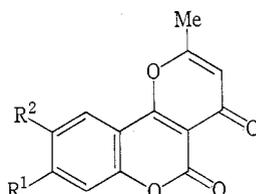
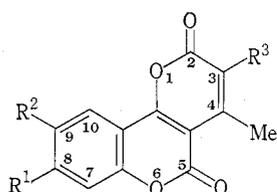


STUDIES IN 4-HYDROXY COUMARINS*

II.† α - AND γ -PYRONES FROM 4-HYDROXY COUMARINS

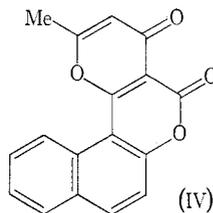
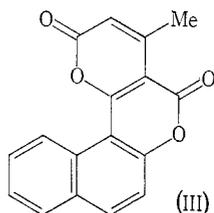
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Arora and Mathur¹ reported that a methyldioxophenylpyranobenzopyran (Ia) possesses anticoagulant activity comparable to that of dicoumarol. It was thought of interest to prepare α - and γ -pyrones having different groups in the benzenoid part of the coumarin ring system and to study their anticoagulant activity.



| | R ¹ | R ² | R ³ |
|------|----------------|----------------|----------------|
| (Ia) | H | H | Ph |
| (Ib) | H | H | H |
| (Ic) | H | Me | H |
| (Id) | OMe | H | H |

| | R ¹ | R ² |
|-------|----------------|----------------|
| (IIa) | H | H |
| (IIb) | H | Me |
| (IIc) | OH | H |



Woods² condensed 4-hydroxycoumarin with ethyl acetoacetate in the presence of trifluoroacetic acid and claimed to have obtained 2-methyl-4,5-dioxo-4*H*,5*H*-pyrano[3,2-*c*]benzopyran (IIa), m.p. 252°, principal absorption bands in the i.r. region, 3344, 1727, 1631, 1613 cm⁻¹. Mustafa *et al.*³ synthesized (IIa), yellow crystals, m.p.

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† Part I, *J. scient. ind. Res. B*, 1962, **21**, 402.

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¹ Arora, R. B., and Mathur, C. N., *Brit. J. Pharmac. Chemother.*, 1963, **20**, 29.

² Woods, L. L., *J. org. Chem.*, 1962, **27**, 696.

³ Mustafa, A., Hsihmat, O. H., Zayed, S. M. A. D., and Ahmed Nawar, A., *Tetrahedron*, 1963, **19**, 1831.

246°, carbonyl stretching frequencies, 1754 cm^{-1} and 1667 cm^{-1} , by different routes and claimed that it was identical in all respects with the compound prepared according to Woods.² On repeating Woods's work, it has now been found that 4-methyl-2,5-dioxo-2*H*,5*H*-pyrano[3,2-*c*]benzopyran (Ib), colourless crystals, m.p. 243°, carbonyl stretching frequency in the i.r. region, 1740 cm^{-1} , is the only isolable product when the condensation is carried out in the presence of trifluoroacetic acid. The mixed m.p. with an authentic sample of (Ib) prepared by using either concentrated sulphuric acid^{3,4} or anhydrous aluminium chloride⁴ was not depressed; but the mixed m.p. with an authentic sample of (IIa), yellow crystals, m.p. 246°, carbonyl stretching frequencies in the i.r. region, 1760 cm^{-1} and 1670 cm^{-1} , prepared according to Mustafa *et al.*³ was depressed by 20°.

This observation is further supported when three substituted 4-hydroxy-coumarins are condensed with ethyl acetoacetate in the presence of trifluoroacetic acid: they yield the same known compounds (Ic), (Id), and (III) which were obtained by using either conc. sulphuric acid or anhydrous aluminium chloride as condensing agent. 3-Acetyl-4-hydroxy-6-methylcoumarin, 3-acetyl-4-hydroxy-7-methoxycoumarin, and 3-acetyl-4-hydroxybenzo[*f*]coumarin when subjected to Claisen condensation followed by cyclization with 25% sulphuric acid gave (IIb), (IIc), and (IV) respectively; demethylation took place during cyclization to yield (IIc). (Ic) and (III) differed considerably from the corresponding (IIb) and (IV) in i.r. spectra and melting point. The carbonyl stretching frequencies in the i.r. region of the above compounds are (Ic), 1745; (Id), 1740; (III), 1745; (IIb), 1760, 1672; (IIc), 1760, 1672; and (IV), 1760, 1670 cm^{-1} .

Experimental

Infrared spectra (CHCl_3) were determined with a Perkin-Elmer 237 grating spectrophotometer. All melting points were uncorrected.

4,9-Dimethyl-2,5-dioxo-2*H*,5*H*-pyrano[3,2-*c*]benzopyran (Ic)

4-Hydroxy-6-methylcoumarin (1 g) was heated with ethyl acetoacetate (1 ml) in trifluoroacetic acid (5 ml) on a sand-bath for 15 hr. After the completion of the reaction, a few millilitres of ethanol were added and the mixture kept overnight. The product which separated was filtered off and washed with sodium bicarbonate solution. The residue was crystallized from acetic acid, colourless crystals, m.p. 197–198° (lit.⁴ 197–198°), yield 0.3 g. Mixed m.p. with an authentic sample prepared by using conc. sulphuric acid as condensing agent was not depressed.

