255. *Thermal Cyclization of* o-*Aroyloxyacetoarones. A New Synthesis of Flavones.*

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o-Aroyloxyacetoarones (II) yield flavones (VII) when heated in glycerol. The method is applicable to the synthesis of flavonols. If glycerol is replaced by benzoic anhydride, 3-benzoylflavones (IX) are obtained. It is believed that a thermally produced Baker–Venkataraman transformation is involved in the cyclization.

The fusion of *o*-hydroxyacetophenones (I) or of *o*-aroyloxyacetophenones (II) with an aromatic acid anhydride and the sodium salt of the corresponding acid (Allan–Robinson reaction) has been extensively used in the synthesis of flavones (VII). The method suffers from the disadvantage that a 3-aroylflavone (IX) is often formed, and that loss occurs in subsequent hydrolysis to the flavone (see Baker and Butt, *J.*, 1949, 2142). It has now been found [see also Bernfeld and Wheeler, *J.*, 1949, pp. 1916 (footnote) and 1917] that thermal cyclization of *o*-aroyloxyacetophenones to flavones can be effected by heating them in anhydrous glycerol (10—20 parts) at about 250° for at least 30 minutes. The product is recovered by dilution with water. The optimum conditions for each ester require to be determined, but it is important that the glycerol employed should be rendered anhydrous by prior distillation under reduced pressure. Addition of a variety of acid and basic catalysts, *e.g.*, boric acid (cf. Duff, *J.*, 1941, 547), phenol, anhydrous sodium carbonate, or potassium cyanide, did not improve the yield, nor was any successful result obtained by replacement of glycerol by liquid paraffin or diphenyl ether.

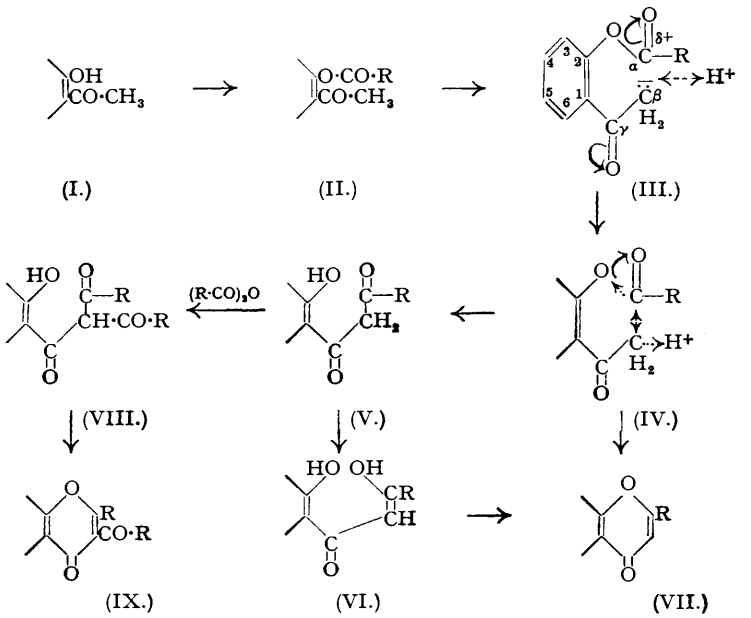
Flavones produced by Thermal Cyclization.—The flavones which have been prepared by this new method are listed in Tables IV and V. Yields obtained by the Baker–Venkataraman process, which is of recognized value in the synthesis of flavones, are given for comparison,

but it should be noted that the yields given for either method are not necessarily the best obtainable. Additional ester groups present in the acetoarone nucleus may be hydrolysed in the cyclization; for example, resacetophenone dibenzoate (No. 7, Table V) gave 7-hydroxyflavone. Work in progress indicates that diflavones can be prepared by thermal cyclization, in glycerol, of diacetylresorcinol esters. The method may also be of use in the synthesis of flavonols; ω-methoxyresacetophenone dibenzoate (No. 11, Table V) gave 7-hydroxy-3-methoxyflavone (39% yield). This flavonol ether was also obtained (32% yield) by the action of a base (potassium carbonate in pyridine) on the ester, the diketone formed cyclizing at once. This seems to be the first direct application of the Baker–Venkataraman method to the synthesis of a flavonol derivative, though Chavan and Robinson's conversion (*J.*, 1933, 368) of ω : 2 : 4 : 6-tetrabenzoyloxyacetophenone into 3 : 5 : 7-tribenzoyloxyflavone by the action of potassium acetate in boiling alcohol probably involves this transformation.

Mechanism of Cyclization.—The yields obtained by the new method vary greatly with the ester taken (see Tables IV and V). A comparison of these yields (Table I), however, indicates that they tend to increase with the acid strength of $R{\cdot}CO_2H$ (see II), the acetoarone nucleus remaining unchanged. This trend in the yields suggests that the mechanism of reaction involves the positive polarization of $C_{(\alpha)}$ of (III).

