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Synthesis in Coumarino-pyrone and Furocoumarin Groups. Part I. Synthesis of 4,2′-Dimethyl-6-ethylcoumarino-7,8-γ-pyrone and 4,4′-Dimethyl-6-ethylcoumarino-7,8-α-pyrone

K. A. Thakar

The Kostanecki acylation of 4-methyl-6-ethyl-8-acetylumbelliferone furnishes two compounds: (A) $C_{18}H_{16}O_5$, m.p. 198°, and (B) $C_{16}H_{14}O_4$, m.p. 335°. Compound (A) on hydrolysis with caustic alkali furnishes (*i*) an acid, $C_{15}H_{12}O_5$, m.p. 240°, and (*ii*) a neutral compound, $C_{16}H_{14}O_4$, m.p. 203°.

From chemical evidences compound (A) has been proved to be 4,2′-dimethyl 3′-acetyl-6-ethylcoumarino-7,8-γ-pyrone and its deacetylated product, 4,2′-dimethyl-6-ethylcoumarino-7,8-γ-pyrone

The product (B), m.p. 335°, has been similarly proved to be isomeric with the coumarino-γ-pyrone (II), m.p. 203°, and is represented as 4,4′-dimethyl-6-ethylcoumarino-7, 8- α-pyrone.

Coumarino- α-pyrones have been synthesised from umbelliferones by the Pechmann reaction[1]. Coumarino- α-pyrones and -γ pyrones have been prepared from *O*-hydroxy-acyl or -aroyl-coumarins by the Kostanecki acylation method[2].

The reaction mass, obtained by the Kostanecki acylation of 4-methyl-6-ethyl-8-acetyl-umbelliferone[3], was fractionally crystallised, furnishing two compounds: (A) $C_{18}H_{16}O_5$, m.p. 198°, and (B) $C_{16}H_{14}O_4$, m.p. 335°. The constitutions of these were determined by a study of their alkali hydrolysis, preparation of a derivative, and by subjecting 4-methyl-6-ethylumbelliferone to the Pechmann reaction.

Alkaline hydrolysis of (A) furnished (*i*) an acid $C_{15}H_{12}O_5$, m.p. 240°, and (*ii*) a neutral compound, $C_{16}H_{14}O_4$, m.p. 203°.

The acid, m.p. 240°, showed a violet ferric reaction, indicating its nature as of the salicylic acid type of compounds. On decarboxylation, the acid provided the known 4-methyl-6-ethylumbelliferone. Hence it can be represented as 4-methyl-6-ethylumbelliferone-8-carboxylic acid (III). The formation of this *o*-hydroxycarboxylic acid during hydrolysis indicates the probable presence of a γ-pyrone ring in compound (A), further

1. Hanzsch and Zurcher, *Ber.*, 1887, **20**, 1328; Sen and Chakravarti, this *Journal*, 1930, **7**, 247; Rangaswami and Sheshadri, *Proc. Ind. Acad. Sci.*, 1937, **6A**, 112.
2. Sethna *et al.*, *J. Chem. Soc.*, 1938, 228; Shah and Shah, *ibid.*, 1938, 1424; Deliwala and Shah, *ibid.*, 1939, 1250; Desai *et al.*, *Proc. Ind. Acad. Sci.*, 1937, **6A**, 185.
3. Limaye and Limaye, *Rasayanam*, 1941, **1**, 201.

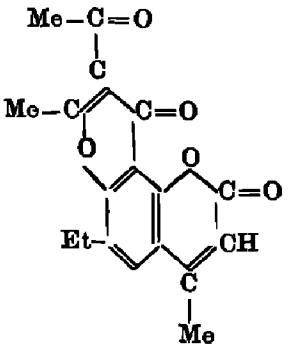
supported by the formation of a 2,4-DNP in quantitative yield (98.2%), assuming one OAc group in (A). It is well known that during the formation of a γ-pyrone ring by the Kostanecki acylation method, acyl group generally enters the 3-position.