8-Methoxy-4-methyl-2,5-dioxo-2*H*,5*H*-pyrano[3,2-*c*]benzopyran (Id)

4-Hydroxy-7-methoxycoumarin was condensed with ethyl acetoacetate in the presence of trifluoroacetic acid using the above procedure. M.p. of the colourless crystals and mixed m.p. with an authentic sample was 237° (lit.⁵ 237°).

4-Methyl-2,5-dioxo-2*H*,5*H*-pyrano[3,2-*c*]benzo[*f*]benzopyran (III)

4-Hydroxybenzo[*f*]coumarin was condensed with ethyl acetoacetate in the presence of trifluoroacetic acid using the above procedure. M.p. and mixed m.p. with an authentic sample was 246° (lit.⁶ 245–246°).

⁴ Patell, J., and Usgaonker, R. N., *J. Indian chem. Soc.*, 1965, **42**, 217.

⁵ Dholakia, V. N., and Trivedi, K. N., *J. Indian chem. Soc.*, 1966, **43**, 804.

⁶ Patell, J., and Usgaonker, R. N., *J. Indian chem. Soc.*, 1966, **43**, 536.

3-Acetoacetyl-4-hydroxy-6-methylcoumarin

A solution of 3-acetyl-4-hydroxy-6-methylcoumarin (1 g) in freshly distilled ethyl acetate (25 ml) was added to pulverized sodium (1 g). The reaction mixture was heated on a water-bath for 6 hr. It was then decomposed with ice and extracted with ether. The aqueous layer on acidification gave *3-acetoacetyl-4-hydroxy-6-methylcoumarin*, which crystallized from dil. acetic acid, yellow needles, m.p. 153°, yield 0.7 g (Found: C, 64.5; H, 4.7. $C_{14}H_{12}O_5$ requires C, 64.6; H, 4.65%).

2,9-Dimethyl-4,5-dioxo-4H,5H-pyrano[3,2-c]benzopyran (IIb)

A solution of 3-acetoacetyl-4-hydroxy-6-methylcoumarin (0.5 g) in 50 ml dil. sulphuric acid (25%) was heated on a sand-bath for 1 hr. The cooled reaction mixture was neutralized with sodium carbonate solution, the separated product was crystallized from dil. acetic acid, yellow needles, m.p. 248°, yield 0.2 g (Found: C, 69.7; H, 3.8. $C_{14}H_{10}O_4$ requires C, 69.4; H, 4.2%).

3-Acetoacetyl-4-hydroxy-7-methoxycoumarin

A solution of 3-acetyl-4-hydroxy-7-methoxycoumarin (1 g) in ethyl acetate (25 ml) was added to pulverized sodium (1 g) and the reaction mixture refluxed on a water-bath for 6 hr. The reaction mixture was worked up as before. *3-Acetoacetyl-4-hydroxy-7-methoxycoumarin* crystallized from dil. acetic acid, yellow needles, m.p. 153°, yield 0.8 g (Found: C, 60.9; H, 4.2. $C_{14}H_{12}O_6$ requires C, 60.9; H, 4.4%).

8-Hydroxy-2-methyl-4,5-dioxo-4H,5H-pyrano[3,2-c]benzopyran (IIc)

A solution of 3-acetoacetyl-4-hydroxy-7-methoxycoumarin (0.7 g) in 75 ml dil. sulphuric acid (25%) was refluxed on a sand-bath for 1 hr. The cooled reaction mixture was basified with sodium hydroxide solution and filtered. The filtrate on acidification gave *8-hydroxy-2-methyl-4,5-dioxo-4H,5H-pyrano[3,2-c]benzopyran*, which crystallized from dil. acetic acid, yellow needles, m.p. 221° (Found: C, 63.4; H, 3.8. $C_{13}H_8O_5$ requires C, 63.9; H, 3.3%).

3-Acetyl-4-hydroxybenzo[f]coumarin

4-Hydroxybenzo[f]coumarin (1 g) was dissolved in acetic acid (5 ml) and phosphorus oxychloride (2 ml) and the reaction mixture was gently refluxed for 40 min and then added to ice-water. *3-Acetyl-4-hydroxybenzo[f]coumarin* crystallized from acetic acid, m.p. 201°, yield 0.68 g. It developed a red coloration with alcoholic ferric chloride solution (Found: C, 70.4; H, 4.1. $C_{15}H_{10}O_4$ requires C, 70.8; H, 4.0%).

3-Acetoacetyl-4-hydroxybenzo[f]coumarin

3-Acetyl-4-hydroxybenzo[f]coumarin (0.5 g) dissolved in ethyl acetate (15 ml) was added to pulverized sodium (0.6 g) and refluxed for 6 hr. On working up the reaction mixture as before, *3-acetoacetyl-4-hydroxybenzo[f]coumarin* crystallized from benzene, yellow needles, m.p. 166°, yield 0.2 g (Found: C, 68.9; H, 4.5. $C_{17}H_{12}O_5$ requires C, 68.9; H, 4.1%).

2-Methyl-4,5-dioxo-4H,5H-pyrano[3,2-c]benzo[f]benzopyran (IV)

3-Acetoacetyl-4-hydroxybenzo[f]coumarin (0.4 g) was refluxed with 25 ml of dil. sulphuric acid (25%) on a sand-bath for 2 hr. On working up the reaction mixture as before, *2-methyl-4,5-dioxo-4H,5H-pyrano[3,2-c]benzo[f]benzopyran* crystallized from acetic acid, yellow needles, m.p. 282°, yield 0.1 g (Found: C, 73.1; H, 3.9. $C_{17}H_{10}O_4$ requires C, 73.4; H, 3.6%).

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