The results of experiments in which glycerol was replaced by benzoic anhydride are also important in relation to the course of the cyclization. Unexpectedly, it was found that at the boiling point (>300°) of the anhydride, cyclization was accompanied by 3-aroylation. Thus *o*-benzoyloxyacetophenone when heated under reflux with benzoic anhydride gave 3-benzoylflavone, and resacetophenone dibenzoate and phloroacetophenone tribenzoate yielded, respectively, 7-benzoyloxy- and 5 : 7-dibenzoyloxy-3-benzoylflavone. Hitherto a basic catalyst, *e.g.*, the sodium salt related to the acid anhydride, or triethylamine (Kuhn and Löw, *Ber.*, 1944, **77**, *B*, 202), has been regarded as essential for Allan–Robinson aroylation of *o*-hydroxy- or *o*-aroyloxy-acetoarones to 3-aroylflavones, but these new results indicate that if the temperature is sufficiently high a catalyst is not required. In this connexion a new method for the removal of benzoic anhydride is described in the experimental section (*E*).

Baker (*J.*, 1933, 1381) showed that the aroylation in question involves the transformation which bears his name. The proposed thermal-cyclization mechanism set out in (III) ⟶ (IX) is similar to that proved by Baker for Allan–Robinson aroylation, but includes the interpretation of his transformation suggested by Doyle *et al.* (*Proc. Roy. Dublin Soc.*, 1948, **24**, 291). At the



high temperatures employed, a proton on $C_{(\beta)}$ of (III) activated by the keto-group ($C_{(\gamma)}$) may through thermal vibration ionize sufficiently to enable an incipient $C_{(\beta)}$–$C_{(\alpha)}$ bond to be formed.

The tendency to bond formation will increase with the positive polarization of $C_{(\alpha)}$, that is, with the strength of $R{\cdot}CO_2H$.

TABLE I.

Yields of flavones obtained by thermal cyclization of esters from acids and phenols.

		Phenolic component and corresponding yields (%).[1]			
Acid.	$k \times 10^5$.	*o*-Hydroxyaceto-phenone.	2-Hydroxy-5-methoxyaceto-phenone.	1-Hydroxy-2-aceto-naphthone.	5-Hydroxy-6-acetyl-indane.
Acetic	1·8	No cyclization	—	—	—
p-Anisic	3·2	—	7 [2,3]	10	—
Cinnamic	3·5	—	5	Trace; 1 hr.; 230°	—
Benzoic	6·5	49; 54 (c); 120 mins.; 260°	5 [2]	56	50 (c)
p-Chlorobenzoic ...	9·3	—	21	70	—
m-Nitrobenzoic ...	35	43 (c); 120 mins.	—	—	—
p-Nitrobenzoic	42	70 (c); 120 mins.	23	*ca.* 80	66 (c)
3 : 5-Dinitrobenzoic	157	67 (c)	20	—	—
o-Nitrobenzoic	656	70 (c); 120 mins.; 200°	—	—	—

[1] (c) indicates yield of crude product before crystallization; otherwise the yield of crystallized product is given. [2] The glycerol used in this cyclization was of greater than 98% purity but not specially dehydrated; this may have reduced the yield. [3] If not stated, heating was for 30 minutes at 250°.

As the $C_{(\beta)}$–$C_{(\alpha)}$ bond forms, the $C_{(\alpha)}$–O single bond lengthens as in a normal Claisen condensation between an ester and a methyl ketone, with formation of the Baker–Venkataraman transition compound (IV). This may cyclize at once to (VII)—the literature contains numerous instances of the direct formation of flavones in the Baker–Venkataraman rearrangement. It will be seen that an internal aldol type of condensation is involved. Alternatively, (IV) may, as in the normal base-catalyzed transformation, pass into the diketone (V and VI) which in the absence of benzoic anhydride cyclizes at the high temperatures employed to (VII). Doyle *et al.* (*loc. cit.*) give examples of *o*-hydroxy-diketones which cyclize to flavones on being heated above the melting point and the mechanism of cyclization has been discussed by Nowlan *et al.* (*J.*, 1950, 340). In presence of benzoic anhydride, however, aroylation of (V) occurs as postulated by Baker (*loc. cit.*) to form the triketone (VIII) which cyclizes to the 3-aroylflavone (IX).

It will be noted that the basis of the above mechanism is that a thermal, and not a base-catalyzed, Baker–Venkataraman reaction is effected by working at a sufficiently high temperature. It should be recalled that the possibility of 3-aroylation of (VII) to give (IX) was eliminated by Baker (*loc. cit.*). Direct aroylation of $C_{(\beta)}$ in (III) is unlikely; dibenzoylmethane was not isolated in experiments in which acetophenone was heated with benzoic anhydride.

This view of the reaction mechanism also suggests that the presence of anionoid (*e.g.*, methoxyl) groups in positions in the acetoarone nucleus which facilitates neutralization of $C_{(\alpha)}$ (III; C_3 and C_5) or of $C_{(\gamma)}$ (III; C_4 and C_6) will also hinder cyclization. Actually as shown in Table I, poor yields were obtained with esters of 2-hydroxy-5-methoxyacetophenone, and (see nos. 19 and 20, Table V) in the synthesis of chrysin and of its dimethyl ether from the benzoates of phloroacetophenone and its 4 : 6-dimethyl ether. Again, it was not found possible to cyclize *o*-acetoxyacetophenone (cf. II; R = Me) by heating it in glycerol; neither chromone nor coumarin was isolated. The anionoid effect of the methyl group tends to neutralize $C_{(\alpha)}$. In line with this result is the fact that it is difficult to transform *o*-acetoxyacetophenone into *o*-hydroxybenzoylacetylmethane. It was found necessary to use as catalyst triphenylmethylsodium, one of the strongest bases available (see Experimental, section *C*). The bases usually employed, *e.g.*, potassium hydroxide in pyridine or metallic sodium in toluene, were ineffective.

