Heterocyclic Letters
Vol. 11| No.3|457-462| May-July|2021
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

CONSTITUTION OF FLAVONE PITGULARIN - C

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Abstract : Constitution of a new flavone Pitgularin - C isolated from Pityrograma triangularis has been confirmed by its synthesis as 3,5- dihydroxy -7 –methoxy - 8 methylflavone (I) by two methods: First method utilised 2 ′-hydroxy–3 ′-methyl -4 ′, 6 ′ dimethoxychalcone (v) as an essential intermediate. AFO oxidation of (V) gave 3-hydroxy-5 ,7-dimethoxy-8-methylflavone (II) which on selective demethylation formed 3 ,5 –dihyroxy-7-methoxy-8-methylflavone (I) . Second method utilised Allan Robinson condensation of 2 –hydroxy- ω ,4,6-trimethoxy -3-methylacetophenone (VII) , Benzoic anhydride and sodium benzoate to get 3,5,7-trimethoxy-8-methylflavone (III) which on demethylation followed by selective methylation gave 3 ,5 –dihyroxy-7-methoxy-8-methylflavone (I)

Key words: Pityrograma triangularis, Pitgularin–C, 3,5–dihyroxy-7-methoxy-8-methylflavone , AFO condensation , Allan Robinson condensation

Introduction

A new pigment Pitgularin –C was isolated from the plant Pityrograma triangularis also called Goldback Fern (Wollenweber et al 1985) [xix] . This compound was on the basis of its spectral data proposed its constitution as 3,5–dihyroxy-7-methoxy-8-methylflavone (I) ***This is a Flavonoid compound .The basic unit of flavone is γ -pyrone which is present as Benzo - γ - pyrone (chromone). This is a class of oxy –heterocyclic chemical compound*** . For this new flavonoid pigment no synthetic support was provided by Wollenweber and his co - workers. This communication reports the synthesis of 3 ,5 –dihyroxy-7-methoxy-8-methylflavone (I) by two unambiguous methods .

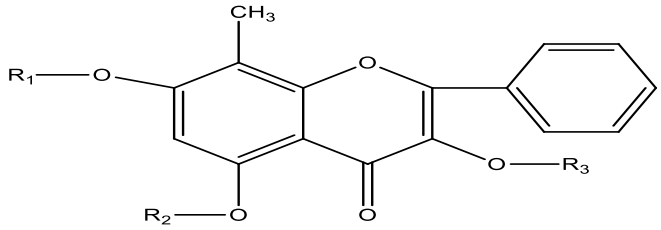
In the ***First method*** : Phloroacetophenone was obtained by Hoesch condensation of Phloroglucinol with acetonitrile .It was subjected to nuclear methylation with methyl iodide to get 2-hydroxy-3-methyl-4,6-dimethoxy acetophenone (VI) along with 2-hydroxy-4,6-dimethoxy acetophenone .The two products were separated by fractional crystallization. Condensation of 2-hydroxy-3-methyl-4,6-dimethoxy acetophenone (VI) with benzaldehyde in the presence of ethanolic potassium hydroxide gave 2 ′-hydroxy-3 ′-methyl -4 ′,6 ′-dimethoxychalcone (V) [v] . This chalcone when subjected to Algar , Flynn and Oyamada oxidation [i ,xii] using hydrogen peroxide gave 3-hydroxy-5 ,7-dimethoxy-8-methylflavone (II). This flavone on selective demethylation using Aluminium chloride –nitrobenzene at room temperature gave 3,5–dihyroxy-7-methoxy-8-methylflavone (I) [vii] .

