[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, M. S. UNIVERSITY]

Iodination of 7-Hydroxy-, and 5-Hydroxy-4-methylcoumarin and Their Methyl Ethers

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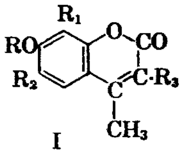
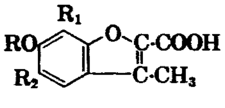
Received April 29, 1958

The iodination of 7-hydroxy- and 5-hydroxy-4-methylcoumarin and their methyl ethers using different molecular proportions of iodine monochloride, iodine and iodic acid, and iodine and ammonia has been studied. The results obtained are given in Table I.

In their studies on the bromination of coumarin derivatives Sethna and co-workers[1,2] found that in the case of 7-hydroxycoumarin derivatives and their methyl ethers the first bromine atom in all cases enters the pyron ring in the 3-position and the subsequent bromine atoms enter the benzene ring. In the 5-hydroxycoumarin derivatives, however, the first bromine atom was found to enter the benzene ring in the 8-position. It was thought of interest to see whether the same pattern would follow in the iodination of these coumarin derivatives.

7-Hydroxy-4-methylcoumarin(I, R,R_1,R_2,R_3 = H) on iodination with one mole of iodine monochloride gave a monoiodo derivative. The methyl ether of this did not give a coumarilic acid derivative on heating with alkali which indicated that the iodine atom had not entered the 3-position. The methyl ether when subjected to Elbs persulfate oxidation gave a good yield of the oxidation product thus indicating that the 6-position must be free, for the Elbs persulfate oxidation of 6-substituted coumarins is very difficult.[3] 7-Hydroxy-8-iodo-4-methylcoumarin (I, R,R_2,R_3 = H; R_1=I) structure has therefore been assigned to the iodination product and 6-hydroxy-7-methoxy-8-iodo-4-methylcoumarin (I, $R=CH_3$; R_1=I; R_2=OH; R_3=H) structure to the Elbs persulfate oxidation product. The mother liquor from the crystallization of the 8-iodo derivative left a mixture from which no other pure product could be isolated. 7-Methoxy-4-methylcoumarin (I, $R=CH_3$; R_1,R_2=H) on iodination with one mole of iodine monochloride gave a monoiodo derivative which was different from the methyl ether of 7-hydroxy-8-iodo-4-methylcoumarin. On hydrolysis this product gave a coumarilic acid derivative which was found, on direct comparison to be the same as 6-methoxy-3-methylcoumarilic acid (II, R,R_1,R_2 = H) obtained on hydrolysis of 7-methoxy-3-bromo-4-methylcoumarin.[4] The monoiodo product is therefore 7-methoxy-3-iodo-4-methylcoumarin (I, $R=CH_3$; R_1,R_2=H; R_3=I).


I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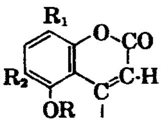
III

On iodination with two moles of iodine monochloride I (R,R_1,R_2,R_3=H) did not give a pure product. However, on iodination with 4 moles of iodine monochloride it gave two diiodo derivatives (A) m.p. 265° and (B) m.p. 248–250°. The methyl ether of (A) gave a monoiodo coumarilic acid derivative indicating that one of the two iodine atoms had entered the 3-position. Further, this methyl ether was found to be the same as the product obtained on further iodination of 7-methoxy-8-iodo-4-methylcoumarin with iodine monochloride. (A) is therefore 7-hydroxy-3,8-diiodo-4-methylcoumarin (I, R,R_2=H; R_1,R_3=I). The methyl ether of (B), also obtained by the iodination of 7-methoxy-4-methylcoumarin with excess of iodine monochloride (6 moles), also gave a monoiodo coumarilic acid derivative. It has therefore the alternate structure: 7-hydroxy-3,6-diiodo-4-methylcoumarin (I, R,R_1=H; R_2,R_3=I).