EXPERIMENTAL.

A. *Preparation of* o-*Hydroxyacetoarones.*—The following *o*-hydroxyacetoarones were prepared according to the methods of the authors cited: *o*-hydroxyacetophenone (Mozingo, *Org. Synth.*, 1941, **21**, 45); ω-methoxyresacetophenone (Slater and Stephen, *J.*, 1920, 312); 2-hydroxy-5-methoxyacetophenone (Baker, Brown, and Scott, *J.*, 1939, 1926); 2-hydroxy-4 : 6-dimethoxyacetophenone (Belton, Nowlan, and Wheeler, *Proc. Roy. Dublin Soc.*, 1949, **25**, 19); 1-hydroxy-2-acetonaphthone (Witt and Braun, *Ber.*, 1914, **47**, 3216; Nowlan, Slavin, and Wheeler, *J.*, 1950, 340); 5-hydroxy-6-acetylindane (Baker, *J.*, 1937, 478). Phloroacetophenone was synthesised by the action of acetic anhydride and sulphuric acid on phloroglucinol (Israelstam and Stephen, *J. S. African Chem. Inst.*,

1943, **26**, 41), but the method in our hands was unreliable. The Hoesch synthesis (Gulati, Seth, and Venkataraman, *Org. Synth.*, 1943, Col. Vol. II, p. 522) was found preferable.

B. *Preparation of Esters of o-Hydroxy-ketones.*—The esters, *o*-acetoxyacetophenone excepted (see below), were prepared by the pyridine–acid chloride method (Doyle *et al.*, *Proc. Roy. Dublin Soc.*, 1948, **24**, 299; Nowlan *et al.*, *loc. cit.*), the yields being usually over 60%. Reference numbers (in parentheses in the text) have been inserted to facilitate cross-reference. *Esters* prepared for the first time are listed in Table II.

TABLE II.

New esters of o-hydroxy-ketones.

Ester no.	Ester.	M. p.	Formula.	Found, %. C.	H.	Cl or S.	Required, %. C.	H.	Cl or S.
8	Resacetophenone di-(*p*-chlorobenzoate)	116—118°	$C_{22}H_{14}O_5Cl_2$	61·8	3·3	Cl, 16·4	61·5	3·3	Cl, 16·6
10	Resacetophenone dicinnamate	114—116	$C_{26}H_{20}O_5$	75·9	4·9	—	75·7	4·9	—
13	2-(*p*-Chlorobenzoyloxy)-5-methoxyacetophenone	116—117	$C_{16}H_{13}O_4Cl$	62·7	4·1	Cl, 11·7	63·1	4·3	Cl, 11·7
16	2-(*p*-Anisoyloxy)-5-methoxyacetophenone	94—95	$C_{17}H_{16}O_5$	68·0	5·2	—	68·0	5·3	—
18	2-(Toluene-*o*-sulphonyloxy)-5-methoxyacetophenone	82—83	$C_{16}H_{16}O_5S$	60·1	4·8	S, 9·9	60·0	5·0	S, 10·0
21	2-Cinnamoyloxy-4 : 6-dimethoxyacetophenone	99	$C_{19}H_{18}O_5$	69·8	5·6	—	69·9	5·5	—
22	*o*-Benzoyloxypropiophenone	58—61 (Methyl alcohol)	$C_{16}H_{14}O_3$	75·4	5·4	—	75·6	5·5	—
24	1-(*p*-Chlorobenzoyloxy)-2-acetonaphthone	129—130	$C_{19}H_{13}O_3Cl$	69·8	4·0	Cl, 11·2	70·3	4·0	Cl, 10·9
26	1-(*p*-Anisoyloxy)-2-acetonaphthone	128—130 (Acetic acid)	$C_{20}H_{16}O_4$	75·2	5·1	—	75·0	5·0	—

These compounds except as otherwise indicated in the m. p. column were crystallized from alcohol All formed colourless to pale yellow crystals.

