536. *Chromones and Flavones. Part I. Iodination of 5- and 7-Hydroxy-2-methylchromone.*

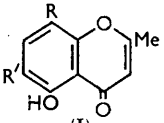
By M. V. SHAH and SURESH SETHNA.

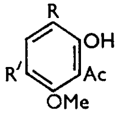
Iodination of 5- or 7-hydroxy-2-methylchromone gave the 8-iodo- or 6 : 8-di-iodo-derivatives.

OFFE[1] iodinated 2-methylchromone and obtained 2-iodomethylchromone. No other work on the iodination of chromones has been reported. In the present paper iodination of 5- and 7-hydroxy-2-methylchromone with iodine and iodic acid or, less well, with iodine and ammonia and with iodine monochloride is described.

5-Hydroxy-2-methylchromone (Ia) on iodination with the theoretical amount of iodine and iodic acid ($5RH + 4I + HIO_3 \longrightarrow 5RI + 3H_2O$) gave the 8-iodo-derivative (Ib). On nitration it gave a compound identical with the iodination product of 5-hydroxy-2-methyl-6-nitrochromone; its methyl ether, on hydrolysis, gave an iodo-ketone different from that obtained by iodination of 2-hydroxy-6-methoxyacetophenone, but the derived methyl ethers were identical. The iodo-ketone obtained in hydrolysis therefore has structure (IIb) and that one obtained by direct iodination has structure (IId).

With twice the above amounts of reagents 5-hydroxy-2-methylchromone gave the 6 : 8-di-iodo-derivative (Ic). Its methyl ether on hydrolysis gave the 3 : 5-di-iodo-ketone (IIc) which was identical with the iodination product of 2-hydroxy-6-methoxyacetophenone.


(I)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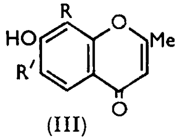
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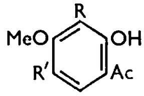
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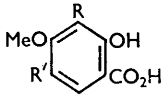
(V)

	a	b	c	d	e
R	H	I	I	H	I
R′	H	H	I	I	OH

7-Hydroxy-2-methylchromone (IIIa), as above, gave first the 8-iodo-derivative (IIIb). Its methyl ether on hydrolysis gave an iodo-ketone and an iodo-acid, both of which underwent Elbs persulphate oxidation smoothly, suggesting that the *para*-position to the hydroxyl group must be free.[2] The hydrolysis products therefore have the 3-iodo-structures (IVb and Vb respectively), and the oxidation products are (IVe) and (Ve) respectively. The same iodo-ketone (IVb) was obtained on direct iodination of peonol.

With three times amounts of iodine and iodic acid 7-hydroxy-2-methylchromone gave the 6 : 8-di-iodo-derivative (III*c*). Its methyl ether on hydrolysis gave a di-iodo-acid, and a di-iodo-ketone identical with that obtained on the iodination of peonol. The di-iodo-acid, on Elbs persulphate oxidation, lost one iodine atom and gave the acid (Ve) obtained as above. The methyl ether of the di-iodo-acid was identical with the product obtained on methylation of the iodination product of β-resorcylic acid.

The di-iodochromone (IIIc), on prolonged heating in acetic acid, lost one iodine atom and gave a mono-iodochromone which must be the 6-iodo-derivative (IIId) as it was different from (IIIb). Its methyl ether on hydrolysis gave a monoiodo-ketone (IVd) and a monoiodo-acid (Vd) different from (IVb) and (Vb). The same iodo-ketone (IVd) was obtained on iodination of peonol with iodine and ammonia. The iodo-ketone, on Elbs persulphate oxidation, lost iodine and gave 2 : 5-dihydroxy-4-methoxyacetophenone.[3]

With iodine and ammonia or iodine monochloride as iodinating agents similar results

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[1] Offe, *Ber.*, 1938, **71**, 1837.
[2] Baker and Brown, *J.*, 1948, 2303.
[3] Bargellini and Aureli, *Atti Accad. Lincei*, 1911, **20**, 118.

were obtained except that the di-iodo-compound from 7-hydroxy-2-methylchromone could not be obtained.

No tri-iodo-derivative could be obtained from either chromone, even with excess of the iodinating agents.

The methyl ethers of the chromones (Ia) and (IIIa) could not be iodinated. Iodine monochloride gave chloro-compounds.

Iodination of resacetophenone was also examined. Segalle,[4] using potassium iodate and potassium iodide in acetic acid, obtained a monoiodo-compound to which no definite structure was assigned. This must be the 3-iodo-derivative as its dimethyl ether was identical with the methyl ether of (IVb). Use of ammonia and iodine, however, gave the 5-iodo-derivative, whose dimethyl ether was identical with the methyl ether of (IVd) described above. Use of double the quantity of the iodinating agent gave the 3 : 5-di-iodo-ketone whose dimethyl ether was identical with the methyl ether of (IVc).