On iodination with excess of iodine monochloride I (R,R_1,R_2,R_3=H) gave a triiodo derivative, the methyl ether of which on hydrolysis gave a diiodo coumarilic acid derivative which must be 6-methoxy-5,7-diiodo-3-methylcoumarilic acid (II, $R=CH_3$; R_1,R_2=I). The triiodocoumarin is therefore 7-hydroxy-3,6,8-triiodo-4-methylcoumarin (I, R=H; R_1,R_2,R_3=I). I ($R=CH_3$; R_1,R_2,R_3=H) did not give any triiodo derivative even on iodination with a large excess of iodine monochloride.

With one mole of iodine monochloride 5-hydroxy-4-methylcoumarin (III, R,R_1,R_2=H) gave a monoiodo derivative. This on methylation gave a product which was the same as the product obtained on iodination of 5-methoxy-4-methylcou-

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(1) V. J. Dalvi and S. M. Sethna, *J. Indian Chem. Soc.*, **26**, 359 (1949).

(2) S. S. Lele, R. J. Parikh, and S. M. Sethna, *J. Indian Chem. Soc.*, **30**, 610 (1953).

(3) V. J. Dalvi, R. B. Desai, and S. M. Sethna, *J. Indian Chem. Soc.*, **28**, 366 (1951).

(4) D. B. Limaye and N. V. Bhide, *Rasayanam*, **1**, 136 (1938) [*Chem. Abstr.*, **33**, 1699 (1939).]

marin (III, $R=CH_3$; $R_1,R_2=H$) with one mole of iodine monochloride. It did not give any coumarilic acid derivative on heating with alkali. Further, on Elbs persulfate oxidation it gave a product in good yield indicating that the 6-position was free. The products obtained on iodination are therefore the 8-iodo-derivatives: (III, $R,R_2=H$; $R_1=I$ and III, $R=CH_3$; $R_1=I$; $R_2=H$ respectively). On iodination with 4 moles of iodine monochloride III ($R=CH_3$; $R_1,R_2=H$) gave only the above monoiodo derivative. However, with a large excess of iodine monochloride (16 moles) it gave a diiodo derivative, the methyl ether of which did not give any coumarilic acid derivative. The diiodo derivative is therefore 5-hydroxy-6,8-diiodo-4-methylcoumarin (III, $R=H$; $R_1,R_2=I$). III($R,R_1,R_2=H$) did not give any triiodo derivative even with a large excess of iodine monochloride. III($R=CH_3$; $R_1,R_2=H$) did not give even the diiodo derivative with large excess of iodine monochloride.

Iodination was also carried out using iodine in the presence of iodic acid. It was assumed that the reaction took place according to the following equation:

$$5RH + 4I + HIO_3 = 5\ RI + 3H_2O$$

I ($R,R_1,R_2,R_3 = H$) on iodination using the above molecular proportions gave a mixture of iodo derivatives from which only the 8-iodo derivative (I, $R,R_2,R_3 = H$; $R_1 = I$) could be easily isolated. When the proportions of iodine and iodic acid were doubled the triiodo derivative (I, $R = H$; $R_1, R_2,R_3 = I$) was obtained. The diiodo derivative could not be isolated. I ($R=CH_3$; $R_1,R_2,R_3=H$) could not be iodinated by this method under similar conditions. III($R,R_1,R_2=H$) on iodination using the molecular proportions given in the above equation gave 5-hydroxy-6,8-diiodo-4-methylcoumarin (III, $R=H$; $R_1,R_2=I$). The moniodo derivative could not be isolated. On iodination with double the quantity of iodine and iodic acid only the 6,8-diiodo product was obtained. The diiodo product was found to be unstable and on prolonged stirring of the reaction mixture iodine was liberated. Iodine was also liberated on crystallization from hot acetic acid. On refluxing the diiodo derivative with 10% sodium hydroxide the iodine atoms were removed and III($R,R_1,R_2=H$) was obtained. III ($R=CH_3$; $R_1,R_2=H$) could not be iodinated at all under similar conditions.

