[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, M. R. SCIENCE INSTITUTE, GUJARAT COLLEGE]

FURANOCOUMARINS AND COUMARINO-α- AND γ-PYRONES

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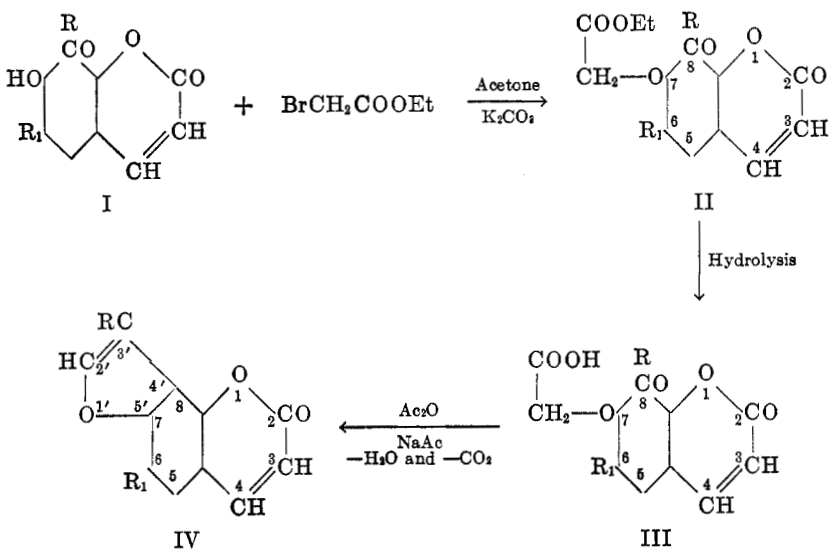
Introductory. The 7-hydroxy-8-acylcoumarin derivatives which are now easily accessible by the Fries migration of 7-acyloxycoumarins (1) are substances of much potential value for the synthetical preparation of heterocyclic compounds like chromono-α-pyrones, flavono-α-pyrones, *o*-hydroxyacylcoumarones and furanocoumarins as well as natural products containing such ring systems, by suitable reactions. The Kostanecki-Robinson acylation of these *ortho*-hydroxyacylcoumarins will lead to chromono-α-pyrones, coumarino-α-pyrones, and flavono-α-pyrones. The degradation of the coumarin ring will lead to the formation of *ortho*-hydroxyacylcoumarones; and the furan ring can be built on, leading to the furanocoumarins. The possibilities of synthesizing the above-mentioned heterocyclic compounds have been realized and some of them are described in this paper.

Furanocoumarins. In recent years, several furanocoumarins have been synthesized by Limaye and his co-workers (2) by treating the dry sodium salt of an *o*-acylhydroxycoumarin or the coumarin in sodium ethoxide with bromoacetic ester. Späth and Pailer (3) used bromoacetal, while Ray, Silooja, and Vaid (4) used chloro- or bromo-acetone in alkaline solution in the above reaction and cyclized the resulting product. Shah and Shah (5) synthesized unsubstituted furanocoumarins from 5-hydroxycoumarin derivatives. Shah and Chudgar (6) synthesized several furanocoumarins from 6-acyl-5-hydroxy-4-methylcoumarins. In this case, the sodium salt method was found unsatisfactory, hence the bromoacetic ester was condensed in dry acetone in presence of potassium carbonate.

Several furanocoumarins without any substituent in either the pyrone or the furan ring are found in nature, *e.g.* psoralene and angelicin. They are the parent substances of other natural furanocoumarins. The present work deals with the synthesis of the furanocoumarins without any substituent in the pyrone ring. They have been derived from (i) 7-hydroxy-8-acetyl- and -8-benzoyl-coumarins, (ii) 7-hydroxy-6-ethyl-8-acetylcoumarin and (iii) 7-hydroxy-6-chloro-8-acetylcoumarin.

The procedure followed for building up the furan ring in the present investigation was to condense the ketocoumarin (I) with bromoacetic ester in acetone solution in the presence of dry potassium carbonate: the coumarin-O-acetic esters (II) were obtained, which on hydrolysis gave the corresponding coumarin-O-acetic acids (III); on treatment with acetic anhydride in the presence of sodium acetate, III underwent ring closure leading to the formation of furanocoumarins (IV). It may be noted here that the acetone solution of iodoacetic ester obtained by treating the chloroacetate in dry acetone with potassium iodide was found to be an excellent substitute for bromoacetate in the above work without any reduction in the yield of the ester (II).