EXPERIMENTAL

Iodinations (*see Table* 1).—(A) *With iodine and iodic acid.* The substance (0·01 mole) was dissolved in the minimum quantity of warm alcohol, and the required quantities of iodine and iodic acid (in water) were added. The mixture was stirred for 2 hr. at room temperature and the iodo-derivative, which separated from the solution or on dilution with water, was crystallised from acetic acid.

TABLE 1.

No.	Compound	Method	Product	M. p.[a]	Yield (%)[b]	Formula	Found I (%)	Reqd. I (%)
1	5-Hydroxy-2-methylchromone	A, B, C	8-Iodo-	171°	49	$C_{10}H_7O_3I$	42·4	42·1
		A, B, C	6 : 8-Di-iodo-	238	52	$C_{10}H_6O_3I_2$	59·7	59·3
2	7-Hydroxy-2-methylchromone	A, B, C	8-Iodo-	213	47	$C_{10}H_7O_3I$	42·5[c]	42·1
		A	6 : 8-Di-iodo-	212	58	$C_{10}H_6O_3I_2$	59·8	59·3
3	2-Hydroxy-6-methoxyacetophenone	A, B, C	5-Iodo-	116	68	$C_9H_9O_3I$	43·7	43·5
		A, B, C	3 : 5-Di-iodo-	111	76	$C_9H_8O_3I_2$	60·4	60·8
4	2-Hydroxy-4-methoxyacetophenone	A	3-Iodo-	152	15	$C_9H_9O_3I$	43·8	43·5
		B	5-Iodo-	161	13	$C_9H_9O_3I$	42·9	43·5
		A, B, C	3 : 5-Di-iodo-	98—99	8	$C_9H_8O_3I_2$	61·2	60·8
5	2 : 4-Dihydroxyacetophenone	A	3-Iodo-	164	82	$C_8H_7O_3I$	45·5	45·7
		B	5-Iodo-	184	15	$C_8H_7O_3I$	45·8	45·7
		A, B, C	3 : 5-Di-iodo-	180	86	$C_8H_6O_3I_2$	63·0	62·9
6	2 : 4-Dihydroxybenzoic acid	A, B, C	3 : 5-Di-iodo-	218[d]	70	$C_7H_4O_4I_2$	62·9	62·8

Completely methylated products of the iodo-compound

No.	M. p.	Formula	Found (%) C	Found (%) H	Found (%) I	Required (%) C	Required (%) H	Required (%) I
1	92—95°	$C_{11}H_9O_3I$	41·7	2·8	39·8	41·8	2·8	40·2
	207—208	$C_{11}H_8O_3I_2$	30·0	1·9	57·4	29·9	1·8	57·5
2	191—192	$C_{11}H_9O_3I$	41·9	2·8	40·8	41·8	2·8	40·2
	162	$C_{11}H_8O_3I_2$	30·2	1·7	57·7	29·9	1·8	57·5
3	71—72	$C_{10}H_{11}O_3I$	38·6	3·7	41·3	39·2	3·6	41·5
	—	—	—	—	—	—	—	—
4	—	—	—	—	—	—	—	—
	—	—	—	—	—	—	—	—
	—	—	—	—	—	—	—	—
5	101—102	$C_{10}H_{11}O_3I$	39·5	3·6	41·8	39·2	3·6	41·5
	145	$C_{10}H_{11}O_3I$	39·1	3·8	41·5	39·2	3·6	41·5
	59—60	$C_{10}H_{10}O_3I_2$	27·7	2·4	59·2	27·8	2·3	58·8
6	183—184	$C_9H_8O_4I_2$	25·0	1·9	58·6	24·9	1·8	58·6

[a] Some of the hydroxy-iodo-derivatives decompose 20—30° below their m. p.s and melt finally at the above temperatures. [b] Yields are those obtained by method A. [c] After drying *in vacuo* at 110° for 3 hr. [d] Nicolet and Sampey (*J. Amer. Chem. Soc.*, 1927, **49**, 1796) report m. p. 193—196° (decomp.).

(B) *With iodine and ammonia.* To the substance (0·01 mole), dissolved in 22% aqueous ammonia (40 ml.), a solution of iodine in potassium iodide in required quantity was added with stirring at room temperature during ½ hr. The mixture was stirred for a further 2 hr. then

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[4] Segalle, *Monatsh.*, 1896, **17**, 314.

poured into excess of dilute ice-cold sulphuric acid. The precipitate was recrystallised from acetic acid. In the iodination of 5-hydroxy-2-methylchromone a mixture of dioxan and ammonia was used. In the case of 2 : 4-dihydroxyacetophenone the iodine solution was added within ½ hr. and the mixture immediately acidified.

(C) *With iodine monochloride.* To the substance (0·01 mole), dissolved in the minimum quantity of acetic acid or alcohol, hydrochloric acid (*d* 1·11; 15 ml.) was added. The mixture was then added to the requisite amount of iodine monochloride and kept for 24 hr. at 50°. The mixture was worked up as usual.

