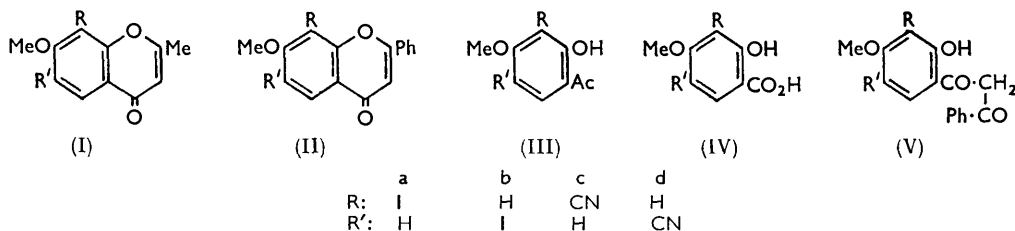


521. Chromones and Flavones. Part III.¹ Synthesis of Some Cyano-chromones and -flavones.

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Cyano-chromones and -flavones have been synthesised by the Rosenmund-von Braun reaction from the iodo-chromones and -flavones and by Kostanecki-Robinson acylation of 3- and 5-cyano-2-hydroxy-4-methoxyacetophenone. The action of alkali and sulphuric acid on the cyano-compounds has been studied.

DA RE *et al.*^{2,3} synthesised 6- and 8-cyano-2,3-dimethylchromone and 4'-cyanoflavone. No other work on the synthesis of cyano-chromones and -flavones has been reported. In the present work two iodochromones⁴ (Ia and b) and an iodoflavone (IIa) were fused with cuprous cyanide (Rosenmund-von Braun reaction), affording the corresponding cyano-chromones (Ic and d) and -flavone (IIc) in good yield. These were demethylated to the corresponding hydroxy-compounds.



In further work the cyano-ketones (IIIc and d) were synthesised by reaction of 3- and 5-iodo-2,4-dimethoxyacetophenone with cuprous cyanide and subsequent partial demethylation with aluminium chloride and then subjected to Kostanecki-Robinson acetylation and benzoylation. The 3-acetyl-8- and -6-cyanochromone and the benzoylflavones obtained were identical with those obtained by the Rosenmund-von Braun method. 3-Acetyl-8-cyano-7-methoxy-2-methylchromone was deacetylated to the cyanochromone (Ic) by hot alkali, but the 6-cyano-isomer gave a mixture of the cyano-ketone (IIIId) and

¹ Part II, Shah and Sethna, *J.*, 1960, 3899.

² Da Re, *Farmaco (Pavia), Edn. Sci.*, 1956, **11**, 678.

³ Da Re, Colleoni, and Verlicchi, *Ann. Chim. (Italy)*, 1958, **48**, 762.

⁴ Shah and Sethna, *J.*, 1959, 2676.

TABLE 1. Products from Rosenmund-von Braun reactions.

No.	Substance	Reaction temp.	Product	Yield (%)	M. p.	C	H	N	Formula	C	H	N	Required (%)
1	Me ether of IIIa	165—170°	3-Cyano-	57	131°	65.0	5.2	6.6	C ₁₁ H ₁₁ O ₃ N	64.4	5.4	6.8	5.4
2	Me ether of IIIb	185—190	5-Cyano-	67	192	64.5	5.9	6.7	C ₁₁ H ₁₁ O ₃ N	64.4	5.4	6.8	5.4
3	Ia	235—240	Ic	63	262	67.0	4.3	6.8	C ₁₂ H ₉ O ₃ N	67.0	4.2	6.5	4.2
4	Ib	245—250	Id	58	249	67.5	4.1	6.3	C ₁₃ H ₉ O ₃ N	67.0	4.2	6.5	4.0
5	IIa	220—225	IIc	54	235	73.5	3.4	5.3	C ₁₇ H ₁₁ O ₃ N	73.6	4.0	5.0	4.0