The presence of a γ-pyrone ring in compound (A) is further supported by the study of the neutral compound (II), m.p. 203°. Compound (II) on further hydrolysis furnished the acid (III), also obtained during hydrolysis of compound (A). A comparison of the molecular formulas of the compounds (A or I) and (II) shows that there is a difference of one acetyl group. Compound (A) has already been shown to contain an acetyl group and it is known that the acetyl group present in the 3-position of a chromone is easily removed. Hence it appears that the neutral compound (II, m.p. 203°) is a deacetylated product of compound (A) possessing a coumarino-γ-pyrone structure. The product (II) did not form any 2,4-DNP and it was also prepared by refluxing compound (I) with Na_2CO_3 solution. The compound (I) is therefore represented as 4,2′-dimethyl-3′-acetyl-6-ethylcoumarino-7,8-γ-pyrone and its deacelylded product as 4,2′ dimethyl-6-ethylcoumarino-7,8-γ-pyrone.

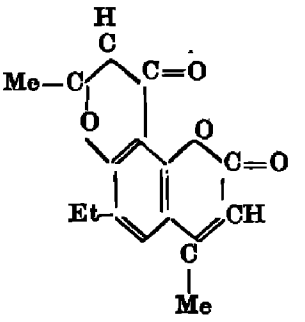
The condensation product (B), m.p. 335°, is isomeric with product (II). That this compound is a coumarino-α-pyrone has been shown by its alkaline hydrolysis, furnishing (*i*) a monobasic acid, m.p. 230° and (*ii*) 4-ethylresorcin. The monobasic acid has a composition $C_{16}H_{16}O_5$ as compared with $C_{16}H_{14}O_4$ of the compound from which the acid is formed. This difference of H_2O in the composition shows that the acid is formed by the opening of the α-pyrone ring. This view has been confirmed by the fact that the acid regenerates the original compound, m.p. 335°, when heated with H_2SO_4. Hence the acid, m.p 230°, can possibly be formulated as β-(4-methyl-5-hydroxy-8-ethylbenzo-α-pyrone-6)-β-methyl-acrylic acid (V).

Coumarino-α-pyrone structure for the compound (B), m.p. 335°, was also supported by the formation of 4-ethylresorcin during hydrolysis, since coumarins on hydrolysis with caustic alkali eliminate α-pyrone ring.

On condensing 4-methyl-6-ethylumbelliferone with acetoacetic ester in presence of H_2SO_4, a product, m.p. 335, was isolated, which was found to be identical with the compound, m.p. 335°, obtained by the Kostanecki acylation method. This compound is therefore represented as 4,4′-dimethyl-6-ethyl-7,8-coumarino-α-pyrone (IV).



(I)



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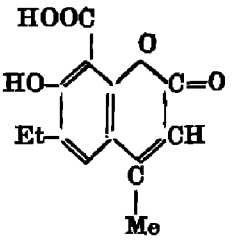
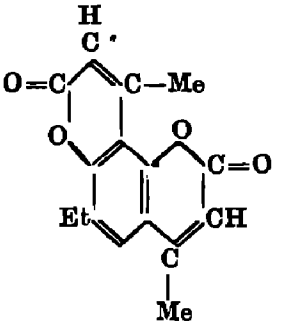
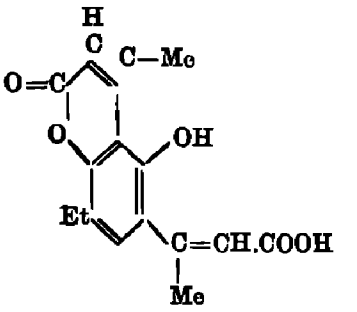


(III)



(IV)



(V)

EXPERIMENTAL

4-Methyl-6-ethylumbelliferone[3] was prepared by condensing 4-ethylresorcinol with acetoacetic ester in presence of P_2O_5 instead of H_2SO_4, used by Limaye[3]. 4-Ethylresorcin (20 g.) was dissolved in acetoacetic ester (20 ml) and P_2O_5 (5 g.) was added to the solution. The mixture was kept overnight and then poured over crushed ice. The resulting precipitate was crystallised from ethanol in colorless needles (15.2g.), m.p. 212°. Mixed m.p. with an authentic sample[3] showed no depression.

4-Methyl-6-ethyl-8-acetylumbelliferone was prepared from 4-methyl-6-ethylumbelliferone by acetylation and subsequent Fries migration.