Esters which have previously been prepared. *o*-Acetoxyacetophenone (1)(Friedlaender and Neudörfer, *Ber.*, 1897, **30**, 1080) was obtained by use of pyridine and acetic anhydride. The yield (70% calc. on *o*-hydroxyacetophenone) of *o*-benzoyloxyacetophenone (2) obtained by Doyle *et al.* (*loc. cit.* p. 304; cf. Baker, *J.*, 1933, 1386) was increased to 83% by using 1·5 mols. of benzoyl chloride in place of 1 mol. The following were also prepared: *o*-(2-nitrobenzoyloxy)acetophenone (3) (Doyle *et al.*, *loc. cit.*); *o*-(3-nitrobenzoyloxy)acetophenone (4), m. p. 91—93° (from alcohol or ligroin) [Virkar (*J. Univ. Bombay*, 1942, **11**, 136) gives m. p. 99—100° (from alcohol)]; *o*-(4-nitrobenzoyloxy)acetophenone (5) (Doyle *et al.*, *loc. cit.*); *o*-(3 : 5-dinitrobenzoyloxy)acetophenone (6), m. p. 138—140° (from aqueous alcohol) [Doyle *et al.* (*loc. cit.*) give m. p. 131—133° (from alcohol–acetone)]; resacetophenone dibenzoate (7) and resacetophenone di-(*p*-anisoate) (9) (Baker, *loc. cit.*); ω-methoxyresacetophenone dibenzoate (11) (Fonseka, *J.*, 1947, 1683) (Found: C, 70·8; H, 4·7. Calc. for $C_{23}H_{18}O_6$: C, 70·8; H, 4·6%); 2-benzoyloxy-5-methoxyacetophenone (12), 2-(*p*-nitrobenzoyloxy)-5-methoxyacetophenone (14), 2-(3 : 5-dinitrobenzoyloxy)-5-methoxyacetophenone (15) and 2-cinnamoyloxy-5-methoxyacetophenone (17) (Doyle *et al.*, *loc. cit.*); phloroacetophenone tribenzoate (19) (Canter, Curd, and Robertson, *J.*, 1931, 1248); 2-benzoyloxy-4 : 6-dimethoxyacetophenone (20) (Gulati and Venkataraman, *J.*, 1936, 268); 1-benzoyloxy-2-acetonaphthone (23) (Bhullar and Venkataraman, *J.*, 1931, 1168); 1-(*p*-nitrobenzoyloxy)-2-acetonaphthone (25) (Virkar, *loc. cit.*); 1-cinnamoyloxy-2-acetonaphthone (27) (Bhalla, Mahal, and Venkataraman, *J.*, 1935, 870); 2-benzoyloxy-3-acetonaphthone (28); 5-benzoyloxy-6-acetylindane (29) and 5-(*p*-nitrobenzoyloxy)-6-acetylindane (30) (Nowlan *et al.*, *loc. cit.*).

C. *Preparation of o-Hydroxydiaroylmethanes (Table III).*—The Baker–Venkataraman transformation was carried out as follows (see Doyle *et al.*, *loc. cit.*): A solution of the ester in pyridine (10—20 parts) was heated under reflux (for 15 minutes unless otherwise stated in Table III) with the transforming agent shown in that Table. The resulting mixture was cooled, diluted with water, and acidified with 10% hydrochloric or acetic acid to precipitate the yellow diketone which, if solid, was recovered by filtration. Otherwise the product was extracted with ether and the extract was washed with aqueous sodium hydrogen carbonate and with 2% aqueous sodium hydroxide. The diketone was precipitated from the alkali hydroxide solution by saturation with carbon dioxide and was re-dissolved in ether. The ethereal solution was washed with water and dried (Na_2SO_4). The residue from the evaporation of the solvent was recrystallized. The new *diketones* obtained in this way are set out in Table III.

Transformation of o-acetoxyacetophenone. A solution of triphenylmethylsodium in absolute peroxide-free ether (200 ml.) was prepared from triphenylchloromethane (16 g.) by Hauser and Hudson's procedure (*Org. Reactions*, 1942, **1**, 286). 150 Ml. of this solution were added in an atmosphere of nitrogen to an anhydrous ethereal solution of *o*-acetoxyacetophenone (ester No. 1) (5 g. in 100 ml.). The yellow precipitate formed was collected after 1 hour and extracted with boiling water (300 ml.) in small successive quantities. The total aqueous extract was acidified with 10% acetic acid and the precipitate formed was dissolved in ether. The ethereal solution was dried (Na_2SO_4) and the solvent evaporated off. The residue (0·3 g.) when twice crystallized from benzene–ligroin formed white needles, m. p. 91—92°, not depressed by admixture with an authentic specimen of *o*-hydroxybenzoylacetylmethane prepared by a Claisen condensation of *o*-hydroxyacetophenone and ethyl acetate as described by Wittig (*Annalen*, 1926, **446**, 169).

TABLE III.

New o-*Hydroxydiaroylmethanes.*

Corresponding ester no.	Diketone.	M. p.	Formula.	Elements.	Found, %.	Required, %.	Yield of crystallized diketone.
8	4-Chloro-2′-hydroxy-4′-(*p*-chlorobenzoyloxy)dibenzoylmethane	205—207°	$C_{22}H_{14}O_5Cl_2$	C	60·9	61·5	14 [1]
				H	3·4	3·3	
				Cl	16·7	16·6	
13	4-Chloro-2′-hydroxy-5′-methoxydibenzoylmethane	100—101	$C_{16}H_{13}O_4Cl$	C	62·9	63·1	90 [2]
				H	4·5	4·3	
				Cl	11·7	11·7	
16	2-Hydroxy-5 : 4′-dimethoxydibenzoylmethane	123—125	$C_{17}H_{16}O_5$	C	67·7	68·0	80 [2]
				H	5·2	5·2	
21	2-Hydroxy-4 : 6-dimethoxybenzoylcinnamoylmethane	126	$C_{19}H_{18}O_5$	C	69·8	69·9	14 [3]
				H	5·6	5·5	
24	4-Chlorobenzoyl-1′-hydroxy-2′-naphthoylmethane	178—180	$C_{19}H_{13}O_3Cl$	C	70·3	70·3	60 [2]
				H	4·1	4·0	
				Cl	11·0	10·9	
26	*p*-Anisoyl-1-hydroxy-2-naphthoylmethane	135—137	$C_{20}H_{16}O_4$	C	74·5	75·0	60 [3]
				H	5·2	5·0	