In ***Second method*** : 2 –hydroxy- ω ,4,6-trimethoxy-3-methylacetophenone (VII) was used as an important intermediate. This was obtained by Hoesch condensation of phloroglucinol with

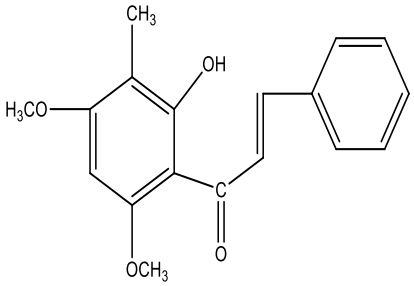
methoxy acetonitrile. ω - methoxy phloroacetophenone thus obtained was subjected to nuclear methylation to get 2 –hydroxy- ω ,4,6-trimethoxy-3-methylacetophenone (VII) along with a side product which was removed by fractional crystallization. Allan Robinson condensation [ii] of 2 –hydroxy- ω ,4,6-trimethoxy-3-methylacetophenone (VII) with benzoic anhydride in the presence of sodium benzoate give the required 3,5,7-trimethoxy-8-methylflavone (III) which was completely demethylated by refluxing with aluminium chloride dry acetone to get 3,5,7-trihydroxy-8-methylflavone (IV) .

This was further subjected to selective methylation at C -7 hydroxyl group in the presence of methyl iodide - potassium bicarbonate to get 3 ,5 –dihyroxy-7-methoxy-8-methylflavone (I) The C-7 hydroxyl group being in conjunction with the carbonyl group was more reactive and could be selectively methylated in flavones [xiii , xiv] . The flavonoid (I) synthesized is proved to be 3 ,5 -dihydroxy -7 methoxy - 8 –methylflavone by UV , PMR and various colour reactions as follows :

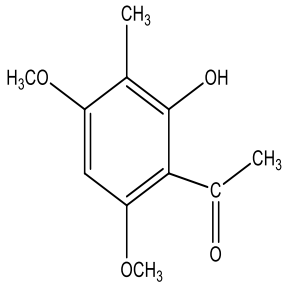
1. The final product when taken in ethanol and then reduced with magnesium powder and hydrochloric acid developed red colouration suggesting a C -3 hydroxy flavone . [xviii]
2. Product when subjected to Asahina Inubuse test did not develop any characteristic colouration showing the presence of free C - 3 hydroxyl group .[iii]
3. UV spectrum of product when examined first in ethanol alone and then in ethanol – aluminium chloride exhibited Bathochromic shift indicating the presence of two free hydroxyl groups at C -3 and C - 5 positions in flavone .
4. This was further supported by UV spectrum that it did not exhibit Bathochromic Shift in the presence of sodium acetate which is specific for C - 7 hydroxy flavone [xi] .
5. The compound did not dissolve in aqueous sodium carbonate indicating the absence of free hydroxyl function at C -7 positions.
6. The product did not give Gibb's test showing C -8 position para to C-5 was not free but had a substituent that is methyl group [vi , x] .
7. PMR spectrum shows broad singlet for C-3 and C -5 hydroxyl groups which are chelated with carbonyl group and slight deshielded peak for C-7 methoxyl group which is in conjugation with C-4 carbonyl.
8. The product when acetylated using acetic anhydride and pyridine give a compound which on the basis of PMR was characterised as diacetyl derivative of (I) .



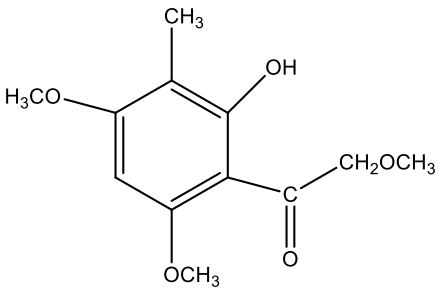
(I) $R_1=CH_3$, $R_2=R_3=H$
(II) $R_1=R_2= CH_3$, $R_3=H$
(III) $R_1=R_2=R_3=OCH_3$
(IV) $R_1=R_2=R_3=OH$



(VI)



(V)



(VII)

Pitgularin –C is a novel flavonoid compound having C- methyl function at C-8 position . All flavonoid compounds including Pitgularin-C are important for human health because of their antioxidant , antibacterial , antiviral and anti-inflammatory activities and they act as free radical scavengers as they are potential reducing agents that protect from oxidative damage which are conferred by the content of hydroxyl groups . In view of the fact that flavonoids are important health enhancing polyphenolic compounds, it is important to synthesise the pigment Pitgularin –C .

Recent research on flavonoids [ix] and there Bio-medical applications has attracted our attention due to their mechanism of action against a variety of health disorders .

