509. *The Synthesis of* iso*Flavones.*

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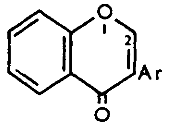
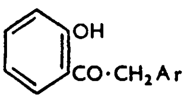
*iso*Flavones are obtained, in some instances in satisfactory yield, by the action of formanilide or formamide on benzyl *o*-hydroxyphenyl ketones. 2-Substituted *iso*flavones can be prepared by heating *o*-acyloxyphenyl benzyl ketones.

Various sources of the $C_{(2)}$-atom in *iso*flavones (I) which would permit of their ready synthesis from benzyl *o*-hydroxyphenyl ketones (2-hydroxydeoxybenzoins) (II) have been investigated.[1] It has now been found that formamide, or preferably formanilide, can in some instances supply the necessary $C_{(2)}$-atom, with yields of *iso*flavone of up to 60%. The technique is simple: the amide and the deoxybenzoin are heated together for about 30 min.; normally the isolation of the *iso*flavone presents little difficulty. The results are summarised in Table 3 and a list of unreactive deoxybenzoins is given on p. 2498.

It is necessary to protect hydroxyl groups in the deoxybenzoin, except that in the 2-position. Electron-attracting radicals, *e.g.*, benzoyl, *p*-nitrobenzoyl, toluene-*p*-sulphonyl, give much better results than the methyl group which tends to inhibit the reaction. Dearoylation occurs when the benzoyl or *p*-nitrobenzoyl derivatives are employed; the products obtained with the latter are harder to purify. The toluene-*p*-sulphonyl group promotes good yields but is difficult to remove from the resulting *iso*flavone, being resistant to the action of cold sulphuric acid, hydrochloric acid in acetic acid at 100°, and refluxing dilute ethanolic potassium hydroxide, though it is smoothly eliminated by hydriodic acid in acetic anhydride under demethylating conditions.



(I)



(II)

The use of esterification for protection of hydroxyl groups is limited. It was not possible to prepare the 4 : 6-di-*O*-benzoyl or -di-*O*-toluene-*p*-sulphonyl derivative of benzyl 2 : 4 : 6-trihydroxyphenyl ketone.

The introduction of a nitro-group in the 4'-position in the deoxybenzoin is advantageous.[2,3] Benzyl 2-hydroxy-4 : 6-dimethoxyphenyl ketone gives no *iso*flavone, while with the corresponding 4-nitrobenzyl ketone yields of 15% (formamide) and 25% (formanilide) are obtained. The production of *iso*flavone is not increased by the use of sulphuric acid as condensing agent, or by addition of formic acid as in the Leukart–Wallach reaction.

The reaction, while useful in particular cases, does not displace as the method of choice the ethoxalyl chloride process[4] which can be employed with polyhydroxydeoxybenzoins without protection of the hydroxyl groups. This advantage also attaches to the method recently described by Farkas[5] in which the $C_{(2)}$-atom is obtained by the action of hydrogen chloride on zinc cyanide.

No useful result was achieved in efforts to extend the scope of the new reaction. A series of experiments in which various 2-hydroxy- and 2-hydroxy-ω-methoxy-acetophenones

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[1] Baker and Ollis, *Sci. Proc. Roy. Dublin Soc.*, 1956, **27**, 119; Warburton, *Quart. Rev.*, 1954, **8**, 67.

[2] Iyer, Shah, and Venkataraman, *Proc. Indian Acad. Sci.*, 1951, **33**, *A*, 116.

[3] Dutta and Bose, *J. Sci. Ind. Res., India*, 1952, **11**, *B*, 413.

[4] (*a*) Baker, Chadderton, Harborne, and Ollis, *J.*, 1953, 1852; (*b*) Baker, Harborne, and Ollis, *ibid.*, p. 1860.

[5] Farkas, *Chem. and Ind.*, 1957, 1212; *Chem. Ber.*, 1957, **90**, 2940.

were heated with formamide or formanilide with view to production of chromones did not give identifiable products.