Iodination of the above coumarins with iodine in potassium iodide solution in the presence of ammonia has also been studied. I ($R,R_1,R_2,R_3=H$) with one mole of iodine gave the 8-iodo-derivative I($R,R_2,R_3=H$); $R_1=I$) described above. With two moles however it gave a diiodo derivative the methyl ether of which remained unchanged on boiling with alkali. Further iodination of this compound using iodine and iodic acid gave the 3,6,8-triiodocoumarin (I, $R=H$; $R_1,R_2,R_3=I$). The diiodo derivative is therefore 7-hydroxy-6,8-diiodo-4-methylcoumarin(I, $R,R_3=H$; $R_1,R_2=I$) not obtained by the above two methods. On refluxing this diiodo coumarin with 10% sodium hydroxide the pyrone ring opened up and an acid was obtained to which the β-methyl-2,4-dihydroxy-3,5-diiodocinnamic acid structure has been assigned. I($R=CH_3$; $R_1,R_2,R_3=H$) could not be iodinated at all by this method.

III ($R,R_1,R_2=H$) on iodination with one mole of iodine by this method gave a mixture of a monoiodo derivative and a diiodo derivative. The monoiodo derivative was found to be different from III ($R,R_2=H$; $R_1=I$) described above and its methyl ether did not give any coumarilic acid derivative on boiling with alkali nor did it undergo Elbs persulfate oxidation. The monoiodo derivative was therefore 5-hydroxy-6-iodo-4-methylcoumarin (III, $R,R_1=H$; $R_2=I$). The diiodo derivative was found, on direct comparison, to be the 6,8-diiodo derivative (III, $R=H$; $R_1,R_2=I$). This was obtained in excellent yield by iodination with two moles of iodine. No triiodo derivative could be prepared by this method. III ($R=CH_3$; $R_1,R_2=H$) could not be iodinated at all by this method.

EXPERIMENTAL

General iodination procedures. The molecular proportions of the starting material and iodine are given in Table I. (A) *With iodine monochloride.* The coumarin derivative (2 g.) was dissolved in a minimum quantity of glacial acetic acid or alcohol and hydrochloric acid (*d* 1.11; 15 ml.) was added. The mixture was then added to a weighed amount of iodine monochloride. The reaction mixture was then kept in an oven at 50° for 24 hr. It was shaken occasionally. The separated iodo derivative was then filtered and washed with the same solvent and then crystallized from acetic acid. In the case of 7-hydroxy-4-methylcoumarin the solvent used was acetic acid and in the case of 5-hydroxy-4-methylcoumarin it was alcohol. In the case of methoxycoumarin derivatives acetic acid was used as solvent. It was found in the case of methoxycoumarins that the iodination products were not readily obtained if hydrochloric acid was used and hence it was not used.

(B) *With iodine and iodic acid.* The coumarin derivative (2 g.) was dissolved in alcohol by warming and the required quantity of iodine crystals were added. To the warm dark colored solution obtained the required amount of iodic acid dissolved in water was added with stirring. The reaction mixture was stirred for 2 hr. further and the iodo derivative which separated was filtered and washed with alcohol. It was crystallized from acetic acid.

(C) *With ammonia and iodine.* The coumarin derivative (2 g.) was dissolved in ammonium hydroxide (20%; 50 ml.) and the required amount of iodine dissolved in potassium iodide solution was added drop-wise with stirring at room temperature during 0.5 hr. The reaction mixture was stirred for a further 1–2 hr. If any product separated it was filtered and washed with ammonia. The filtrate was then poured into excess of dilute ice cold sulfuric acid. The precipitate obtained was washed with water and crystallized from acetic acid. The monoiodo derivatives remained in solution in ammonia while the diiodo derivatives separated out as ammonium salts which on crystallization from acetic acid gave the free iodo derivatives.

