# SEARCH FOR PHYSIOLOGICALLY ACTIVE COMPOUNDS

## Part XXIV. Synthesis of 7, 8-Furano, Pyrono and 3-Methyl-4-Phenylcoumarins

BY M. SUBRAMANYAM RAJU AND N. V. SUBBA RAO

*(Department of Chemistry, Osmania University, Hyderabad-500007, A.P.)*

Received February 9, 1974

ABSTRACT

7-Hydroxy-3-methyl 4-phenylcoumarin and α-methyl dihydrofurano, α and γ-pyrono ring systems have been built on 7, 8-position of 4-phenylcoumarin. The bacteriostatic activity of these compounds as well as that of mammeisin and mesuol isolated from *Mesua ferrea* seeds has been evaluated. Structure-activity relationship among these compounds is discussed.

MAMMEISIN (I) and mesuol (II), 4-phenylcoumarin derivatives have been isolated from *Mesua ferrea* seeds[1-4]. Bacteriostatic examination of these 4-phenylcoumarins revealed that they were active against gram + ve and − ve organisms even at a dilution of 5 ppm (Table I). Therefore, it was considered desirable to synthesise some 4-phenylcoumarins with a view to test their physiological activity. In the present paper, the synthesis and bacteriostatic activity of 7-hydroxy-3-methyl-4-phenylcoumarin and also a few 4-phenylcoumarins possessing a hetero ring at 7: 8 positions are described.

Perkin condensation of 2, 4-dihydroxy benzophenone with propionic anhydride and sodium propionate yielded 7-propoxy-3-methyl-4-phenylcoumarin which on acid hydrolysis gave 7-hydroxy-3-methyl-4-phenylcoumarin (III). This compound exhibited lactone carbonyl at 1720 $cm^{-1}$ and unsaturated side phenyl at 755 $cm^{-1}$ and 695 $cm^{-1}$. Further, it also gave pink colour with magnesium and hydrochloric acid. Methyl and allyl ethers of (III) have also been prepared.

α-Methyl dihydrofurano ring system has been built at 7, 8-position of 7-hydroxy-4-phenylcoumarin by adopting the following procedure. Among the methods available for the synthesis of α-methyl dihydro furano ring system[5-7] the method due to Arnold and Moran[7] has been chosen, because of mild conditions made use of in the method. 7-Hydroxy-4-phenylcoumarin[8] (IV *a*) has been allylated, with allylbromide in acetone-potassium

carbonate. The resulting 7-O-allyl compound (IV *b*) has been subjected to Claisen rearrangement, yielding 7-hydroxy-8-allyl-4-phenylcoumarin (IV *c*), which on treatment with hydrobromic acid in acetic acid give the corresponding 7-hydroxy-8-$\beta$-bromopropyl-4-phenylcoumarin (IV *d*). The cyclization of this could be effected by potassium carbonate in boiling acetone, resulting in the formation of 4-phenyl 2′, 3′-dihydro-2′-methyl furano (5′, 4′ : 7, 8) coumarin (V). It showed a prominent absorption at 1736 $cm^{-1}$ due to the coumarin carbonyl.

4-Phenyl-$\alpha$-pyrono (6′, 5′ : 7, 8) coumarin (VI) has been prepared from 7-hydroxy-4-phenylcoumarin (IV), by first heating with hexamine in glacial acetic acid to give the 8-formyl compound (IV *e*). It gave red colour with alcoholic ferric chloride indicative of chelated carbonyl. (IV *e*) has been subjected to Perkin reaction making use of acetic anyhydride and fused sodium acetate, yielding 4-phenyl-$\alpha$-pyrono (6′, 5′ : 7, 8)-coumarin (VI). It did not show colouration with alcoholic ferric chloride but exhibited two distinct absorptions in the carbonyl region one at 1690 $cm^{-1}$ and the other at 1736 $cm^{-1}$ due to the two carbonyls.

