# SEARCH FOR PHYSIOLOGICALLY ACTIVE COMPOUNDS

## Part XXV. Synthesis of 7, 8-Furano- and Pyrono-3-Methyl-2-(2-Furyl)-Chromones

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ABSTRACT

α-Methyldihydrofurano, γ and α-pyrono ring systems have been built on 7, 8-position of 2-(2-furyl)-3-methyl chromone. The structure-activity relationship among 2-(2-furyl)-chromones is discussed.

7-METHOXY FLAVONE (I) is the simplest of Benzpyrones, possessing appreciable fish toxicity.[1] Karanjin (II), an angular furano-3-methoxy flavone, was reported to exhibit considerable toxicity to fish.[2] The fish toxicity of 2-(2-furyl)-chromones[3] (Table I) revealed that among them 7-methoxy-3-methyl-2-(2-furyl)-chromone III (*a*) has been found to possess the highest toxicity. It was therefore considered worthwhile to build heterocyclic systems such as α-methyl-dihydrofurano, γ and α-pyrono rings at 7, 8-positions of 3-methyl-2-(2-furyl)-chromone and evaluate the physiological activity of the compounds thus synthesized.

7, 8-*Dihydrofurano*-2-(2-*furyl*) – α-3-*dimethylchromone*.—Among the methods available for the synthesis of α-methyl dihydrofurano ring systems,[4-6] the method due to Arnold and Moran[7] has been chosen, because of the mild conditions adopted throughout. Adopting this method, 7-hydroxy-3-methyl-2-(2-furyl)-chromone III (*b*) has been allylated, with allylbromide in acetone-potassium carbonate. The resulting 7-0-allyl compound III (*c*) has been subjected to Claisen rearrangement. That the allyl group migrates to 8-position has been established in the case of flavonoids.[4] The resulting 7-hydroxy-8-allyl-compound III (*d*) has been subjected to hydrobromic acid addition in polar solvents like acetic acid to give the desired 7-hydroxy-8-β-bromo propyl chromone III (*e*). This bromo compound has been cyclised in acetone-potassium carbonate to result in the formation of the title compound (IV). This compound showed in 95% ethanol, three distinct absorptions $\lambda_{max}$ 261 nm (3·15), 316 nm (3·01) and 363 nm (3·96). It showed a prominent absorption at $\nu$ 1624 $cm^{-1}$ in ir due to the chromone carbonyl.