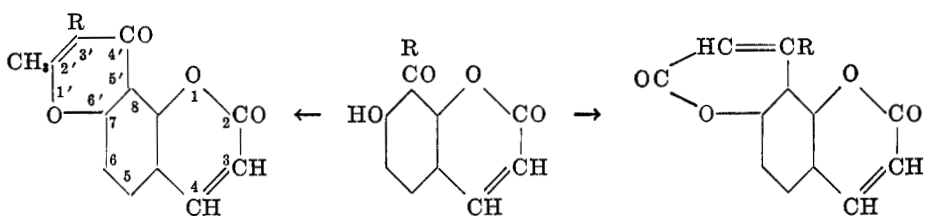
I II III IV

R = CH_3 or C_6H_5; R_1 = H, Et, Cl

COUMARINO-α-PYRONES (DICOUMARINS) AND CHROMONO-α-PYRONES

Coumarino-α-pyrones were first prepared by Hantzsch and Zurcher (7) and later by Sen and Chakravarti (8), and Ramaswami and Seshadri (9) by condensing umbelliferones with malic acid in the presence of sulfuric acid or resorcinol with an excess of ethyl acetoacetate in the presence of alcoholic hydrogen chloride.

Another way of synthesizing the above compounds is to subject *o*-hydroxyacylcoumarin to the Kostanecki-Robinson acylation getting either chromono- or coumarino-α-pyrones (V and VI):



V VI

R = CH_3 or Ph R = Ph

Various chromono-α-pyrones as well as coumarino-α-pyrones have been synthesized by several investigators (10), but they have been derived from coumarins with a 4-methyl group in the pyrone ring. With a view to synthesizing the above type of compounds unsubstituted in 4-position of the coumarin ring, the *ortho*-hydroxyacylcoumarins mentioned earlier were treated with acetic anhydride in the presence of sodium acetate under the conditions of Kostanecki-Robinson reaction.

This reaction has now been extensively investigated and its course has been established. It has been shown that coumarins and chromones are formed in this reaction and the formation of chromone or coumarin is dependent not only on the acid anhydride and its sodium salt but also on the nature of the *ortho*-hydroxyphenyl ketone (11).

7-Hydroxy-8-acetylcoumarin on treatment with acetic anhydride in the presence of fused sodium acetate gave a product which has been assigned the structure 2′-methyl-3′-acetyl-5′:6′(8:7)-chromono-α-pyrone (VII, R = $COCH_3$; R_1 = H) as it is insoluble in cold alkali and gives no ferric chloride color test. Similarly 7-hydroxy-6-ethyl-8-acetylcoumarin, 7-hydroxy-6-chloro-8-acetylcoumarin and 7-hydroxy-6-bromo-8-acetylcoumarin were subjected to the above reaction under similar conditions and the products obtained have been assigned the following structures on similar grounds:

6-ethyl-2′-methyl-3′-acetyl-5′:6′:(8:7)-chromono-α-pyrone

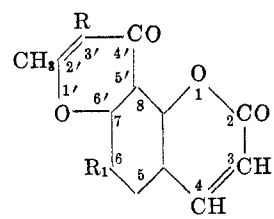
(VII:R_1 = Et; R = $COCH_3$)

6-chloro-2′-methyl-5′:6′(8:7)-chromono-α-pyrone

(VII: R_1 = Cl; R = H)

6-bromo-2′-methyl-5′:6′(8:7)-chromono-α-pyrone

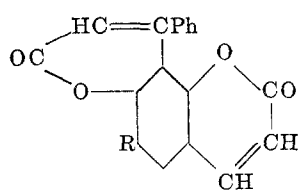
(VII: R_1 = Br; R = H)



VII

The above chromono-α-pyrones were treated with alkali; the solution on acidification gave the original ketocoumarin, the γ-pyrone ring undergoing the ketonic fission. 6-Bromochromono-α-pyrone gave the styryl derivative with benzaldehyde in the presence of sodium ethoxide, confirming the chromono ring.