7-Hydroxy-4-phenylcoumarin has been acetylated and the resulting 7-O-acetyl compound (IV *f*) has been subjected to Fries migration with anhydrous aluminium chloride to give rise to 7-hydroxy-8-acetyl-4-phenylcoumarin (IV *g*). It gave deep violet colour with alcoholic ferric chloride. (IV *g*) has been subjected to Claisen condensation with ethyl acetate in the presence of sodium to yield the corresponding $\beta$-diketone, which could be directly cyclised with dilute hydrochloric acid to 4-phenyl-2-methyl-$\gamma$-pyrono (6′, 5′ : 7, 8) coumarin (VII). It gave no colouration with alcoholic ferric chloride. It showed two distinct absorptions in the carbonyl region one at 1639 $cm^{-1}$ due to the chromone carbonyl and the other at 1736 $cm^{-1}$ due to the lactone carbonyl.

*Bacteriostatic testing.*—The bacteriostatic activity has been carried out against *Staphylococcus aureus*, *Bacillus subtilis* and *Bacillus coli* by the tube dilution technique at two dilutions 10 ppm and 100 ppm. 4-Phenyl-$\alpha$-pyrono (6′, 5′ : 7, 8) coumarin has shown activity against both gram + ve and − ve organisms at a dilution of 5 ppm. The 4-phenyl-2′-methyl-$\gamma$-pyrono (6′, 5′ : 7, 8) coumarin is found to be active at dilutions of 100 ppm towards *S. aureus*, *B. subtilis* and *B. coli* and 10 ppm towards *B. coli*. These results on synthetic 4-phenylcoumarins are not active, $\alpha$-pyrono and $\gamma$-pyrono-4-phenylcoumarins exhibited considerable activity comparable to that shown by mammeisin and mesuol.

TABLE I

*Bacteriostatic activity of 4-phenylcoumarins*

| Compounds | S. A. | A. B. | B. S. | A. B. | B. C. | A. B. |
|---|---|---|---|---|---|---|
| *1. Mammeisin | − | − | − | − | − | − |
| *2. Mesuol | − | − | − | − | − | − |
| 3. 7-Hydroxy-4-phenylcoumarin | + | ± | + | ± | + | − |
| 4. 7-Methoxy-4-phenylcoumarin | + | + | + | + | + | ± |
| 5. 7-Allyloxy-4-phenylcoumarin | ± | ± | + | + | + | − |
| 6. 7-Hydroxy-3-methyl-4-phenyl-coumarin | + | ± | + | ± | + | ± |
| 7. 7-Methoxy-3-methyl-4-phenyl-coumarin | + | + | + | + | + | ± |
| 8. 7-Allyloxy-3-methyl-4-phenyl-coumarin | + | ± | + | ± | + | ± |
| 9. 4-Phenyl-2′, 3′-dihydro-2′-methyl furano (5′, 4′ : 7, 8) coumarin | + | ± | + | + | + | + |
| *10. 4-Phenyl-α-pyrono (6′, 5′: 7, 8) coumarin | − | − | − | − | − | − |
| 11. 4-Phenyl-2 -methyl-γ-pyrono-(6′, 5′: 7, 8) coumarin | + | − | + | − | + | − |

* Active at 5 ppm. A= 10 ppm. B=100 ppm.

S.A.= *Staphylococcus aureus*; B.S., *Bacillus subtilis*; B.C= *Bacillus coli*.

\+ Full growth; − No growth; ± Partial growth.

## EXPERIMENTAL

### 1. *7-Hydroxy-3-Methyl-4-Phenylcoumarin*

(*a*) *7-Propoxy-3-methyl-4-phenylcoumarin*.—2, 4-Dihydroxy benzophenone (1 g) was refluxed with propionic anhydride (1·9 ml) and sodium propionate

(1·5 g) on an oil-bath at 180° for six hours. After keeping overnight, water was added, filtered and crystallised from alcohol as colourless needles (0·95 g), mp 112–14° (Found: C, 77·36; H, 6·10. $C_{19}H_{18}O_3$ requires C, 77·56; H, 6·13%).