TABLE I

*Fish toxicity of* 2-(2-*furyl*)-*chromones*

Conc. 20 ppm

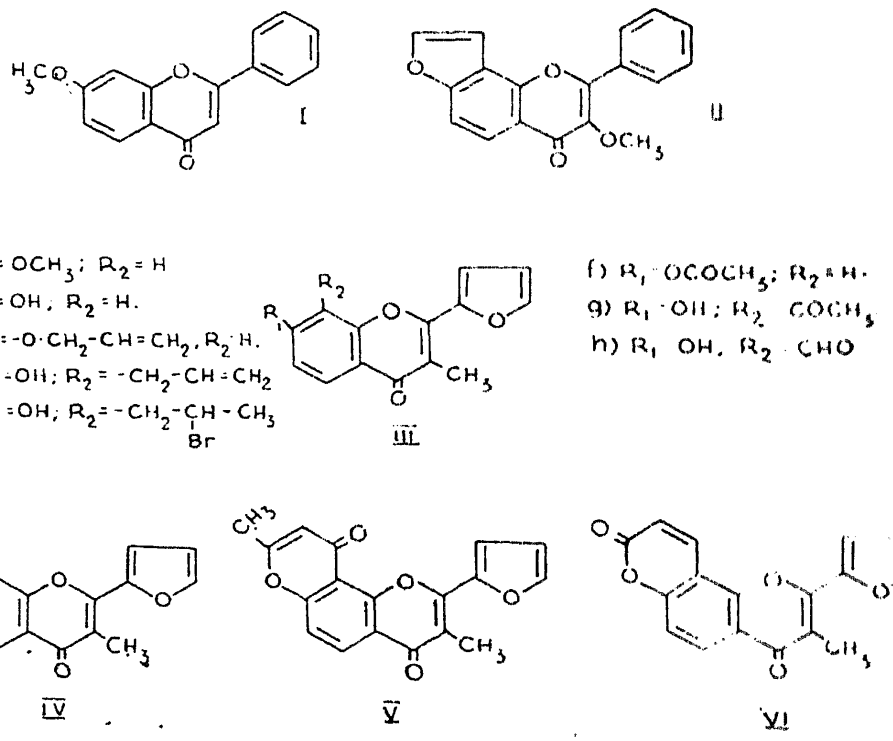
| 2-(2-Furyl)-chromone | Turning time Min. | Sec. | Remarks |
|---|---|---|---|
| 1. 7-Hydroxy .. | Not active | | |
| 2. 7-Methoxy .. | 2 | 30 | |
| 3. 7-Allyloxy .. | 13 | 40 | |
| 4. 7-Hydroxy-3-methyl .. | 10 | 22 | |
| 5. 7-Methoxy-3-methyl .. | 1 | 42 | |
| | 2 | 12 | at 10 ppm |
| 6. 7-Allyloxy-3-methyl .. | 5 | 12 | |
| 7. 7-Hydroxy-8-allyl-3-methyl .. | 4 | 24 | |
| 8. 7-Methoxy-8-allyl-3-methyl .. | 4 | 10 | |
| 9. 7-Hydroxy-3-phenyl .. | 22 | 14 | |
| 10. 7-Methoxy-3-phenyl .. | 18 | 00 | |
| 11. 5, 7-Dihydroxy .. | 21 | 42 | (gelatin added) |
| 12. 5, 7-Dimethoxy .. | 10 | 12 | |
| 13. 5, 7-Dihydroxy-3-phenyl .. | 19 | 42 | |
| 14. 7, 8-Dihydrofurano-α-3-dimethyl .. | 13 | 50 | |
| 15. 7,8-γ-Pyrono-α-3-dimethyl .. | 15 | 20 | |
| 16. 7, 8-Pyrono-3-methyl .. | 25 | 20 | |

7, 8-γ-*Pyrono*-2-(2-*furyl*)-α-3-*dimethyl chromone*.—7-Hydroxy-2-(2-furyl)-3-methyl chromone III (*h*) has been acetylated and the 7-0-acetyl compound III (*f*) has been subjected to Fries migration with anhydrous aluminium chloride to give rise to 7-hydroxy-8-acetyl chromone III (*g*). This chromone gave deep violet colour with alcoholic ferric chloride. It has been subjected to Claisen condensation with ethyl acetate in the presence of sodium to yield the corresponding β-diketone which was directly cyclised with acetic acid containing traces of hydrochloric acid to give the title compound V,

It gave no colouration with ferric chloride. The compound showed absorption $\lambda_{max}$ 252 nm (4·26), 312 nm (4·08) and 372 nm (4·19). In ir, it was single carbonyl absorption at $\nu$ 1624 $cm^{-1}$ due to the chromone carbonyl.

7, 8-*α-Pyrono*-2-(2-*furyl*)-3-*methylchromone*.—Of the several methods available for the introduction of a formyl group, Duff reaction has been made use of to prepare 7-hydroxy-8-formyl-2-(2-furyl)-chromone III (*h*) by heating 7-hydroxy-2-(2-furyl)-3-methyl chromone III (*b*) with hexamine in acetic acid. The 7-hydroxy-8-formyl chromone, which gave deep wine red colour with alcoholic ferric chloride indicative of chelated carbonyl has been subjected to Perkin reaction by reacting with acetic anhydride and fused sodium acetate to give 7, 8-α-pyrono-2-(2-furyl)-3-methylchromone (VI). The compound did not show any colouration with alcoholic ferric chloride. In uv, it exhibited three distinct absorptions $\lambda_{max}$ 252 nm (4·26), 312 nm (4·08) and 372 nm (4·19). In ir it showed two distinct absorptions in the carbonyl region one at $\nu$ 1690 $cm^{-1}$ due to the lactone carbonyl and the other at $\nu$ 1632 $cm^{-1}$ due to the chromone carbonyl.