Preparation of the methyl ethers. The iodo derivatives of the hydroxycoumarins were methylated by refluxing their

TABLE I

Coumarin	Iodinating Agent and Proportions[a]	Product Obtained[b]	M.P., °C.[c]	Yield, %	Formula	Analysis, Iodine %	
						Found	Required
7-Hydroxy-4-methyl- (I, R, R_1, R_2, R_3 = H)	A (1:1)	8-Iodo (I, R, R_2, R_3 = H; R_1 = I)	268	25	$C_{10}H_7O_3I$	41.91	42.06
	B (5:2:1)			40			
	C (1:1)			82			
	A (1:4)	3,8-Diiodo- (I, R, R_2 = H; R_1, R_3 = I)	264	22	$C_{10}H_6O_3I_2$	58.75	59.34
		3,6-Diiodo- (I, R, R_1 = H; R_2, R_3 = I)	249	40	$C_{10}H_6O_3I_2$	59.12	59.34
	A (1:16)	3,6,8-Triiodo- (I, R = H; R_1, R_2, R_3 = I)	254	36	$C_{10}H_5O_3I_3$	68.69	68.77
	B (5:4:2)			59			
	C (1:2)	6,8-Diiodo- (I, R, R_3 = H; R_1, R_2 = I)	230	66	$C_{10}H_6O_3I_2$	59.87	59.34
7-Methoxy-4-methyl- (I, R = CH_3; R_1, R_2, R_3 = H)	A (1:1)	3-Iodo- (I, R = CH_3; R_1, R_2 = H; R_3 = I)	162	42	$C_{11}H_9O_3I$	39.85	40.19
	A (1:6)	3,6-Diiodo- (I, R = CH_3; R_1 = H; R_2, R_3 = I)	248	75	$C_{11}H_8O_3I_2$	57.34	57.46
5-Hydroxy-4-methyl- (III, R, R_1, R_2 = H)	A (1:1)	8-Iodo- (III, R, R_2 = H; R_1 = I)	242	38	$C_{10}H_7O_3I$	42.41	42.06
	A (1:8)	6,8-Diiodo- (III, R = H; R_1, R_2 = I)	230	42[d]	$C_{10}H_6O_3I_2$	59.28	59.34
	B (5:2:1)			68[d]			
	C (1:2)			73[d]			
	C (1:1)	6-Iodo- (III, R, R_1 = H; R_2 = I)	175	30	$C_{10}H_7O_3I$	41.97	42.06
5-Methoxy-4-methyl- (III, R = CH_3; R_1, R_2 = H)	A (1:1)	8-Iodo- (III, R = CH_3; R_2 = H; R_1 = I)	254	42	$C_{11}H_9O_3I$	39.98	40.19

A = Iodine monochloride; B = Iodine + Iodic acid; C = NH_4OH + Iodine.

[a] The figures in the brackets indicate molecular proportions. A (substance:iodine monochloride), B (substance:iodine:iodic acid), C (substance:iodine). [b] All the iodo derivatives are crystallized from glacial acetic acid. [c] All melting points are uncorrected. Hydroxy iodo derivatives start decomposing about 30–40° below their melting points and finally melt at the above temperatures. Methoxy iodo derivatives are sharp melting. [d] 5-Hydroxy-6,8-diiodo derivative is unstable and starts decomposing on boiling in acetic acid. The yields given are of the crude product.