Ipriflavone was found to be suitable for reducing symptoms of osteoporosis. Flavonihippopha was suitable for ischemic heart disease treatment . Six flavonoids [xv] have been identified as novel cellular antioxidants. Flavonoids like quercetin , herbacetin and isobavachalcone are discovered as the most promising flavonoids with anti-inflammatory [viii , xvi] potential against covid-19 .

Dietary flavonoids [xvii] like Catechin (from green tea) , Apigenin (from celery) , flavanol Quercetin glycosides (from apples,berries and onion) and flavanone naringenin from citrus fruits exhibit cancer preventive properties , obesity prevention and anti covid -19 properties .

Result and Discussion

EXPERIMENTAL METHOD 1:

Synthesis of 2′-hydroxy-3′-methyl -4′,6′-dimethoxychalcone (V)

A solution of 2-hydroxy-3-methyl-4,6-dimethoxy acetophenone (VI) (1gm) and distilled benzaldehyde (1.2 ml) was treated with Potassium hydroxide (3 g in 10 ml alcohol) and left at room temperature for 48 hours . It was diluted with water and excess benzaldehyde was removed by ether extraction . The alkaline solution was acidified to get 2′-hydroxy-3′-methyl -4′,6′-dimethoxychalcone (V) . It was separated , washed with water and recrystallized from chloroform - benzene as orange crystals .

m . p . 140-41 ^{0}

PMR Spectrum : δ , $CDCl_3$, TMS as an internal standard :

2.00 (3H , s , 1 x $-CH_3$) , 3.90-3.93 (6H , multiplet ,2 x $-OCH_3$) .6.00 (1 H,s ,C-5'-OH) ,7.25-7.70 (6H, m , C-α-H) , 7.85 (1H, d , J=16 Hz ,C- β –H) , 13.90 (1H , s , -OH)

3-hydroxy-5 ,7-dimethoxy-8-methylflavone (II)

A solution of 2′-hydroxy-3′-methyl -4′,6′-dimethoxychalcone (V) in a mixture of pyridine (5ml) and water (2ml) was treated with potassium hydroxide (12 ml , 10%) and warmed to 60 - 70 ^{0} . Hydrogen peroxide was added with stirring for 5 minutes. Insoluble fraction was removed and clear alkaline solution on acidification gave 3-hydroxy-5 ,7-dimethoxy-8-methylflavone (II) . It was then crystallised from ethanol as pale yellow needles 300 mg . m.p 190-91^0

UV Spectrum (λ max) :

MeOH : 270 , 320, 356 nm

MeOH + $AlCl_3$: 280 , 350 , 408 nm

MeOH + $AlCl_3$ + HCl : 278 , 350 , 402 nm

MeOH + CH_3COONa : 270 , 322 , 356 nm

PMR Spectrum (δ, $CDCl_3$, TMS as an internal standard)

2.00 (3H , s , 1X - CH_3) , 3.85 (6H ,s , 2 X - OCH_3) ,6.60 (1H , s , C_6-H) , 7.50 – 7.70 (5H ,m , - C_6H_5) , 9.60 (1H , s , C -3- OH)

3 ,5 –dihyroxy-7-methoxy-8-methylflavone (I) :

A solution of 3-hydroxy-5 ,7-dimethoxy-8-methlyflavone (II) 200 mg in nitrobenzene was heated with anhydrous aluminium chloride 500 mg at 50 ^{0} at water bath for 30 minutes . The reaction mixture was cooled and then treated with petroleum ether till the nitrobenzene was removed . The reaction product was treated with water (50 ml) and conc . Hydrochloric acid (20 ml) and then heated on steam bath for 20 minutes . The demethylation product thus obtained was extracted with Ethyl acetate and purified with fractional crystallization . The flavone (I) thus obtained was crystallised from alcohol as small needles , (100 mg) , m.p.198 ^{0} .