Demethylation products from compounds mentioned in column 4 above.^a

1	IIIc	169°	63.0	5.1	7.2	C ₁₀ H ₉ O ₃ N	62.8	4.7	7.3	62.8	4.7	7.3	4.7
2	IIId	180	62.3	4.8	7.5	C ₁₀ H ₉ O ₃ N	62.8	4.7	7.3	62.8	4.7	7.3	4.7
3	7-Hydroxy-8-cyano-2-methylchromone	368	65.2	3.5	7.2	C ₁₁ H ₇ O ₃ N	65.7	3.5	7.0	65.7	3.5	7.0	3.5
4	7-Hydroxy-6-cyano-2-methylchromone	340	65.9	3.7	7.2	C ₁₁ H ₇ O ₃ N	65.7	3.5	7.0	65.7	3.5	7.0	3.5
5	7-Hydroxy-8-cyanoflavone	315	72.9	3.9	5.2	C ₁₆ H ₉ O ₃ N	73.0	3.5	5.3	73.0	3.5	5.3	3.5

Nos. 3, 4, and 5 dissolve in sodium hydrogen carbonate solution with effervescence. No. 5 shows intense violet fluorescence with sulphuric acid.

TABLE 2. Kostanecki-Robinson "Acetylation" (A) or "Benzoylation" (B).

Ketone	Reaction	Product *	Yield (%)			Found (%)			Required (%)			
			(%)	M. p.	C	H	N	Formula	C	H	N	
IIIc	A	3-Acetyl-8-cyano-7-methoxy-2-methylchromone	39	230°	65.3	4.0	5.8	C ₁₄ H ₁₁ O ₄ N	65.4	4.3	5.4	4.3
	B	3-Benzoyl-8-cyano-7-methoxyflavone	50	258	76.0	3.8	3.6	C ₂₄ H ₁₅ O ₄ N	75.6	4.0	3.7	4.0
IIId	A	3-Acetyl-6-cyano-7-methoxy-2-methylchromone	33	220	65.7	4.4	5.3	C ₁₄ H ₁₁ O ₄ N	65.4	4.3	5.4	4.3
	B	3-Benzoyl-6-cyano-7-methoxyflavone	57	281	75.0	4.3	3.8	C ₂₄ H ₁₅ O ₄ N	75.6	4.0	3.7	4.0

* Obtained also by heating the corresponding 3-acyl-6- or -8-iodo-chromone or -flavone (see Part II) with cuprous cyanide for 10 min., for chromones at 220° and for 8- and 6-iodoflavone at 250° and 285° respectively.

TABLE 3. Products of hydrolysis by sulphuric acid.

No.	Parent	H ₂ SO ₄ (% by wt.)	Product *	Yield (%)	Found (%)			Required (%)				
					M. p.	C	H	Formula	C	H	N	
1	Ic and 3-Ac of Ic	70	7-Hydroxy-2-methylchromone	36	249°	59.8	4.0	—	C ₁₁ H ₉ O ₆	60.0	3.7	—
2	8-Cyano-7-hydroxy-2-methylchromone	95 ^a	7-Hydroxy-2-methylchromone-8-carboxylic acid	36	259	59.8	4.0	—	C ₁₁ H ₉ O ₆	60.0	3.7	—
3	Id and 3-Ac of Id	70	7-Hydroxy-2-methylchromone-6-carboxylic acid	45, 33	302	60.5	4.0	—	C ₁₁ H ₉ O ₆	60.0	3.7	—
4	Id	50	7-Methoxy-2-methylchromone-6-carboxylic acid	36	245	61.3	4.4	—	C ₁₂ H ₁₀ O ₅	61.5	4.3	—
5	IIc and 3-Bz of IIc	70	7-Hydroxyflavone	—	240	—	—	—	—	—	—	—
6	IIc	50	(i) 8-Carbamoyl-7-methoxyflavone ^b and (ii) 7-Methoxyflavone-8-carboxylic acid	37	296	69.1	4.6	—	C ₁₇ H ₁₃ O ₄ N	69.1	4.4	—
7	8-Cyano-7-hydroxyflavone	50	7-Hydroxyflavone-8-carboxylic acid	18	216	68.7	4.6	—	C ₁₇ H ₁₃ O ₅	68.9	4.1	—
8	IIc and 3-Bz of IIc	70	7-Hydroxyflavone-6-carboxylic acid	46	242	67.9	3.7	—	C ₁₈ H ₁₀ O ₅	68.1	3.6	—
				50, 45	311	67.8	3.6	—	C ₁₈ H ₁₀ O ₅	68.1	3.6	—