(*b*) *7-Hydroxy-3-methyl-4-phenylcoumarin.*—7-Propoxy-3-methyl-4-phenylcoumarin (0·7 g) was hydrolysed by boiling with 5% alcoholic hydrochloric acid (20 ml) for eight hours. The alcohol was removed under reduced pressure and water was added. The product was filtered and crystallised from alcohol as yellow crystals (0·55 g) mp 216–18° (Found: C, 76·12; H, 4·80. $C_{16}H_{12}O_3$ requires C, 76·19; H, 4·76%). This compound responded to the magnesium and hydrochloric acid test.

2. *7-Methoxy-3-Methyl-4-Phenylcoumarin*

7-Hydroxy-3-methyl-4-phenylcoumarin (0·5 g) was refluxed with dimethyl sulphate (0·30 ml), anhydrous potassium carbonate (3 *g*) and dry acetone (25 ml) for 8 hours. The acetone solution was filtered and evaporated. The product was crystallised from alcohol as square plates (0·35 g), mp 132–33° (Found: C, 76·59; H, 5·30. $C_{17}H_{14}O_3$ requires C, 76·78; H, 5·26%).

3. *7-Allyloxy-3-Methyl-4-Phenylcoumarin*

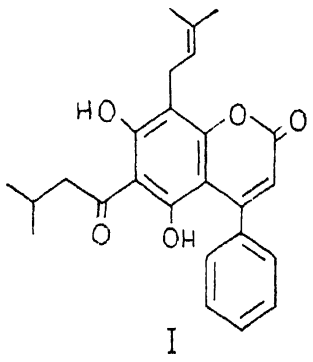
7-Hydroxy-3-methyl-4-phenylcoumarin (0·5 g) was refluxed in dry acetone (30 ml) with ignited potassium carbonate (1·5 g) and allyl bromide (0·4 ml) for six hours. The solvent was distilled off and water was added to precipitate the crude allyloxy compound. Crystallisation from alcohol furnished the 7-allyl ether as stout prisms (0·33 g), mp 84° (Found; C, 77·98; H, 5·41. $C_{19}H_{16}O_3$ requires C, 78·07; H, 5·48%).

4. *4-Phenyl-2′, 3′-Dihydro-2′-Methyl Furano* (5′, 4′: 7, 8) *Coumarin*

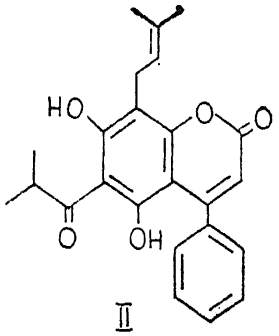
(*a*) *7-Allyloxy-4-phenylcoumarin.*— 7-Hydroxy-4-phenylcoumarin[8] (2 g) was refluxed in dry acetone (100 ml), ignited potassium carbonate (4·0 g) and allyl bromide (1·2 ml) for six hours. The acetone was distilled off and crude allyloxy compound was precipitated after adding water to it. It was crystallised from alcohol, as stout prisms (1·6 g), mp 85° (Found: C, 77·50; H, 4·96. $C_{18}H_{14}O_3$ requires C, 77·71; H, 5·04%).

(*b*) *7-Hydroxy-8-allyl-4-phenylcoumarin.*—The 7-allyloxy-4-phenyl-coumarin (1 g) was heated under reduced pressure at 190–5° for two hours. The product obtained was crystallised from alcohol as colourless needles

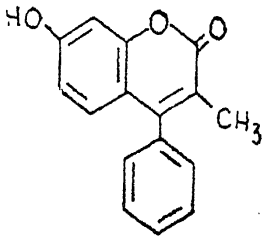
(0·75 g), mp 192–3° (Found: C, 77·45; H, 5·20. $C_{18}H_{14}O_3$ requires C, 77·71; H, 5·03%).