4,2′-Dimethyl-6-ethyl-3′-acetylcoumarino-7-8-γ-pyrone (I).— A mixture of the above acetylumbelliferone (5 g.), fused sodium acetate (5 g.), and acetic anhydride (10 ml) was heated at 160-70° for 3 hr. and then poured on water when a tarry substance was obtained. It solidified on keeping for 3 days. The solid was crystallised from ethanol, using a small quantity each time; m.p. 175° (crude). Repeated crystallisation from ethanol or toluene raised its m.p. to 198°. It is insoluble in cold caustic alkali and shows negative ferric chloride reaction. (Found: C, 69.02; H, 4.76. $C_{18}H_{16}O_5$ requires C, 69.23; H, 5.13%). The ethanolic mother liquor (B) was preserved for further treatment.

2,4-DNP of (I).—To compound (I) (0.0104 g.), dissolved in aldehyde-free ethanol, an excess of 2,4-dinitrophenylhydrazine sulphate solution was added in hot condition. On keeping the reaction mixture overnight, an orange precipitate gradually separated. The solid was filtered, washed with 5*N*-HCl, and dried; m.p. 277°, yield 0.0172 g. (% of carbonyl group found: 9.412; expected: 9.40). (Found: N, 11.22. $C_{24}H_{20}O_8N_4$ requires N, 11.39%).

4,2′-Dimethyl-6-ethylcoumarino-7,8-γ-pyrone (II).—The pyrone (I, 2 g.) was refluxed with NaOH solution (20 ml) for 1hr. The solid soon went into solution which was diluted and distilled. The distillate showed presence of acetone. The residue in the flask was cooled and filtered. The filtrate on acidification provided a sticky solid which was extracted with ether. The solid dissolved partially leaving behind a residue (C). The ether solution was extracted with dilute $NaHCO_3$ solution (D). On evaporating the ether, a yellow solid was obtained. It was crystallised from boiling ethanol, m.p. 203°, yield 0.3 g. (Found: C, 70.39; H, 5.06. $C_{16}H_{14}O_4$ requires C, 71.11; H, 5.18%).

4-Methyl-6-ethylumbelliferone-8-carboxylic Acid (III).—The $NaHCO_3$ extract (D), mentioned above, was acidified. The resulting solid was crystallised from glacial acetic acid in fine needles, m.p. 240° (decomp.). The acid developed a deep violet colour with EtOH-$FeCl_3$. On decarboxylation it yielded 4-methyl-6-ethylumbelliferone. (Found: C, 62.48; H, 4.63; equiv., 252.3. $C_{13}H_{12}O_5$ requires C, 62.90; H, 4.84%; equiv., 248).

4,4'-Dimethyl-6-ethylcoumarino-7,8-α-pyrone (IV).—The ethanolic mother liquors (B) were evaporated and the residue was washed repeatedly with small quantitites of boiling ethanol. The insoluble residue was crystallised from glacial acetic acid, m.p. 335°. It showed no colour with $FeCl_3$ solution. (Found: C, 70.49; H, 5.01. $C_{16}H_{14}O_4$ requires C, 71.11; H, 5.18%).

By Pechmann Reaction.—To 4-methyl-6-ethylumbelliferone (5 g.), dissolved in acetoacetic ester (50 ml), H_2SO_4 (conc., 5ml) was slowly added. The reaction mass was kept with occasional shaking for a week when a yellow solid separated. It was filtered, washed with a dilute solution of NaOH, and crystallised from glacial acetic acid, m.p. 335°. Mixed m.p. with the compound, prepared above, showed no depression.

β-(4-Methyl-5-hydroxy-8-ethyl-α-benzopyrone-6)-β-methylacrylic Acid (V).—The preceding pyrone (IV, 0.44 g.) was refluxed with *N*-NaOH solution (6 ml) for 15 min. The alkaline solution after filtration was acidified when a sticky mass separated. It was extracted with ether. The ethereal solution was extracted with $NaHCO_3$ solution. The resulting solid obtained on acidifying the bicarbonate solution was subjected to the same process of purification twice, m.p 230° (decomp.), yield 0 09 g. The acid did not titrate sharp. (Found: C, 66.18; H, 5.28. $C_{16}H_{16}O_5$ requires C, 66.67; H, 5.56%).

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Department of Chemistry,
Marathwada University,
Aurangabad.

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