* Nos. 2, 4, 6 (ii), and 7 are soluble in sodium hydrogen carbonate solution with effervescence whereas Nos. 3 and 8 form a sodium salt with sodium hydrogen carbonate. Nos. 2, 3, 7, and 8 give a reddish-violet colour with alcoholic ferric chloride and melt with effervescence. Nos. 2, 3, 6 (ii), 7, and 8 were decarboxylated when heated with quinoline and copper powder, and the products were compared with authentic specimens.

^a Heated on a steam-bath for 3 hr. ^b Yielded 7-hydroxyflavone-8-carboxylic acid when heated in acetic acid with hydriodic acid.

the acid (IVd). 3-Benzoyl-8- and -6-cyano-7-methoxyflavone, on treatment with alkali, gave the acids (IVc and d) and small quantities of the β -diketones (Vc and d) identical with those synthesised by the Baker-Venkataraman transformation of the *O*-benzoyl derivatives of the cyano-ketones (IIIc and d). The β -diketones cyclised to the cyanoflavones (IIc and d) in concentrated sulphuric acid. When the cyano-chromones and -flavones were treated with 70% sulphuric acid, demethylation, deacylation (in the case of 3-acyl compounds), and hydrolysis of the cyano-group to carboxyl occurred. In the cases (Ic) and (IIc) the cyano-group was eliminated. When 50% sulphuric acid was used no demethylation was observed.

EXPERIMENTAL

Rosenmund-von Braun Synthesis (see Table 1).—The iodo-derivative (0.01 mole) was stirred with cuprous cyanide (0.02 mole) for 10 min. at the temperature specified in Table 1. The mixture was powdered and extracted with acetone or alcohol; the product recrystallised from alcohol in needles. Addition of copper sulphate (0.001 mole) or the cyano-derivative (trace) from a previous run to the reaction mixture improved the yield.⁵

Kostanecki-Robinson "Acetylations" (see Table 2).—The cyano-ketone (2 g.) was heated with freshly fused sodium acetate (5 g.) and acetic anhydride (25 ml.) at 170–180° for 8 hr. The mixture was then added to cold water; the product crystallised from acetic acid (charcoal) in needles.

Kostanecki-Robinson "Benzoylations" (see Table 2).—The cyano-ketone (1 g.) was heated with freshly fused sodium benzoate (3 g.) and benzoic anhydride (10 g.) at 170–180° for 8 hr. The mixture was then treated repeatedly with hot water and sodium hydrogen carbonate, and the residue crystallised from acetic acid (charcoal), forming needles.

Alkaline Hydrolysis.—(a) 3-Acetyl-8-cyano-7-methoxy-2-methylchromone was heated with 2% alcoholic sodium carbonate solution for $\frac{1}{4}$ hr. The product obtained on acidification was extracted first with sodium hydrogen carbonate solution and then with sodium hydroxide, and 3-cyano-2-hydroxy-4-methoxybenzoic acid (IVc), m. p. 234–235° (effervescence) (Found: C, 55.9; H, 3.4; N, 7.8. $C_9H_7O_4N$ requires C, 56.0; H, 3.7; N, 7.3%), and 3-cyanopeonol (see Table 1) were isolated. The residue was the cyanochromone (Ic).