Preparation of Methyl Ethers.—The iodo-derivatives were methylated by refluxing their acetone solutions with dimethyl sulphate in presence of anhydrous potassium carbonate.

Hydrolysis of Iodochromones.—Hydrolysis by boiling 10% sodium hydroxide solution gave the results shown in Table 2.

TABLE 2. *Hydrolysis products of the iodochromones.*

2-Methyl-chromone	Products [a]	M. p.	Formula	Found (%)			Required (%)		
				C	H	I	C	H	I
8-Iodo-5-methoxy	2-Hydroxy-3-iodo-6-methoxyacetophenone	57°	$C_9H_9O_3I$	36·9	3·1	43·4	37·0	3·1	43·5
6 : 8-Di-iodo-5-methoxy	2-Hydroxy-3 : 5-di-iodo-6-methoxyacetophenone	—	—	—	—	—	—	—	—
8-Iodo-7-methoxy	(1) 2-Hydroxy-3-iodo-4-methoxyacetophenone	—	—	—	—	—	—	—	—
	(2) 2-Hydroxy-3-iodo-4-methoxybenzoic acid	218 [b]	$C_8H_7O_4I$	33·0	2·5	43·5	32·6	2·4	43·2
6-Iodo-7-methoxy	(1) 2-Hydroxy-5-iodo-4-methoxyacetophenone	—	—	—	—	—	—	—	—
	(2) 2-Hydroxy-5-iodo-4-methoxybenzoic acid	245 [b]	$C_8H_7O_4I$	32·9	2·3	42·9	32·6	2·4	43·2
6 : 8-Di-iodo-7-methoxy	(1) 2-Hydroxy-3 : 5-di-iodo-4-methoxyacetophenone [b]	—	—	—	—	—	—	—	—
	(2) 2-Hydroxy-3 : 5-di-iodo-4-methoxybenzoic acid	217 [b]	$C_8H_6O_4I_2$	22·6	1·2	61·1	22·9	1·4	60·5

[a] For acetophenones see Table 1. [b] With effervescence.

5-*Hydroxy*-8-*iodo*-2-*methyl*-6-*nitrochromone*.—The iodo-chromone (Ib) (1 g.) was dissolved in glacial acetic acid (40 ml.) and cooled below 10°. Nitric acid (*d* 1·42; 10 ml.) was added dropwise with stirring. The mixture was added to ice after 24 hr. and the precipitate crystallised from acetic acid in thick yellowish needles, m. p. 215—216° (decomp.) (Found: N, 4·4; I, 36·3. $C_{10}H_6O_5NI$ requires N, 4·0; I, 36·6%). The same *product* was obtained by iodination of 5-hydroxy-2-methyl-6-nitrochromone [5] with iodine and iodic acid.

2 : 5-*Dihydroxy*-3-*iodo*-4-*methoxyacetophenone* (IVe).—The iodo-ketone (IVb) (1 g.) was dissolved in 10% aqueous sodium hydroxide (40 ml.) and oxidised with potassium persulphate (0·92 g. in 20 ml. of water) (cf. Baker and Brown [2]). The *product* crystallised from acetic acid in yellow needles (0·22 g.), m. p. 174° (decomp.) (Found: C, 35·0; H, 2·9; I, 41·1. $C_9H_9O_4I$ requires C, 35·0; H, 2·9; I, 41·2%).

2 : 5-*Dihydroxy*-3-*iodo*-4-*methoxybenzoic Acid* (Ve).—The iodo-acid (Vb) (1·5 g.) was oxidised as described before. The *product* crystallised from water in yellowish needles (0·3 g.), m. p. 212° (effervescence) (Found: C, 31·3; H, 2·5; I, 41·7. $C_8H_7O_5I$ requires C, 31·0; H, 2·3; I, 41·0%). The same product was obtained from the acid (Vc).

7-*Hydroxy*-6-*iodo*-2-*methylchromone* (IIId).—The di-iodo-chromone (IIIc) was refluxed with acetic acid for 4 hr. The solution became deep red. After cooling, it was added to ice-cold sodium hydrogen sulphite solution. The *product* crystallised in colourless needles (from acetic acid), m. p. 258—260° (decomp.) (Found: I, 42·5. $C_{10}H_7O_3I$ requires I, 42·1%). The *methyl ether* crystallised from alcohol in needles, m. p. 238° (Found: C, 41·4; H, 2·9; I, 40·7. $C_{11}H_9O_3I$ requires C, 41·8; H, 2·8; I, 40·2%).

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ORGANIC CHEMISTRY LABORATORIES, MAHARAJA SAYAJIRAO UNIVERSITY OF BARODA,
BARODA, INDIA.
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[5] Naik and Thakor, *Proc. Ind. Acad. Sci.*, 1953, *A*, **37**, 774.