TABLE II

METHYL ETHERS OF THE HYDROXY IODOCOUMARINS MENTIONED IN TABLE I

Coumarin	M.P., °C.	Formula	C		H		I	
			Found	Required	Found	Required	Found	Required
7-Methoxy-8-iodo-4-methyl- (I, R = CH_3; R_1 = I; R_2, R_3 = H)	199	$C_{11}H_9O_3I$	41.85	41.77	2.69	2.84	40.46	40.19
6,7-Dimethoxy-8-iodo-4-methyl- (I, R = CH_3; R_1 = I; R_2 = OCH_3; R_3 = H)	218	$C_{12}H_{11}O_4I$	41.71	41.62	2.92	3.18	36.91	36.70
7-Methoxy-3,8-diiodo-4-methyl- (I, R = CH_3; R_2 = H; R_1, R_3 = I)	262	$C_{11}H_8O_3I_2$	29.52	29.86	2.16	1.81	58.03	57.46
7-Methoxy-3,6-diiodo-4-methyl- (I, R = CH_3; R_1 = H; R_2, R_3 = I)	248	$C_{11}H_8O_3I_2$	29.82	29.86	2.30	1.81	57.34	57.46
7-Methoxy-3,6,8-triiodo-4-methyl- (I, R = CH_3; R_1, R_2, R_3 = I)	217	$C_{11}H_7O_3I_3$	23.08	23.25	1.02	1.23	67.48	67.08
7-Methoxy-6,8-diiodo-4-methyl- (I, R = CH_3; R_1, R_2 = I; R_3 = H)	212	$C_{11}H_8O_3I_2$	29.92	29.86	1.89	1.81	57.18	57.46
5-Methoxy-8-iodo-4-methyl- (III, R = CH_3; R_1 = I; R_2 = H)	254	$C_{11}H_9O_3I$	41.80	41.77	3.24	2.84	39.98	40.19
5-Methoxy-6,8-diiodo-4-methyl- (III, R = CH_3; R_1, R_2 = I)	224	$C_{11}H_8O_3I_2$	30.20	29.86	1.59	1.81	57.31	57.46
5-Methoxy-6-iodo-4-methyl- (III, R = CH_3; R_1 = H; R_2 = I)	155	$C_{11}H_9O_3I$	41.91	41.77	2.91	2.84	39.81	40.19

acetone solutions with dimethyl sulfate in the presence of anhydrous potassium carbonate.

6-Hydroxy-7-methoxy-8-iodo-4-methylcoumarin (I, R = CH_3; R_1 = I; R_2 = OH; R_3 = H). 7-Methoxy-8-iodo-4-methylcoumarin (1 g.) was dissolved in sodium hydroxide solution (10%, 40 ml.) by warming on a steam bath. It was then oxidized with potassium persulfate (0.9 g. in 40 ml. water) according to the procedure described by Parikh and Sethna.[5] The product obtained crystallized from acetic acid in plates, m.p. 234°. It dissolved in sodium hydroxide solution to give a deep yellow solution.

Anal. Calcd. for $C_{11}H_9O_4I$: C, 39.77; H, 2.70; I, 38.30. Found: C, 40.22; H, 2.68; I, 38.03.

6-Methoxy-3-methylcoumarilic acid (II, R = CH_3; R_1, R_2 = H). 7-Methoxy-3-iodo-4-methylcoumarin (0.5 g.) was refluxed with alcoholic potassium hydroxide (10%, 30 ml.) for 2 hr. on a steam bath. The product obtained, on acidification of the diluted solution, was purified through sodium bicarbonate solution. It crystallized from dilute alcohol in needles, m.p. 186° (dec.). Mixed melting point with the compound prepared by hydrolyzing 7-methoxy-3-bromo-4-methylcoumarin[4] was not lowered.

6-Methoxy-7-iodo-3-methylcoumarilic acid (II, R = CH_3; R_1 = I; R_2 = H). 7-Methoxy-3,8-diiodo-4-methylcoumarin (0.5 g.) was refluxed with alcoholic potassium hydroxide (10%, 40 ml.). The product obtained on working up the reaction mixture as above crystallized from glacial acetic acid in needles, m.p. 222° (dec.). It gave a violet color with sulfuric acid.

Anal. Calcd. for $C_{11}H_9O_4I$: C, 39.70; H, 2.70; I, 38.30. Found: C, 40.12; H, 3.12; I, 38.31.

The methyl ester was prepared by refluxing 6-methoxy-7-iodo-3-methylcoumarilic acid (0.3 g.) in methyl alcohol (25 ml.) with concentrated sulfuric acid (5 ml.) on a steam bath for 8 hr. It crystallized from dilute alcohol in colorless needles, m.p. 180°.