These compounds, No. 8 excepted, were recrystallized from alcohol. No. 8 was recrystallized from acetone.

[1] Transforming agent, anhydrous potassium carbonate (2·2 mols.); time of heating 2 hours. [2] Transforming agent, ethyl sodioacetoacetate (excess). [3] Transforming agent, powdered potassium hydroxide (1—2 mols.).

TABLE IV.

New flavones obtained from the corresponding esters (Table II) by cyclization in glycerol (method 1) or through the corresponding diketones (Table III) (method 2).

Corresponding ester no.	Pyrone formed.[1]	M. p.	Formula.	Elements.	Found, %.	Required, %.	Yield (%) of pyrone from ester, method 1.	Yield (%) of pyrone from ester, method 2.
8	4′-Chloro-7-hydroxyflavone	277—278°	$C_{15}H_9O_3Cl$	C	65·6	66·1	23	11 [2]
				H	3·6	3·3		
				Cl	13·1	13·0		
13	4′-Chloro-6-methoxyflavone	175—177	$C_{16}H_{11}O_3Cl,H_2O$ [3]	C	63·4	63·1	21	60
				H	4·3	4·3		
				Cl	11·7	11·7		
16	6 : 4′-Dimethoxyflavone	194—195	$C_{17}H_{14}O_4$	C	72·5	72·3	7 [4]	40
				H	5·1	5·0		
22	3-Methylflavone	66—67 [5]	$C_{16}H_{12}O_2$	C	80·7	81·4	21	Ester did not transform.
				H	5·2	5·1		
24	4′-Chloro-α-naphthaflavone	236—238	$C_{19}H_{11}O_2Cl$	C	74·3	74·4	70	50
				H	3·6	3·6		
				Cl	11·5	11·6		

[1] These compounds were colourless to pale yellow. 3-Methylflavone was recrystallized from light petroleum (b. p. 40—60°), and the other flavones from alcohol. The time and temperature of heating in glycerol for 3-methylflavone were 2 hours and 260°. The conditions for the other flavones were 30 minutes and 250°. The proportion of ester to glycerol was 1 : 20, except with nos. 8 and 22 when it was 1 : 10. [2] The yield in the transformation of this ester was low (see No. 8, Table III). Cyclization was effected in this instance by dissolving the diketone in three parts of concentrated sulphuric acid and diluting the mixture with water after 30 minutes. Hydrolysis of the 4′-(*p*-chlorobenzoyloxy)-group in the diketone [4-chloro-2′-hydroxy-4′-(*p*-chlorobenzoyloxy)dibenzoylmethane] occurred during the cyclization (see Baker, *J.*, 1933, 1382, and footnote 6, Table V). [3] This flavone contained one mol. of water of crystallization (cf. Bernfeld and Wheeler, *J.*, 1949, 1918). [4] The glycerol used with this ester was not specially dehydrated; it contained over 98% of glycerol. [5] The mixture obtained by pouring the glycerol solution into water was kept at 0° for 48 hours and extracted with ether. The ethereal solution was washed with 2% aqueous potassium hydroxide, and with water, and was dried (Na_2SO_4). The solvent was evaporated off and the residue was recrystallized from light petroleum (b. p. 40—60°) to yield colourless crystals, m. p. 66—67°, which did not depress the m. p. (72—74°) of an authentic specimen of 3-methylflavone prepared by the Allan–Robinson aroylation method (see below).

It was not found possible to transform 2-(toluene-*o*-sulphonyloxy)-5-methoxyacetophenone (ester No. 18) or *o*-benzoyloxypropiophenone (ester No. 22).

D. *Preparation of* 4-*Pyrones* (Tables IV and V).—These compounds were obtained from the esters of the *o*-hydroxy-ketones by the following methods:

Method 1. *Direct cyclization of* o-*aroyloxyacetoarones.* The ester was heated in glycerol (10—20 parts; previously distilled at 1 mm.) for the time and at the temperature shown in Tables IV and V,

TABLE V.