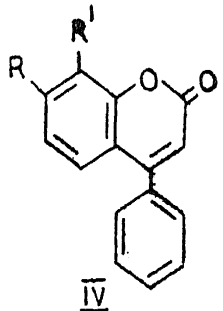

I




II




III




IV

a) R = OH; R' = H

b) R = $OCH_2-CH=CH_2$; R' = H

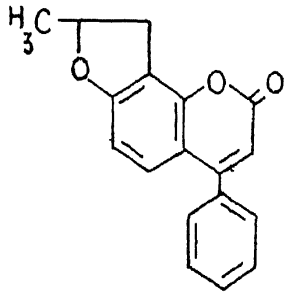
c) R = OH; R' = $-CH_2-\underset{Br}{CH}=CH_2$

d) R = OH; R' = $-CH_2-\underset{Br}{CH}-CH_3$

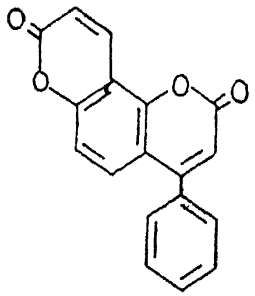
e) R = OH; R' = CHO

f) R = $-O\cdot CO\cdot CH_3$; R' = H

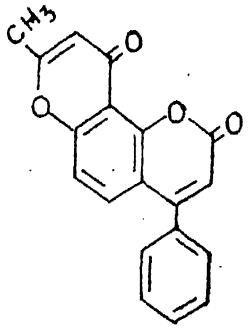
g) R = OH; R' = $-COCH_3$




V




VI




VII

CHART

(*c*) *7-Hydroxy-8-β-bromopropyl-4-phenylcoumarin.*—A solution of 7-hydroxy-8-allyl-4-phenylcoumarin (0·6 g) in glacial acetic acid (10 ml) was heated with hydrobromic acid (48%, 4 ml) on a water-bath at 50° for eight hours, cooled and poured into crushed ice (60 g) and stirred. The solid separated was filtered, washed, dried and crystallised from alcohol as brown needles (0·45 g), mp 188° (Found: C, 60·33; H, 4·21. $C_{18}H_{15}O_3Br$ requires C, 60·17; H, 4·18%). This compound gave positive test for bromine,

(*d*) *4-Phenyl 2', 3'-dihydro-2'-methyl furano* (5', 4' : 7, 8) *coumarin.*—The above bromo-4-phenylcoumarin (0·3 g) was suspended in dry acetone (40 ml) and treated with ignited potassium carbonate (30 g). The mixture was heated under reflux for six hours. Acetone was distilled off and the residue was poured into water and left in a refrigerator for twelve hours. The product was crystallised from ethylacetate-petroleum ether mixture (1 : 3) as colourless rectangular rods (0·25 *g*), mp 176° (Found: C, 77·68; H, 5·12. $C_{18}H_{14}O_3$ requires C, 77·71; H, 5·04%). Mixed melting point with the 7-hydroxy-8-β-bromopropyl-4-phenylcoumarin was found to be depressed.

5. *4-Phenyl-α-Pyrono* (6', 5': 7, 8) *Coumarin*

(*a*) *7-Hydroxy-8-formyl-4-phenyl coumarin.*—A solution of 7-hydroxy-4-phenylcoumarin (1 g) in glacial acetic acid (30 ml) was mixed with hexamine (4 g) and then heated on a boiling water-bath for six hours. The solution was then treated with hot dilute hydrochloric acid (1 :1, 20 ml), followed by further heating for half an hour. It was diluted to 200 ml and left overnight in an ice chest. The reaction mixture was then extracted with ether and the ether extract was washed with sodium bicarbonate to remove acid impurities. Removal of the solvent gave a solid which on crystallisation from alcohol was yellow plates (0·7 g), mp 157·8° (Found C, 72·01; H, 3·65. $C_{16}H_{10}O_4$ requires C, 72·18; H, 3·76%).