UV Spectrum (λ max) :

MeOH : 264 , 318 , 359 nm

MeOH + $AlCl_3$: 275 , 352 , 412 nm

MeOH + $AlCl_3$ + HCl : 275 , 351 , 404 nm

MeOH + CH_3COONa : 264 , 321, 359 nm

PMR Spectrum (δ, $CDCl_3$, TMS as an internal standard) :

1.95 (3H , s , 1 x $-CH_3$) , 3.85 (3 H , s , 1H X $-OCH_3$) , 6.60 (1H , s , C_6 – H) , 7.62 – 7.82 (5H , m , - C_6H_5) , 13.45 -13.6 (2H , bs , C_3 and C_5 – OH)

EXPERIMENTAL METHOD 2 :

Synthesis of 3,5,7-trimethoxy-8-methylflavone (III) :

A mixture of 2 –hydroxy- ω ,4,6-trimethoxy - 3 -methylacetophenone (VII) , Benzoic anhydride and sodium benzoate were heated under reduced pressure in oil bath at 175-80 ^{0} for 4 hours . It was cooled and the residue was taken up in aqueous sodium hydroxide (30ml , 10%) . It was heated under reflux for 15 minutes , cooled and then saturated with carbon dioxide . The solid that separated out was filtered out . The reaction product 3,5,7-trimethoxy-8-methylflavone (III) thus obtained crystallized from methyl alcohol as colourless needles 1.5 gm m .p . 159-60 ^{0} .

PMR Spectrum (δ, $CDCl_3$, TMS as an internal standard) :

1.90 (3H , s , 1 X – CH_3) , 3.90 (9H , m , 3 X – OCH_3) , 6.50 (1H , s , C_6 –H) , 7.60-7.80 (5 H , m , - C_6H_5)

3,5,7-Trihydroxy-8-methylflavone (IV) :

A solution of 3,5,7-trimethoxy-8-methylflavone (III) in dry benzene 60ml was treated with anhydrous aluminium chloride 2 gm. The reaction mixture was refluxed on a water bath for 4 hours , the solvent was distilled off from the reaction mixture under reduced pressure , the residue thus obtained was treated with dilute hydrochloric acid (25 ml) in cold , then it was heated on a steam bath for one hour with occasional shaking. The reaction product when cooled gave (IV) as yellow solid. It recrystallized from alcohol to give 3,5,7-trihydroxy-8-methylflavone (IV) as small needles 400 mg . m.p 261-262 ^{0}.

UV Spectrum (λ max) :

MeOH	:	268 , 325 , 362 nm
MeOH + $AlCl_3$	:	280 , 355 , 412 nm
MeOH + $AlCl_3$ + Hcl	:	280 , 355 , 408 nm
MeOH + CH_3COONa	:	280 , 332 , 400 nm

3 ,5 –Dihydroxy-7-methoxy-8-methylflavone (I)

A solution of 3,5,7-trihydroxy-8-methylflavone (IV) 500 mg in dry acetone (50ml) was treated with dry potassium carbonate (2.5 gms) and then methyl iodide (0.2 ml) was added to this solution. It was refluxed on water bath for 8 hours . The reaction product thus obtained was treated with water and it was found to be a mixture of 3 ,5 –dihyroxy-7-methoxy-8-methylflavone (I) and a little unreacted product which was removed by treating with sodium carbonate 10% . Compound (I) thus obtained crystallized from ethyl alcohol as pale yellow needles , 150 mg , m.p. 198 ^{0} . It gave green colourtion with ethanolic ferric chloride.

UV Spectrum (λ max) :

MeOH	:	265 , 318 , 358 , nm
MeOH + $AlCl_3$	:	275 , 350 , 410 nm
MeOH + $AlCl_3$ + Hcl	:	275 , 350 , 405 nm
MeOH + CH_3COONa	:	265 , 320 , 360 nm

PMR Spectrum (δ , CD_3COCD_3 , TMS as an internal standard) :

1.95 (3H , s , 1 X – CH_3) , 3.85 (3H , s , 1 X - OCH_3) , 6.60 (1H ,s , C_6-H) ,7.60 – 7.80 (5 H , m , - C_6H_5) , 13.50-13.8 (2H , bs , C_3 and C_5 – OH)

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Received on June 3, 2021