The possibility of a thermally induced Baker–Venkataraman transformation of *o*-acyloxyacetoarones into the corresponding *o*-hydroxy-1 : 3-diketone or flavone was first shown by Venkataraman [6] and later studied in this laboratory (see, for example, O'Toole and Wheeler [7]). Heating alone or in glycerol was employed. It has now been found (see Table 4) that 2-acyloxydeoxybenzoins when heated at 250° give the corresponding 2-substituted *iso*flavones, in some instances in satisfactory yield. This reaction parallels the ready manner in which these compounds undergo the Baker–Venkataraman base-catalysed transformation,[8] which may also be brought about thermally.[6,7] As in the formamide method polyhydroxydeoxybenzoins do not react well. No advantage was obtained by using glycerol as a solvent.

EXPERIMENTAL

The methods used in the preparation mentioned in Tables 1 and 2 were: (1) acetylation by acetic anhydride and a trace of perchloric acid; (2) methylation by methyl sulphate, acetone, and potassium carbonate; (3) esterification by pyridine and acid chloride; (4) sulphonylation by toluene-*p*-sulphonyl chloride, acetone, and potassium carbonate; (5) Schotten–Baumann method.

TABLE 1. *Deoxybenzoins (benzyl phenyl ketones) prepared by methods other than those given for them in the literature.*

Deoxybenzoin	Ketone from which prepared	Method (see text)	Form (solvent)	M. p. (found)	M. p. (lit.)
Benzyl 2 : 4-diacetoxyphenyl ketone	Benzyl 2 : 4-dihydroxyphenyl [a]	1	Needles (AcOH)	135—136°	136° [b]
Benzyl 2 : 4-dibenzoyloxyphenyl ketone	,, ,,	3	Yellow needles (AcOH)	110—112	95—96 [c]
2-Hydroxy-4-methoxyphenyl 4-nitrobenzyl ketone	2 : 4-Dihydroxyphenyl 4-nitrobenzyl [d]	2	Plates (EtOH)	134—136	136 [d]
2-Hydroxy-4 : 6-dimethoxyphenyl 4-nitrobenzyl ketone	4-Nitrobenzyl 2 : 4 : 6-trihydroxyphenyl [e]	2	Needles (EtOH)	150	148
Benzyl 2-hydroxy-4 : 5-dimethoxyphenyl ketone	Benzyl 2 : 5-dihydroxy-4-methoxyphenyl [g]	2	Plates (EtOH)	93	94 [h]

[a] Badcock, Cavill, Robertson, and Whalley, *J.*, 1950, 2961. [b] Chapman and Stephen, *J.*, 1923, **123**, 404. [c] Bhumgara, Desai, and Waravdekar, *Proc. Indian Acad. Sci.*, 1947, **25**, *A*, 322. [d] Joshi and Venkataraman, *J.*, 1934, 513. [e] Ref. 3. [f] Ref. 2. [g] Ballio and Pocchiari, *Gazzetta*, 1949, **79**, 913. [h] Bargellini and Martegiani, *Atti R. Accad. Lincei*, 1911, **20**, 183.

Benzyl 2-Hydroxy-5-methoxyphenyl Ketone.—A mixture of aluminium chloride (50 g.), *p*-dimethoxybenzene (24 g.), phenylacetyl chloride (24 g.), and ether (200 ml.) was refluxed for 8 hr. Material insoluble in ether was heated for 30 min. with 10% hydrochloric acid, and the product extracted with ether. The extract yielded to aqueous sodium hydroxide the required *deoxybenzoin* which crystallised from light petroleum (b. p. 40—60°) in yellow needles (16 g.), m. p. 45° (Found: C, 74·4; H, 5·8. $C_{15}H_{14}O_3$ requires C, 74·3; H, 5·8%). The ethanolic ferric colour was deep green. Ballio and Pocchiari [9] prepared this compound in a crude form but did not characterise it.