7-Hydroxy-8-benzoylcoumarin, 7-hydroxy-6-ethyl-8-benzoylcoumarin, and 7-hydroxy-6-chloro-8-benzoylcoumarin were subjected to the above acetylation. The reation took place smoothly and the products obtained were found to be insoluble in cold alkali and did not give any ferric chloride color test and on heating with alkali, were recovered unchanged. Hence they have been assigned the structure, 4′-phenyl-coumarino-5′:6′(7:8)-α-pyrone (VIII).



R_1 = H, Et, and Cl.

VIII

TABLE I

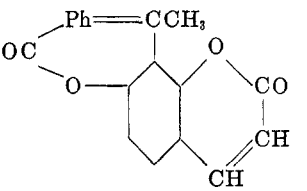
THE FOLLOWING FURANOCOUMARINS AND RELATED COMPOUNDS WERE SIMILARLY PREPARED. THEIR PHYSICAL PROPERTIES AND ANALYSES ARE TABULATED BELOW

(Unless otherwise mentioned, they were crystallized from ethanol.)

Name of the Compound	m.p., °C.	Crystalline Form	Formula	Analysis	
				Calc'd	Found
Ethyl 8-benzoylcoumarin-7-O-acetate	174	Lustrous plates	$C_{20}H_{16}O_6$	C, 68.19 H, 4.55	C, 67.72 H, 4.50
8-Benzoylcoumarin-7-O-acetic acid	160	Needles	$C_{18}H_{12}O_6$	Equiv., 162	Equiv. (titration) 161.1
Furano-3′-phenyl-4′:5′(7:8)-coumarin	121	Lustrous needles	$C_{17}H_{10}O_3$	C, 77.85 H, 3.82	C, 77.75 H, 3.78
8-Acetyl-6-ethylcoumarin-7-O-acetic acid	155	Needles	$C_{15}H_{14}O_6$	Equiv., 145	Equiv. (titration) 143.9
Furano-3′-methyl-6-ethyl-4′:5′(7:8)-coumarin	111	Short needles	$C_{14}H_{12}O_3$	C, 73.68 H, 5.26	C, 73.16 H, 5.29
Ethyl 6-chloro-8-acetylcoumarin-7-O-acetate	147	Shining plates	$C_{15}H_{13}ClO_6$	Cl, 10.94	Cl, 10.86
6-Chloro-8-acetylcoumarin-7-O-acetic acid	195	Thin needles	$C_{13}H_9ClO_6$	Equiv., 148.25	Equiv. (titration) 148.0
Furano-3′-methyl-6-chloro-4′:5′(7:8)-coumarin	219	Clusters of needles	$C_{12}H_7ClO_3$	Cl, 15.14	Cl, 14.92

N. B., Ethyl 8-acetyl-6-ethylcoumarin-7-O-acetate could not be crystallized from any solvent, hence it was hydrolyzed directly.

7-Hydroxy-8-acetylcoumarin on acetylation using acetic anhydride in the presence of fused sodium phenylacetate gave 3′-phenyl-4′-methyl coumarino-



IX

5′:6′:(7:8)-α-pyrone (IX). This compound is insoluble in cold alkali, does not give a ferric chloride color test, and is recovered unchanged on heating with alkali.

EXPERIMENTAL

FURANO-3′-METHYL-4′:5′(7:8) COUMARIN

(*a*) *Formation of ethyl 8-acetylcoumarin-7-O-acetate.* 7-Hydroxy-8-acetylcoumarin (1 g.) and ethyl bromoacetate (1 g.) were dissolved in acetone (100 ml.); dry K_2CO_3 (1 g.) was added and the mixture was refluxed for 20 hours ($CaCl_2$ guard tube). The solution then was filtered from K_2CO_3 and the residue was washed thoroughly with acetone. Acetone and the excess of bromoacetate were removed in a current of air. The solid obtained was crystallized from alcohol as lustrous plates, m.p. 117°; yield, 0.6 g.

Anal. Calc'd for $C_{15}H_{14}O_6$: C, 62.07; H, 4.83.

Found: C, 61.85; H, 4.79.

(*b*) *Hydrolysis. Formation of 8-acetylcoumarin-7-O-acetic acid.* The above ester (1 g.) suspended in alkali (10 ml., 8%) was heated on water-bath for an hour. The solution was acidified and the solid was collected and crystallized from alcohol, needles, m.p. 208°. Yield, 0.7 g.