(*b*) *4-Phenyl-α-pyrono* (6', 5' : 7, 8) *coumarin.*—A mixture of 7-hydroxy-8-formyl-4-phenylcoumarin (0·3 g), acetic anhydride (10 ml) and freshly fused sodium acetate (1·0 g) was gently boiled under reflux at 180–5° for twelve hours. Then the cooled reaction mixture was decomposed using ice-water and the solid that separated out was filtered, dried, recrystallised from alcohol as brown crystals (0·25 g), mp 90° (Found: C, 74·41; H, 3·56. $C_{18}H_{10}O_4$ requires C, 74·49; H, 3·45%). In aqueous alcoholic solution it exhibited a violet fluorescence and in concentrated sulphuric acid a weak blue fluorescence.

6. *4-Phenyl-2'-Methyl-γ-Pyrono* (6', 5': 7, 8) *Coumarin*

(*a*) *7-Hydroxy-8-acetyl-4-phenylcoumarin.*—A mixture of 7-acetoxy-4-phenylcoumarin[9] (1·0 g) and powdered anhydrous aluminium chloride, (2·5 g) was heated on a metal bath first at 140° and when the reaction mixture melted, the temperature raised slowly at 160°. After maintaining for one hour at that temperature, the mixture was cooled. The reaction product was decomposed using cold hydrochloric acid and the substance obtained

was crystallised twice from alcohol as colourless rectangular rods (0·6 g), mp 126–8° (Found: C, 72·75; H, 4·36. $C_{17}H_{12}O_4$ requires C, 72·85; H, 4·29%). Alcoholic ferric chloride gave an intense red colour.

(*b*) *4-Phenyl-2′-methyl-γ-pyrono* (6′, 5′ : 7, 8) *coumarin.*—7-Hydroxy-8-acetyl-4-phenylcoumarin (0·45 g) was dissolved in freshly distilled ethyl acetate (15 ml) and to it pulverised sodium (1·5 g) was added with cooling. The reaction mixture was then boiled under reflux for about 2 hours. Then the excess sodium was decomposed using small quantities of methanol and the mixture decomposed using dilute hydrochloric acid. The residue obtained on dilution was extracted with ether, washed with water and dried with sodium sulphate. The product obtained after removal of ether was crystallised from alcohol, when the 4-phenyl-2′-methyl-γ-pyrono (6′, 5′ : 7, 8) coumarin appeared as brown crystals (0·2 g), mp 226° (Found: C, 74·85; H, 4·01. $C_{19}H_{12}O_4$ requires C, 74·99; H, 3·95%).

## Acknowledgements

One of the authors (M. S. R.) is thankful to the Central Council for Research in Indian Medicine and Homoeopathy for the financial assistance.

## References

1. Subramanyam Raju, M. and Subba Rao, N. V. — *Indian J. Chem.*, 1969, **7**, 1278.
2. Datta, P., Deb, N. and Bose, P. K. — *Indian Chem. Soc.*, 1940, **17**, 277.
3. Chakraborthy, D. P. and Bose, P.K. — *Proc. Natl. Inst Sci.*, 1960, **26 A** (Suppl.), 1.
4. ——— and Das, B. C. .. — *Tetrahedron Letters*, 1966, **46**, 5727.
5. Adams, R., Roman, M. and Sperry, E. — *J. Amer. Chem. Soc.*, 1921, **44**, 178.
6. Krishnaswamy, B. and Seshadri, T. R. — *Proc. Indian Acad. Sci.*, 1941, **13 A**, 143.
7. Arnold, E. and Moran, A. H. — *J. Amer. Chem. Soc.*, 1942, **64**, 2986.
8. Pechmann, H. and Hancke, E. — *Ber.*, 1901, **34**, 356.
9. Adolfsonn. .. — *Ibid.*, 1918, **51**, 821.