Known pyrones obtained from the corresponding esters (*o*-acyloxyacetoarones) by cyclization in glycerol (method 1). Yields obtained by application of the Baker–Venkataraman transformation and cyclization of the resulting diketones (method 2) are given for comparison

Corresponding ester no. and experimental details, if not 30 minutes, 250°, and 10 parts of glycerol.	Pyrone formed.	Confirmation of identity of product obtained by method 1.[1]	Yield (%) [2] of pyrone from ester. See section D above: method 1.	method 2.
No. 2; 120 mins.; 260°	Flavone [3]	A.S. (method 2)	49 [4]	80 [5]
			54 *	—
No. 3; 120 mins.; 200°	2′-Nitroflavone [3]	M. p. (*a*)	70 *	40 * (*a*)
No. 4; 120 mins.	3′-Nitroflavone [3]	M. p. (*a*)	43 *	45 * (*b*)
No. 5; 120 mins.	4′-Nitroflavone [3]	M. p. (*a*)	70 *	38 * (*a*)
No. 6	3′ : 5′-Dinitroflavone	M. p. (*a*)	67 *	—
No. 7	7-Hydroxyflavone	A.S. (*c*)	53	48 [6]
No. 9	7-Hydroxy-4′-methoxyflavone (pratol)	M. p. and m. p. of acetyl derivative in agreement with (*c*)	16 *	22 (*c*)
No. 11	7-Hydroxy-3-methoxyflavone	A.S. (*d*)	39	32 (method 3); see below
No. 12; glycerol (20 parts)	6-Methoxyflavone	A.S. (*a*)	5 [7]	53 (*a*)
No. 14; glycerol (20 parts)	4′-Nitro-6-methoxyflavone	A.S. (*a*)	23	18 (*a*)
No. 15; glycerol (20 parts)	3′ : 5′-Dinitro-6-methoxyflavone	A.S. (*a*)	20	53 (*a*)
No. 17; glycerol (20 parts)	6-Methoxy-2-styrylchromone	A.S. (*a*)	5	48 (*a*)
No. 19	5 : 7-Dihydroxyflavone (chrysin)	M. p. (*e*) [8]	7	—
No. 20; 60 mins.; 220°; glycerol (5 parts)	5 : 7-Dimethoxyflavone	A.S. (*f*) [9]	Trace	43 (*f*)
No. 23; glycerol (20 parts)	α-Naphthaflavone [3]	A.S. (*g*)	56	26 (*h*)
No. 25; glycerol (20 parts)	4′-Nitro-α-naphthaflavone	M. p. (*b*)	*ca.* 80	80 (*b*); cf. (*i*)
No. 26; glycerol (20 parts)	4′-Methoxy-α-naphthaflavone	A.S. (method 2); m. p. (*g*)	10	50 (see Table III)
No. 27; 60 mins.; 230°; glycerol (20 parts)	2-Styryl-7 : 8-benzchromone	M. p. (*j*)	Trace	—
No. 28; 5 hours; 260°	6 : 7-Benzflavone (linear naphthaflavone) [10]	M. p. (*k*)	20	70 (*k*)
No. 29; glycerol (20 parts)	6-Phenylindano-(5′ : 6′-2 : 3)-4-pyrone [3,11]	M. p. (*k*) [12]	50 *	85 (*k*)
No. 30; glycerol (20 parts)	6-(*p*-Nitrophenyl)indano-(5′ : 6′-2 : 3)-4-pyrone	M. p. (*k*) [12]	66 *	56 (*k*)

[1] A. S. (method 2) indicates mixed m. p. with authentic specimen prepared from the ester by application of the Baker–Venkataraman transformation and cyclization of the resulting diketone. A. S. (*a*, etc.) indicates mixed m. p. with authentic specimen prepared as described in reference (*a*, etc.) (see below). M. p. (*a*, etc.) indicates m. p. in agreement with that given in reference (*a*, etc.) (see below). [2] * Shows that the yield given is that of crude product before crystallization; otherwise the yield of crystallized product is given. [3] Optimum conditions of cyclization determined in a series of experiments; otherwise the yields given are not necessarily maximum. [4] The crude product (10·1 g.; m. p. 91—93°) obtained by heating *o*-benzoyloxyacetophenone (20 g.) in glycerol and pouring the reaction mixture into water was kept at 0° for 48 hours and then crystallized from ligroin (400 ml.) (see Mozingo and Adkins, *J. Amer. Chem. Soc.*, 1938, **60**, 673). The solvent when evaporated in stages to 80 ml. yielded flavone (9 g.; m. p. 97°). [5] The over-all yield (42%) obtained by Doyle *et al.* (*loc. cit.*) in the conversion of *o*-hydroxyacetophenone into flavone by the Baker–Venkataraman method, *o*-C_6H_4(OH)(COMe) ⟶ *o*-C_6H_4(O·COPh)(COMe) ⟶ *o*-C_6H_4(OH)(CO·CH_2·COPh) ⟶ flavone, has now been improved to about 60% by (i) increasing the yield in the esterification as described at *B* above and (ii) using the technique of Mozingo and Adkins (*loc. cit.*) for the cyclization of *o*-hydroxydibenzoylmethane. [6] Resacetophenone dibenzoate (ester No. 7) was transformed into 2-hydroxy-4-benzoyloxydibenzoylmethane (50% crude yield) by use of solid potassium hydroxide and pyridine (see C above), and the diketone was cyclized to 7-hydroxyflavone with sulphuric acid [see reference (*c*) below, and footnote 2, Table IV]. [7] The glycerol used in this cyclization was not specially dehydrated. It contained over 98% of glycerol. [8] The glycerol reaction mixture when diluted with water was extracted with ether, and the ethereal solution was washed with water and dried (Na_2SO_4). The oil remaining on evaporation of the solvent was twice extracted with boiling water to remove phloroacetophenone and benzoic acid if present, and the residue was crystallized from glacial acetic acid (charcoal); m. p. 275° [lit. (*e*) 275°]. [9] The glycerol reaction mixture when diluted with water was extracted with ether, and the extract was washed with dilute sodium hydroxide and with water and dried (Na_2SO_4). The residue obtained on evaporation of the solvent and recrystallized from aqueous alcohol had m. p. 143° [lit. (*f*) 143°]. [10] This cyclization was carried out by Dr. N. V. Nowlan (private communication). [11] This cyclization, the first application of the new method, was effected by Slavin (M.Sc. thesis, University College,