Synthesis of iso*Flavones (see Table 3).*—Normally the benzyl 2-hydroxyphenyl ketone (1 g.) was heated for 30—60 min. (A) with formamide (2—3 ml.) under reflux in nitrogen or (B) with formanilide (1·5 g.) at 250°. The product obtained with formamide was poured into

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[6] Venkataraman, *Proc. Nat. Inst. Sci., India*, 1939, **5**, 255.

[7] O'Toole and Wheeler, *J.*, 1956, 4411.

[8] Baker, *J.*, 1933, 1381; Ollis and Weight, *J.*, 1952, 3826; Gupta and Seshadri, *J. Sci. Ind. Res., India*, 1957, **16**, *B*, 116.

[9] Ballio and Pocchiari, *Gazzetta*, 1949, **79**, 913.

TABLE 2. *New deoxybenzoins (benzyl phenyl ketones).*

Deoxybenzoin	Ketone from which prepared	Method (see above)	Form (solvent)	M. p.	Ethanolic Fe^{3+} colour	Found (%) C	Found (%) H	Found (%) N or S	Formula	Required (%) C	Required (%) H	Required (%) N or S
2-Benzoyloxyphenyl benzyl ketone	Benzyl 2-hydroxyphenyl [a]	3	Needles (EtOH)	94°	—	79·8	5·3	—	$C_{21}H_{16}O_3$	79·7	5·1	—
Benzyl 2-cinnamoyloxyphenyl ketone	,, ,,	3	Aggregates (EtOH)	99	—	80·8	5·5	—	$C_{23}H_{18}O_3$	80·7	5·3	—
Benzyl 2-hydroxy-4-*p*-nitrobenzoyloxyphenyl ketone	Benzyl 2 : 4-dihydroxyphenyl [b]	3	Yellow plates (EtOH)	178—180	Reddish-violet	67·0	4·2	3·6	$C_{21}H_{15}O_6N$	66·8	4·0	3·7
Benzyl 2-hydroxy-4-toluene-*p*-sulphonyloxyphenyl ketone	,, ,,	4	Needles (EtOH)	117	Red	66·4	4·7	8·2	$C_{21}H_{18}O_5S$	66·0	4·8	8·4
4-Benzoyloxy-2-hydroxyphenyl 4-methoxybenzyl ketone	2 : 4-Dihydroxyphenyl 4-methoxybenzyl [c]	5	Needles (AcOH and EtOH)	120—121	Red	73·1	5·1	—	$C_{22}H_{18}O_5$	72·9	5·0	—
2-Hydroxy-4-*p*-nitrobenzoyloxyphenyl 4-methoxybenzyl ketone	,, ,,	3	Yellow prisms (EtOH)	166—167	Red	65·2	4·5	3·2	$C_{22}H_{17}O_7N$	64·9	4·2	3·4
2-Hydroxy-4-toluene-*p*-sulphonyloxyphenyl 4-methoxybenzyl ketone	2 : 4-Dihydroxyphenyl 4-methoxybenzyl [c]	4	Prisms (EtOH)	91	Red	64·2	4·8	7·6	$C_{22}H_{20}O_6S$	64·1	4·9	7·8
2 : 4-Diacetoxyphenyl 4-nitrobenzyl ketone	2 : 4-Dihydroxyphenyl 4-nitrobenzyl [d]	1	Prisms (AcOH)	157—158	—	60·6	4·1	3·2	$C_{18}H_{15}O_7N$	60·5	4·2	3·9
2 : 4-Dibenzoyloxyphenyl 4-nitrobenzyl ketone	,, ,,	3	Yellow prisms (AcOH)	159—185[e]	—	70·6	3·7	2·5	$C_{28}H_{19}O_7N$	69·9	4·0	2·9
Benzyl 2-hydroxy-6-methoxyphenyl ketone	Benzyl 2 : 6-dihydroxyphenyl [f]	2	Needles (Aq. AcOH)	66	Green	73·8	5·9	(OMe 12·7)	$C_{15}H_{14}O_3$	74·3	5·8	(OMe, 12·8)
Benzyl 2 : 4 : 6-triacetoxyphenyl ketone [g]	Benzyl 2 : 4 : 6-trihydroxyphenyl [h]	1	Plates (Aq. AcOH)	125—126	—	64·9	5·0	—	$C_{20}H_{18}O_7$	64·9	4·9	—
Benzyl 2 : 4 : 6-tribenzoyloxyphenyl ketone	,, ,,	3	Prisms (Aq. AcOH)	175	—	75·6	4·1	—	$C_{35}H_{24}O_7$	75·5	4·4	—
4-Nitrobenzyl 2 : 4 : 6-triacetoxyphenyl ketone	4-Nitrobenzyl 2 : 4 : 6-trihydroxyphenyl [i]	1	Prisms (Aq. AcOH)	133—134	—	57·4	4·2	3·7	$C_{20}H_{17}O_9N$	57·8	4·1	3·4
4-Nitrobenzyl 2 : 4 : 6-tribenzoyloxyphenyl ketone	,, ,,	3	Needles (AcOH)	126—128	—	70·4	3·7	1·7	$C_{35}H_{23}O_9N$	70·0	3·8	2·3