Anal. Calcd. for $C_{12}H_{11}O_4I$: C, 41.62; H, 3.18; I, 36.70. Found: C, 41.72; H, 3.52; I, 36.83.

6-Methoxy-5-iodo-3-methylcoumarilic acid (II, R = CH_3; R_1 = H; R_2 = I) was obtained from 7-methoxy-3,6-diiodo-4-methylcoumarin by refluxing with alcoholic potassium hydroxide (10%, 40 ml.) as above. It crystallized from dilute acetic acid in colorless needles, m.p. 218° (dec.). It gave a violet color with sulfuric acid.

Anal. Calcd. for $C_{11}H_9O_4I$: C, 39.77; H, 2.70; I, 38.30. Found: C, 39.81; H, 2.75; I, 38.01.

The methyl ester was prepared as described before. It crystallized from petroleum ether (60–80°) in colorless needles, m.p. 160°.

Anal. Calcd. for $C_{12}H_{11}O_4I$: C, 41.62; H, 3.18; I, 36.70. Found: C, 41.99; H, 2.72; I, 36.81.

6-Methoxy-5,7-diiodo-3-methylcoumarilic acid (II, R = CH_3; R_1, R_2 = I) was prepared from 7-methoxy-3,6,8-triiodo-4-methylcoumarin (1 g.) by refluxing with alcoholic potassium hydroxide (10% in 50% alcohol) as above. It crystallized from glacial acetic acid in colorless needles, m.p. 270° (dec.).

Anal. Calcd. for $C_{11}H_8O_4I_2$: C, 28.82; H, 1.74; I, 55.46. Found: C, 28.76; H, 1.84; I, 55.91.

The methyl ester was prepared as described before. It crystallized from dilute alcohol in colorless needles, m.p. 160°.

Anal. Calcd. for $C_{12}H_{10}O_4I_2$: C, 30.52; H, 2.12; I, 53.81. Found: C, 30.20; H, 2.61; I, 53.79.

6-Hydroxy-5-methoxy-8-iodo-4-methylcoumarin (III, R = CH_3; R_1 = I; R_2 = OH). 5-Methoxy-8-iodo-4-methylcoumarin (1 g.) was dissolved in sodium hydroxide (10%, 40 ml.) by warming on a steam bath and by adding a little pyridine. It was then oxidized with potassium persulfate (0.9 g. in 40 ml. water) as described before. The product obtained crystallized from acetic acid in needles, m.p. 270°. It dissolves in sodium hydroxide solution to give a deep yellow solution.

Anal. Calcd. for $C_{11}H_9O_4I$: C, 39.77; H, 2.70; I, 38.30. Found: C, 39.81; H, 2.29; I, 38.49.

β-Methyl-2,4-dihydroxy-3,5-diiodocinnamic acid was prepared from 7-hydroxy-6,8-diiodo-4-methylcoumarin (1 g.) by refluxing with alcoholic potassium hydroxide (10%; 50 ml.) for 1 hr. It crystallized from glacial acetic acid in needles, m.p. 242° (dec.). Attempts to cyclize it to the original coumarin did not succeed as on boiling with concentrated hydrochloric acid iodine was liberated.

Anal. Calcd. for $C_{10}H_8O_4I_2$: C, 26.90; H, 1.79; I, 56.95. Found: C, 27.13; H, 1.38; I, 56.72.

Methyl β-methyl 2,4-dimethoxy-3,5-diiodocinnamate. Simultaneous methylation and esterification of the above acid was carried out by refluxing its acetone solution with excess of dimethyl sulfate in presence of anhydrous potassium carbonate. It crystallized from alcohol in needles, m.p. 169°. It decolorized dilute potassium permanganate solution and bromine in acetic acid.

Anal. Calcd. for $C_{13}H_{14}O_4I_2$: C, 31.96; H, 2.86; I, 52.04. Found: C, 31.89; H, 3.19; I, 51.63.

BARODA, INDIA

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[5] R. J. Parikh and S. M. Sethna, *J. Indian Chem. Soc.*, 27, 369 (1950).