CHART-1




*Fish toxicity*.—The method of Krishnaswamy and Seshadri[7] was adopted for evaluating fish toxicity of 7, 8-heterocyclic-2-(2-furylic)-3-methyl chromones as well as simple 2-(2-furyl)-chromones whose synthesis was reported in an earlier communication (*loc. cit.*), using locally available fresh water fish *Barbus ticto* as test animal. The toxicity data (Table I) revealed that 7-

methoxy-2-(2-furyl)-3-methyl chromones possessed the highest activity. 7-Methoxy-, and 7-allyloxy-, 2-(2-furyl)-3-methyl chromones also showed appreciable toxicity. 3-Methyl-2-(2-furyl)-chromones have higher toxicity than 3-phenyl-2-(2-furyl)-chromones. The introduction of heterocyclic systems at 7, 8-positions (Sl. No. 14, 15 and 16) did not show any improvement in the toxicity of these compounds, perhaps due to their poor solubility in aqueous ethanol. In general, hydroxy compounds exhibit lower toxicity compared to their methyl ethers. These results are in accord with the findings reported earlier for 3-methyl and 3-phenyl flavones from our laboratories[8].

## Experimental

### 7-, 8-*Dihydrofurano*-2-(2-*Furyl*)-α-3-*Dimethylchromone* (IV)

(*a*) 7- *Allyloxy*-2-(2-*furyl*)-3-*methylchromone*. — 7-Hydroxy-2-(2-furyl)-3-methylchromone (5 g) and allylbromide (0·76 ml) were dissolved in acetone (50 ml). Freshly ignited potassium carbonate (3 g) was added and refluxed for 6 hours under dry conditions. Acetone was distilled off and the product was precipitated by the addition of water. It was collected and recrystallised from alcohol as colourless rectangular rods (3 g), mp 121° (Found: C, 72·2; H, 5·0; $C_{17}H_{14}O_4$ requires: C, 72·3; H, 4·9%).

(*b*) 7-*Hydroxy*-8-*allyl*-2-(2-*furyl*)-3-*methylchromone*.–7-Allyloxy-2-(2-furyl)-3-methylchromone (2 g) was subjected to Claisen migration by heating under reduced pressure at 210° for 3 hours. The solid first melted, became a liquid and finally solidified. The hard mass was repeatedly extracted with potassium hydroxide solution (5%; 4 × 10 ml) and the clear solution was acidified with 5 N hydrochloric acid. The product was filtered, washed to remove traces of alkali and recrystallised from alcohol as pale yellow needles (1·5 g), mp 267-8° (Found: C, 72·4; H, 5·0; $C_{17}H_{14}O_4$ requires: C, 72·3; H, 4.9%).

(*c*) 7-*Hydroxy* – 8 – β-*bromopropyl*–2–(2-*furyl*) –3-*methylchromone*.— 7–Hydroxy-8-allyl-2-(2-furyl)-3-methylchromone (1 g) was dissolved in glacial acetic acid (10 ml). Hydrobromic acid (15%; 2 ml) was added and the solution was heated on a waterbath for half-an-hour. Cold-water was added to precipitate the product. The resulting yellow product was filtered, washed repeatedly to remove traces of hydrobromic acid and recrystallised from alcohol as yellow plates (700 mg), mp 200° (Found: C, 56·1; H, 4·0; $C_{17}H_{15}O_4$ Br requires: C, 56·0; H, 4·1%). The compound gave positive test for bromine with sodium fusion extract with dilute nitric acid and silver nitrate.

(*d*) 7, 8-*Dihydrofurano*-2-(2-*furyl*)-α-3-*dimethylchromone*.— The abov chromone (500 mg) was dissolved in dry acetone (20 ml) containing anhydrou potassium carbonate (1 g) and refluxed for three hours. On working u the reaction mixture and crystallising the product from alcohol gave colour less plates (250 mg), mp 169° (Found: C, 72·4; H, 4·8; $C_{17}H_{12}O_4$ requires C, 72·3; H, 4·9%). The compound did not show the presence of bromin with sodium fusion extract.