[a] Chadha, Mahal, and Venkataraman, *J.*, 1933, 1459. [b] Ref. *a* of Table 1. [c] Baker and Eastwood, *J.*, 1929, 2897. [d] See Table 1. [e] Presumably decomposition occurred on melting. [f] Karmarkar, Shah, and Venkataraman, *Proc. Indian Acad. Sci.*, 1952, **36**, *A*, 552. [g] Gupta and Seshadri[8] state that this compound (m. p. 118—120°; no analysis) was obtained by the action of (1) acetic anhydride and perchloric acid or (2) acetyl chloride and pyridine on the corresponding trihydroxydeoxybenzoin; they mention that Mehta and Seshadri (*J.*, 1954, 3823) obtained by method 2 a compound with the same m. p. which was incorrectly formulated as 2 : 4 : 6-triacetoxyphenyl α-acetylbenzyl ketone. The analysis (C, 63·8; H, 5·1%) given by Mehta and Seshadri is not satisfactory for benzyl 2 : 4 : 6-triacetoxyphenyl ketone. [h] Ref. *b* of Table 1. [i] Ref. 3.

water. When formanilide was used the material was directly treated with an organic solvent. Purification was by crystallisation, in some instances after chromatography on alumina on which the unchanged deoxybenzoin was strongly adsorbed. Further details of some of the preparations are given below. The numbering refers to Table 3.

Nos. 7 *and* 8. Dearoylation occurred in these experiments. 7-Hydroxy*iso*flavone was extracted from a chloroform solution of the product by aqueous sodium hydroxide.

Nos. 10 *and* 14. The toluene-*p*-sulphonyl group was removed by refluxing the *iso*flavone produced with hydriodic acid in acetic anhydride as for demethylation. 7 : 4′-Dihydroxy*iso*flavone is the naturally occurring daidzein.

TABLE 3. iso*Flavones prepared by the action of formamide* (*A*) *or formanilide* (*B*) *on the corresponding benzyl* o-*hydroxyphenyl ketone. The order is that of increasing yield.*

