

from benzene to give III as yellow coloured dles.

3'-Bi-4H-1-benzopyran]-4, 4'-diones (IV)

To a solution of III (0.002 mol) in a minimum ntity of isoamyl alcohol was added freshly sublim- selenium dioxide (0 5g), and the reaction mixture luxed at 165-170° in an oil-bath for 48 hr, filtered t and isoamyl alcohol removed by steam dstillation give a solid which on crystallization from a suitable ivent gave IV(Table 1)

cknowledgement

he authors thank Dr F M Dean, Department of Organic Chemistry, University of Liverpool, Liverpool,England for PMR spectra and Dr R T Pardasani, Chemistry Department, University of Manchester, England for mass spectra. One of them (RRS) is thankful to the CSIR, New Delhi, for the award of a research fellowship.

References

1 Shah M V, *Curr Sci*, **31** (1962) 57
2 Schonberg A & Sina A, *J Am chem Soc*, **72** (1950) 3396
3 Narsimhachari N, Rajagopalan D & Seshadri T R, *J scient ind Res*, **12B** (1953) 287
4 Ahluwalia V K & Prakash C, *Indian J Chem*, **15B** (1977) 331