Dublin, 1948; see Bernfeld and Wheeler, *J.*, 1949, 1916). [12] These compounds were purified by extraction with chloroform and treatment of the extract as described in footnote 9.

(*a*) Doyle *et al.*, *Proc. Roy. Dublin Soc.*, 1948, **24**, 291. (*b*) Virkar, *J. Univ. Bombay*, 1942, **11**, 136. (*c*) Baker, *J.*, 1933, 1381. (*d*) Allan and Robinson, *J.*, 1924, **125**, 2192. (*e*) Robinson and Venkataraman, *J.*, 1926, 2344. (*f*) Gulati and Venkataraman, *J.*, 1936, 268. (*g*) Bhullar and Venkataraman, *J.*, 1931, 1165. (*h*) Mahal and Venkataraman, *J.*, 1934, 1767. (*i*) Anand and Venkataraman, *Proc. Indian Acad. Sci.*, 1947, **26**, 279. (*j*) Bhalla, Mahal, and Venkataraman, *J.*, 1935, 868. (*k*) Nowlan, Slavin, and Wheeler, *J.*, 1950, 340.

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usually 30 minutes and 250°. A current of dry nitrogen or coal gas was passed through the reaction vessel. The resulting mixture, while still warm, was poured into 10 volumes of cold water, and the precipitated product when sufficiently solid was recovered by filtration and crystallized. If the product did not solidify an extraction procedure (see Table IV, footnote 5, and Table V, footnotes 8, 9, and 12) was employed. It was not possible to cyclize *o*-acetoxyacetophenone (ester No. 1), resacetophenone dicinnamate (ester No. 10), or 2-(toluene-*o*-sulphonyloxy)-5-methoxyacetophenone (ester No. 18) to pyrones by the glycerol dehydration method.

Method 2. The *o*-hydroxy-diketone obtained by transformation of the corresponding ester (see section C above) was boiled with glacial acetic acid containing a few drops of hydrochloric acid, and the resulting pyrone separated by controlled addition of water (see Nowlan *et al.*, *loc. cit.*). The diketones from esters Nos. 7 and 8 were cyclized with concentrated sulphuric acid (see Table V, footnote 6, and Table IV, footnote 2).

Method 3. When resacetophenone dicinnamate (ester No. 10) and ω-methoxyresacetophenone dibenzoate (ester No. 11) were subjected to the Baker–Venkataraman transformation, spontaneous cyclization of the intermediate diketone to the corresponding pyrone occurred. Details are given below.

Preparation of 3-*methylflavone by Allan–Robinson aroylation of* o-*hydroxypropiophenone.* A mixture of *o*-hydroxypropiophenone (2 ml.), benzoic anhydride (20 g.), and potassium benzoate (4 g.) was heated under reflux (mechanical stirring) at 160—180° for 6 hours. Excess of benzoic anhydride was removed by boiling the product with 5% aqueous sodium carbonate (400 ml.) for 2 hours (see section E below). Aqueous (10%) potassium hydroxide was added to strong alkalinity in the cold, and the solid which formed on keeping at 0° was recovered by filtration. It was crystallized from light petroleum (b. p. 40—60°) and, after rejection of the oil which first separated, was obtained as colourless needles, m. p. and mixed m. p. with the product of the dehydration of *o*-benzoyloxypropiophenone in glycerol (Table IV, No. 22), 72—74°. Yield 1 g. (31%).

4-*Pyrones obtained by method* 3 (*spontaneous cyclization of the intermediate Baker–Venkataraman diketone*; *see above*). Resacetophenone dicinnamate (ester No. 10), when treated with potassium hydroxide (3·0 mols.) in pyridine as described in section C above, gave, on acidification of the reaction mixture, 7-hydroxy-2-styrylchromone (62%), m. p. 238—241° (from alcohol) (Found: C, 77·3; H, 4·6. Calc. for $C_{17}H_{12}O_3$: C, 77·3; H, 4·5%). Gulati, Seth, and Venkataraman (*J.*, 1934, 1766) give m. p. 239°.

Similarly ω-methoxyresacetophenone dibenzoate (ester No. 11) when heated under reflux with potassium carbonate and pyridine for 1 hour gave on acidification 7-hydroxy-3-methoxyflavone (32%), m. p. 233—234° (from alcohol–ethyl acetate). The m. p. was not depressed by admixture with an authentic specimen prepared by the salt–anhydride aroylation method as described by Allan and Robinson (*J.*, 1924, **125**, 2194), who give m. p. 227°.