No.	*iso*Flavone	Ketone from which prepared	Yield of *iso*flavone (%)		Form (solvent)	M. p. and mixed m. p. unless otherwise stated
			A	B		
1	5 : 7-Dimethoxy-4′-nitro	2-Hydroxy-4 : 6-dimethoxyphenyl 4-nitrobenzyl[a]	15	25	Plates (C$_6$H$_6$)	220°[b]
2	7-Methoxy-4′-nitro	2-Hydroxy-4-methoxyphenyl 4-nitrobenzyl[a]	25	35	Needles (COMe$_2$)	245[c]
3	7-Benzyloxy-3′ : 4′-methylenedioxy (*O*-benzyl-ψ-baptigenin)	4-Benzyloxy-2-hydroxyphenyl 3 : 4-methylenedioxybenzyl[d]	25	—	Needles (EtOH–AcOH)	168[d]
4	*iso*Flavone	Benzyl 2-hydroxyphenyl[e]	30	—	Plates (EtOH)	132[f]
5	7-Methoxy	Benzyl 2-hydroxy-4-methoxyphenyl[g]	30	—	Plates (MeOH)	155—156[h]
6	7-Benzyloxy-4′-methoxy (*O*-benzylformononetin)	4-Benzyloxy-2-hydroxyphenyl 4-methoxybenzyl[d]	30	—	Plates (EtOH and EtOAc)	182[d]
7	7-Hydroxy	4-Benzoyloxy-2-hydroxyphenyl benzyl[i]	—	40	Plates (Aq. AcOH)	208—210[h]
8	,, ,,	Benzyl 2-hydroxy-4-*p*-nitrobenzoyloxyphenyl[j]	—	40	Plates (Aq. AcOH)	208—210[h]
9	7-Benzyloxy	Benzyl 4-benzyloxy-2-hydroxyphenyl[h]	45	—	Plates) (EtOH)	171[h]
10	4′-*Methoxy*-7-*toluene*-p-*sulphonyloxy*	2-Hydroxy-4-toluene-*p*-sulphonyloxyphenyl 4-methoxybenzyl[j]	—	50	Plates (C$_6$H$_6$)	168[k]
11	6-Methoxy	Benzyl 2-hydroxy-5-methoxyphenyl[l]	—	50	Prisms (COMe$_2$ and AcOH)	174[m]
12	7-Hydroxy-4′-methoxy (formononetin)	2-Hydroxy-4-*p*-nitrobenzoyloxyphenyl 4-methoxybenzyl[j]	—	50	Plates (Aq. AcOH)	253—254[d]
13	,, ,,	4-Benzoyloxy-2-hydroxyphenyl 4-methoxybenzyl[j]	—	60	Plates (Aq. AcOH)	253—254[d]
14	7-*Toluene*-p-*sulphonyloxy*	Benzyl 2-hydroxy-4-toluene-*p*-sulphonyloxyphenyl[j]	—	60	Needles	212—213[n]

[a] See Table 1. [b] M. p. and m. p. of corresponding 4′-amino*iso*flavone in agreement with ref. 2. [c] Ref. 3. [d] Mahal, Rai, and Venkataraman, *J.*, 1934, 1769. [e] Ref. *a* of Table 2. [f] Authentic sample supplied by Professor J. Algar (Algar and McKenna, *Proc. Roy. Irish Acad.*, 1944, **49**, *B*, 225). [g] Ref. 4(*a*). [h] Mahal, Rai, and Venkataraman, *J.*, 1934, 1120. [i] Baker, ref. 8. [j] See Table 2. [k] New compound (Found: C, 65·8; H, 4·5; S, 7·4. $C_{23}H_{18}O_6S$ requires C, 65·4; H, 4·3; S, 7·6%). [l] See above after Table 2. [m] M. p.s of 6-methoxy-, 6-hydroxy-, and 6-acetoxy-*iso*flavone in agreement with m. p.s reported by Ballio and Pocchiari.[9] [n] New compound (Found: C, 67·3; H, 4·1; S, 8·0. $C_{22}H_{16}O_5S$ requires C, 67·3; H, 4·1; S, 8·2%); the *iso*flavone in sulphuric acid solution exhibited a blue fluorescence in ultraviolet light.

Nos. 12 *and* 13. Dearoylation occurred in these experiments.