7, 8-γ-*Pyrono*-2-(2-*Furyl*)-α-3-*Dimethylchromone*

(*a*) 7-*Acetoxy*-2-(2-*furyl*)-3-*methylchromone*.— 7-Hydroxy-2- (2-furyl)-3 methylchromone (1 g) was dissolved in acetic anhydride (5 ml) was adde and refluxed in an oil-bath for three hours. The reaction mixture, afte cooling, was poured over crushed ice. The resulting solid was filtered, drie and recrystallised from benzene petroleum-ether as colourelss plate (750 mg), mp 146° (Found: C, 67·6; H, 4·3; $C_{16}H_{12}O_5$ requires C, 67·6: H,4·2%).

(*b*) 7-*Hydroxy*-8-*acetyl*-2-(2-*furyl*)-3-*methylchromone*. — The foregoin acetoxychromone (700 mg) was intimately mixed with anhydrous aluminium chloride (5 g) and heated on an oil-bath at 130° for three hours. The reac tion mixture was decomposed with crushed ice. The resulting compoun was filtered, dried and recrystallised from benzene petroleum-ether a colourless rectangular rods (600 mg), mp 212° (Found: C, 67·5; H, 4·3 $C_{16}H_{12}O_5$ requires: C, 67·6; H, 4·2%). The compound gave violet colourat tion with alcoholic ferric chloride.

(*c*) 7, 8-γ-*Pyrono*-2-(2-*furyl*)-α-3-*dimethylchromone*—7-Hydroxy-8-acetyl-2 (2-furyl)-3-methylchromone (500 mg) was dissolved in freshly distille ethylacetate (5 ml). Pulverised sodium (2 g) was added and heated on water-bath for two hours. The solution became light yellow in the beginnin and deep-red later on. Ethyl acetate was distilled off and the exces sodium left over was destroyed by adding methanol. To the resultin deep-brown solution, glacial acetic acid (5 ml) and concentrated hydro chloric acid (1 ml) were added and refluxed on a water-bath for three hours. Methanol was removed under reduced pressure and the product was precipitated by the addition of ice-cold water. The product was collec ted and recrystallised from alcohol as colourless plates (300 mg), mp 186 (Found: C, 70·0; H, 3·9: $C_{18}H_{12}O_5$ requires: C, 70·1; H, 3·8%). The compound was insoluble in dilute alkali and did not give any colouration with alcoholic ferric chloride.

7, 8-*α-Pyrono*-2-(2-*Furyl*)-3-*Methylchromone*

(*a*) *7-Hydroxy-8-formyl-2-(2-furyl)-3-methylchromone.* — 7-Hydroxy-2-(2-furyl)-3-methylchromone (1 g) was dissolved in glacial acetic acid (10 ml) and hexamine (3 g) was added. More acetic acid was added to dissolve any hexamine left undissolved. The reaction mixture was heated on a water-bath for 2 hours. The solution developed intense red colouration; cold-water was added to precipitate the product. The resulting hexamine complex was decomposed by heating 1N hydrochloric acid (10 ml). The solid obtained was filtered and recrystallised from alcohol as yellow plates (750 mg), mp 222 (Found: C, 66·5; H, 3·7; $C_{15}H_{10}O_5$ requires: C, 66·6; H, 3·8%). The compound gave deep wine-red colouration with alcoholic ferric chloride.

(*b*) 7, 8-*α-Pyrono*-2-(2-*furyl*)-3-*methylchromone.*—The above formyl chromone (500 mg) was dissolved in acetic anhydride (10 ml) and freshly fused sodium acetate (1·5 g) was added and the reaction mixture was refluxed in an oilbath for four hours. The solution after cooling was poured over crushed ice. The resulting oily product was taken up in other, washed repeatedly with water. The ethereal layer was dried over anhydrous sodium sulphate and ether removed. The resulting viscous mass was titurated with methanol. The compound separated was recrystallised from methanol as colourless plates (250 mg), mp 141° (Found: C, 70·6; H, 3·3: $C_{18}H_{10}O_5$ requires: C, 70·6; H, 3·2%). The compound did not give any colouration with alcoholic ferric chloride solution.

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