TABLE II

THE FOLLOWING CHROMONO- OR COUMARINO-α-PYRONES SIMILARLY OBTAINED FROM 8-ACETYL OR 8-BENZOYL-COUMARIN DERIVATIVES ARE TABULATED BELOW WITH THEIR PROPERTIES AND ANALYSES

Name of the Compound	m.p., °C.	Crystalline Form and Solvent	Formula	Analysis	
				Calc'd	Found
6-Ethyl-2′-methyl-3′-acetyl-5′:6′(8:7)-chromono-α-pyrone	246	Needles, ethanol	$C_{17}H_{14}O_5$	C, 68.45 H, 4.70	C, 68.08 H, 4.65
6-Ethyl-4′-phenylcoumarino-5′:6′(8:7)-α-pyrone	180	Granules, ethanol	$C_{20}H_{14}O_4$	C, 75.46 H, 4.40	C, 75.50 H, 4.47
6-Chloro-2′-methyl-5′:6′(8:7) chromono-α-pyrone	296	Sandy powder, acetic acid	$C_{13}H_7ClO_4$	Cl, 13.53	Cl, 13.43
6-Chloro-4′-phenylcoumarino-5′:6′(8:7)-α-pyrone	250	Needles, ethanol	$C_{18}H_9ClO_4$	Cl, 10.94	Cl, 10.61
6-Bromo-2′-methyl-5′:6′(8:7)-α-pyrone	305	Needles, acetic acid	$C_{13}H_7BrO_4$	Br, 26.06	Br, 25.8

Anal. $C_{13}H_{10}O_6$ requires: Neut. equiv., 131. Found: Neut. equiv., (by titration) 130.3.

(*c*) *The above acid* (0.5 g.), fused sodium acetate (2 g.), and acetic anhydride (10 g.) were refluxed at 160–170° for an hour. Then the mixture was poured into cold water; the solid was collected and crystallized from alcohol as white needles, m.p. 148°. Yield, 0.3 g.

Anal. Calc'd for $C_{12}H_8O_3$: C, 72.00; H, 4.00.

Found: C, 71.88; H, 3.98.

2'-Methyl-3'-acetyl-5':6'(8:7)-chromono-α-pyrone. A mixture of 7-hydroxy-8-acetylcoumarin (1.5 g.), acetic anhydride (7 ml.), and fused sodium acetate (3.5 g.) was refluxed for 12 hours at 160–170° ($CaCl_2$ guard tube). Then it was treated with cold water; the solid that separated was collected, washed with water, and crystallized from alcohol as granules, m.p. 227°. Yield, 0.8 g.

Anal. Calc'd for $C_{15}H_{10}O_5$: C, 66.66; H, 3.7.

Found: C, 66.51; H, 3.65.

Action of alkali. The above chromono-α-pyrone (1 g.) was dissolved in alcohol and KOH (10 ml., 15%) was added and the mixture was refluxed for 3 hours on water-bath. Then it was acidified and the solid was crystallized from alcohol as plates, m.p. 168°; the mixture melting point with 7-hydroxy-8-acetylcoumarin remained undepressed.

4'-Phenylcoumarino-5':6'(8:7)-α-pyrone. 7-Hydroxy-8-benzoylcoumarin (1 g.) was treated with acetic anhydride (10 ml.) and sodium acetate (5 g.) at 160–170° for 12 hours as above. On working it up similarly, the product crystallized from alcohol as needles, m.p. 238°.

Anal. Calc'd for $C_{18}H_{10}O_4$: C, 74.48; H, 3.45.

Found: C, 74.73; H, 3.52.

The *styryl* derivative obtained by condensing the above 6-bromochromono-α-pyrone with benzaldehyde in sodium ethoxide crystallized from dilute alcohol as long needles, m.p. 132°.

Anal. Calc'd for $C_{20}H_{11}BrO_4$: Br, 20.25. Found: Br, 20.10.

3'-Phenyl-4'-methyl-coumarino-5':6'-(8:7)-α-pyrone was prepared from 7-hydroxy-8-acetylcoumarin (3 g.) by refluxing it with acetic anhydride (10 ml.) in the presence of fused sodium phenylacetate (3 g.) at 160–170° for 12 hours. The product obtained as before crystallized from acetic acid, lustrous needles, m.p. > 305°.

Anal. Calc'd for $C_{19}H_{12}O_4$: C, 74.99; H: 3.95.

Found: C, 74.84; H: 3.90.

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