E. *Cyclizations using Benzoic Anhydride.*—(*a*) Methods available for removing excess of aromatic acid anhydride from the product of Allan–Robinson aroylations include (i) treatment with aqueous sodium carbonate (Baker, *J.*, 1933, 1388; Baker, Flemons, and Winter, *J.*, 1949, 1562), (ii) extraction with light petroleum (Sethna and Shah, *J. Indian Chem. Soc.*, 1940, **17**, 601), and (iii) extraction with carbon disulphide (Trivedi, Sethna, and Shah, *ibid.*, 1943, **20**, 171).

A method which may be of use where sulphonation is unlikely has now been devised. It consists in dissolving the reaction product in cold concentrated sulphuric acid, and adding the solution slowly with cooling to excess of water or aqueous sodium hydroxide. The anhydride is immediately hydrolysed to the acid.

(*b*) *Preparation of* 3-*benzoylflavone.* A mixture of *o*-benzoyloxyacetophenone (1 g.) and benzoic anhydride (3 g.) was heated at the b. p. under an air condenser for 15 minutes. The product was dissolved in cold concentrated sulphuric acid (40 ml.), and the acid solution was added under good cooling to excess (400 ml.) of 10% aqueous sodium hydroxide. Insoluble material was recovered by filtration and dissolved in ether. The ethereal solution was extracted with 2% aqueous sodium hydroxide washed with water, and dried (Na_2SO_4). The residue remaining on removal of the solvent separated from methyl alcohol in white needles, m. p. 130—132° (yield 0·2 g.) (Found: C, 80·9; H, 4·3%; *M*, 332. $C_{22}H_{14}O_3$ requires C, 81·0; H, 4·3%; *M*, 326).

3-Benzoylflavone (1·4 g.; m. p. not depressed by addition of the product obtained from *o*-benzoyloxyacetophenone and benzoic anhydride as described in the preceding paragraph) was also prepared by heating a mixture of *o*-hydroxyacetophenone (1·8 ml.), benzoic anhydride (20 g.), and sodium benzoate (4 g.) at 180° for 6 hours (mechanical stirring). Excess of benzoic anhydride was hydrolysed by boiling the product under reflux for 2 hours with 5% aqueous sodium carbonate (200 ml.). The liquid when cold was rendered strongly alkaline with 10% aqueous sodium hydroxide, and the insoluble solid residue was recovered and recrystallized from aqueous methyl alcohol.

An improved yield of 3-benzoylflavone (2·3 g.) was obtained by replacing sodium benzoate in the above preparation by triethylamine (5 g.) (see Kuhn and Löw, *Ber.*, 1944, **77**, 202). The residue insoluble in the aqueous alkali was obtained as an oil which solidified after it had been kept at 0° for 12 hours.

(*c*) *Preparation of* 7-*benzoyloxy*-3-*benzoylflavone.* A mixture of resacetophenone dibenzoate (4 g.)

and benzoic anhydride (16 g.) was heated at the b. p. under reflux for 30 minutes in an atmosphere of nitrogen. The solid obtained on cooling was ground with sodium carbonate solution (cf. Baker, *J.*, 1933, 1388), and the supernatant liquid decanted after storage. The product, 7-benzoyloxy-3-benzoylflavone, separated from alcohol in crystals (0·8 g.) having m. p. 167°. Baker (*loc. cit.*) gives the same m. p. (Found : C, 77·3; H, 4·0. Calc. for $C_{29}H_{18}O_5$: C, 78·0; H, 4·0%). The identity of the compound was confirmed by debenzoylation with sulphuric acid to 7-hydroxy-3-benzoylflavone, m. p. 265°, by the method due to Trivedi, Sethna, and Shah (*J. Indian Chem. Soc.*, 1943, **20**, 171) who give m. p. 264—265°

(*d*) *Preparation of* 5 : 7-*dibenzoyloxy*-3-*benzoylflavone*. A mixture of phloroacetophenone tribenzoate (1 g.) and benzoic anhydride (5 g.) was heated at the b. p. for 10 minutes in an atmosphere of nitrogen. The product obtained on cooling was extracted with ligroin in the cold to remove benzoic anhydride (cf. Sethna and Shah, *J. Indian Chem. Soc.*, 1940, **17**, 601), and the residue was crystallized from alcohol (charcoal) and ligroin. It formed colourless crystals (0·1 g.), m. p. 169° (Found : C, 76·4; H, 4·3. Calc. for $C_{36}H_{22}O_7$: C, 76·3; H, 3·9%). Trivedi, Sethna, and Shah (*loc. cit.*) give m. p. 167—168° for 5 : 7-dibenzoyloxy-3-benzoylflavone.

(*e*) *Action of benzoic anhydride on acetophenone*. A mixture of acetophenone (1 g.) and benzoic anhydride (5 g.) was heated under reflux at the b. p. for periods of from 30 minutes to 6 hours. The product did not yield dibenzoylmethane.

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