The following deoxybenzoins did not yield *iso*flavones when heated with formamide or formanilide: benzyl 2-hydroxy-6-methoxyphenyl ketone (Table 2); benzyl 2-hydroxy-4 : 6-dimethoxyphenyl ketone; [10] benzyl 2-hydroxy-3 : 4-dimethoxyphenyl ketone; [9] benzyl

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[10] Badcock, Cavill, Robertson, and Whalley, *J.*, 1950, 2961.

2-hydroxy-4 : 5-dimethoxyphenyl ketone (Table 1); benzyl 2-hydroxy-3 : 4 : 6-trimethoxyphenyl ketone.[9]

o-Hydroxyacetophenone when heated with benzamide in glycerol for 7 hr. at 250° gave flavone in 2% yield. No useful result was obtained when 2-hydroxy-4 : 6-dimethoxyphenyl 4-nitrobenzyl ketone (Table 1) and benzanilide were heated together at 250° for 30 min.

*2-Hydroxy-4-toluene-*p*-sulphonyloxyacetophenone*, which was obtained from resacetophenone by treatment with toluene-*p*-sulphonyl chloride and pyridine, separated from aqueous acetic acid in needles, m. p. 80—81° (Found: C, 58·8; H, 4·8; S, 10·4. $C_{15}H_{14}O_5S$ requires C, 58·7; H, 4·6; S, 10·4%). It did not give any identifiable compound when heated with formanilide.

The following 2-acyloxydeoxybenzoins (see Table 2) did not yield an *iso*flavone when heated: 2 : 4-dibenzoyloxyphenyl 4-nitrobenzyl ketone; benzyl 2 : 4 : 6-triacetoxyphenyl ketone; benzyl 2 : 4 : 6-tribenzoyloxyphenyl ketone; 4-nitrobenzyl 2 : 4 : 6-tribenzoyloxyphenyl ketone.

A mixture of 2-benzoyloxyphenyl benzyl ketone (Table 2) (0·7 g.) was heated in glycerol (10 ml.) at 250° for 30 min. and the product was poured into water (100 ml.). 2-Phenyl*iso*flavone separated from dilute acetic acid in needles (0·4 g.), m. p. and mixed m. p.[11] 150°.

TABLE 4. *2-Substituted* iso*flavones prepared by heating 2-acyloxydeoxybenzoins for 30 min. at 250°.*

*iso*Flavone	Ketone from which prepared	Yield of *iso*flavone (%)	Form (solvent)	M. p. and mixed m. p. unless otherwise stated
7-Benzoyloxy-2-phenyl	Benzyl 2 : 4-dibenzoyloxyphenyl [a]	8	Prisms (EtOH)	185—186° [b]
7-Acetoxy-2-methyl	Benzyl 2 : 4-diacetoxyphenyl [a]	40	Prisms (C_6H_6)	162 [c]
5 : 7-Diacetoxy-2-methyl-4′-nitro	4-Nitrobenzyl 2 : 4 : 6-triacetoxyphenyl [d]	50	Prisms (EtOH–$COMe_2$)	190 [e]
7-Acetoxy-2-methyl-4′-nitro	2 : 4-Diacetoxyphenyl 4-nitrobenzyl [d]	60	Needles ($COMe_2$)	245

[a] See Table 1. [b] Gupta and Seshadri.[8] [c] Baker and Robinson, *J.*, 1925, **127**, 1981. [d] See Table 2. [e] Dutta and Bose [3] give m. p. 190°. The diacetoxy*iso*flavone when deacetylated by treatment with sulphuric acid for 1 hr. at 0° gave 5 : 7-dihydroxy-2-methyl-4′-nitro*iso*flavone, m. p. and mixed m. p.[3] 260°. [f] Ref. 3.

Benzyl 2-cinnamoyloxyphenyl ketone (Table 2) gave no useful result when heated in glycerol.

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[11] Chadha, Mahal, and Venkataraman, *J.*, 1933, 1459.