(b) 3-Acetyl-6-cyano-7-methoxy-2-methylchromone on similar treatment with 5% alcoholic sodium carbonate solution for 2 hr. gave 5-cyano-2-hydroxy-4-methoxybenzoic acid (IVd), m. p. 232–233° (effervescence) (Found: C, 56.0; H, 3.7; N, 7.5%), and 5-cyanopeonol (see Table 1).

(c) 3-Benzoyl-8-cyano-7-methoxyflavone was refluxed with 10% alcoholic potassium hydroxide for 2 hr. The product obtained on acidification was treated with aqueous sodium hydrogen carbonate, and the cyano-phenolic acid (IVc) separated. The undissolved product, 3-cyano-2-hydroxy-4-methoxydibenzoylmethane (Vc), crystallised from alcohol in needles, m. p. 230° (Found: C, 69.4; H, 4.5; N, 4.8. $C_{17}H_{13}O_4N$ requires C, 69.1; H, 4.4; N, 4.7%). On treatment with concentrated sulphuric acid it yielded the cyano-flavone (IIc). This β -diketone was also synthesised from 2-benzoyloxy-3-cyano-4-methoxyacetophenone [prepared from the ketone (IIIc) by reaction with benzoyl chloride and pyridine], m. p. 182° (from alcohol) (Found: C, 69.4; H, 4.2; N, 5.1. $C_{17}H_{13}O_4N$ requires C, 69.1; H, 4.4; N, 4.7%). This ketone (2 g.) in benzene (30 ml.) was refluxed with pulverised sodium (0.3 g.) for 4 hr. and the precipitated sodium salt was decomposed with acetic acid to afford the β -diketone.

(d) 3-Benzoyl-6-cyano-7-methoxyflavone, on similar treatment with alcoholic potassium hydroxide, gave the acid (IVd) and 5-cyano-2-hydroxy-4-methoxydibenzoylmethane (Vd), m. p. 204° (Found: C, 69.1; H, 4.5; N, 4.3%). This was also synthesised from 2-benzoyloxy-5-cyano-4-methoxyacetophenone [prepared from the ketone (IIId)], m. p. 195–196° (Found: C, 69.5; H, 4.4; N, 4.2%). This ketone, when refluxed in toluene with sodium for 4 hr. and worked up as above, yielded the β -diketone.

6-Cyano-7-methoxyflavone (IIId).—The above β -diketone was dissolved in concentrated sulphuric acid and kept for 4 hr. The product, obtained by pouring the mixture over ice, crystallised in needles, m. p. 226–227°, from alcohol (Found: C, 73.1; H, 4.3; N, 5.1. $C_{17}H_{11}O_3N$ requires C, 73.6; H, 4.0; N, 5.0%).

Sulphuric Acid Hydrolysis (see Table 3).—The cyano-compound (0.5 g.) was gently refluxed

⁵ Cf. Koelsch and Whitney, *J. Org. Chem.*, 1941, **6**, 795.

with sulphuric acid (25 ml.), of the specified strength, for 3 hr. The product obtained by pouring the mixture on ice was treated with aqueous sodium hydrogen carbonate to separate the acid. Both the *acid* and the residue, if any, were crystallised from dilute alcohol.

Demethylations (see Table 1).—The cyano-ketones were partially demethylated with aluminium chloride in the dry state or by heating them in dry nitrobenzene solution on a steam-bath for 3 hr. The product obtained after steam-distillation of nitrobenzene was purified by extraction with alkali. It crystallised from alcohol in needles. The cyano-chromones and -flavones were demethylated by heating their acetic acid solutions with hydriodic acid at 120—125° for 3 hr. The mixture was poured into sodium hydrogen sulphite solution and the *product* was extracted with alkali. It crystallised as needles from acetic acid. In the case of (II_d), 7-hydroxy-2-methylchromone-6-carboxylic acid was obtained by use of hydriodic acid; hence it was demethylated by aluminium chloride at 120° (3 hr.).

In general, demethylations with aluminium chloride were smooth, whereas those with hydriodic acid gave undesirable coloured products especially at reaction temperatures above 130°.

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