[Jour. Indian Chem. Soc., Vol. 48, No. 3, 1971]

Reactions of Nitriles : Part VII. Cyanoethylation of Hydroxycoumarins

J. R. Merchant, J. R. Patell and (Mrs.) N. V. Barve

Cyanoethylation of some hydroxycoumarins has been investigated. The cyanoethyl derivatives obtained were hydrolysed to the corresponding acids. Cyclisation of the acids gave pyronochromanones.

In continuation of our work on the cyanoethylation of hydroxycoumarins[1,2,3], we now report the cyanoethylation of some 7-hydroxycoumarin derivatives and 6-amino-7-methylcoumarin.

When 7-hydroxycoumarin[4] was treated with acrylonitrile in presence of 10% sodium hydroxide solution as catalyst the compound (Ia) was obtained. Compound (Ia) on hydrolysis with concentrated hydrochloric acid yielded the acid (Ib). Cyclisation of the acid (Ib) with polyphosphoric acid gave a mixture of pyronochromanones which were separated by chromatography. Elution with benzene gave the isomer (IIa), m.p. 207–09°, ν, 1740, 1610 (coumarin), 1670 (chromanone) cm^{-1}. The n.m.r. spectrum is in agreement with the structure (IIa) and shows the aromatic proton signals as singlets [$\delta(CD_3SOCD_3)$ 8·08 and 6·87].

The fraction eluting from benzene-ether (1 : 1) was the isomer (IIIa), m.p. 217–19°, ν, 1720, 1600, 1555 (coumarin), 1680 (chromanone) cm^{-1}. The n.m.r. spectrum is in agreement with the structure (IIIa) and shows the aromatic protons as doublets [$\delta(CDCl_3)$ 7·62 and 6·92 (J = 9 c/sec)].

An attempt to synthesise (IIa) from 7-hydroxychromanone[5] by a Pechmann condensation with malic acid in the presence of sulphuric acid led to the formation of a pyronochromanone $C_{12}H_8O_4$, m.p. 201–03°, λmax (log ϵ) in methanol, 265 (4·46), 300–305 (3·98–3·97) and 335–340 (3·55–3·52) mμ; ν, 1740, 1620, 1590 (coumarin), 1690 (chromanone) cm^{-1}, which was different from the two isomers obtained above (m.m.p.) and hence must have the only other possible structure (IVa). Its u.v. spectrum is in agreement with the u.v. spectra of the pyronochromanones derived from 5-hydroxycoumarin derivatives reported earlier[2].

In a similar manner, cyanoethylation of 7-hydroxy-4-methylcoumarin[6], 3-ethyl-7-hydroxy-4-methylcoumarin[7], 3,4-dimethyl-7-hydroxycoumarin[8] and 7-hydroxy-4-methyl-3-propylcoumarin[7] yielded the corresponding cyanoethyl derivatives (Ic), (Ie), (Ig) and (Ii)

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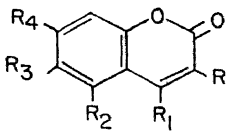
which on hydrolysis with concentrated hydrochloric acid gave the acids (Id), (If), (Ih) and (Ij) respectively.



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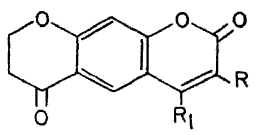

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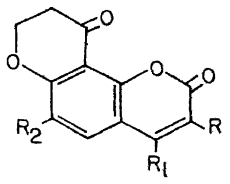

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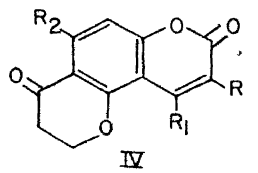

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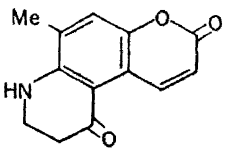

V

	R	R_1	R_2	R_3	R_4
a)	H	H	H	H	$O(CH_2)_2CN$
b)	H	H	H	H	$O(CH_2)_2CO_2H$
c)	H	Me	H	H	$O(CH_2)_2CN$
d)	H	Me	H	H	$O(CH_2)_2CO_2H$
e)	Et	Me	H	H	$O(CH_2)_2CN$
f)	Et	Me	H	H	$O(CH_2)_2CO_2H$
g)	Me	Me	H	H	$O(CH_2)_2CN$
h)	Me	Me	H	H	$O(CH_2)_2CO_2H$
i)	Pr	Me	H	H	$O(CH_2)_2CN$
j)	Pr	Me	H	H	$O(CH_2)_2CO_2H$
k)	Me	Me	H	Et	$O(CH_2)_2CN$
l)	Me	Me	H	Et	$O(CH_2)_2CO_2H$
m)	H	Me	H	Me	$O(CH_2)_2CN$
n)	H	Me	H	Me	$O(CH_2)_2CO_2H$
o)	H	Me	H	Br	$O(CH_2)_2CN$
p)	H	Me	H	Br	$O(CH_2)_2CO_2H$
q)	Pr	Me	H	Et	$O(CH_2)_2CN$
r)	Pr	Me	H	Et	$O(CH_2)_2CO_2H$
s)	H	H	H	$NH(CH_2)_2CN$	Me
t)	H	H	H	$NH(CH_2)_2CO_2H$	Me

	R	R_1
a)	H	H
b)	H	Me
c)	Et	Me
d)	Me	Me

	R	R_1	R_2
a)	H	H	H
b)	H	Me	H
c)	Et	Me	H
d)	Me	Me	H
e)	Pr	Me	H
f)	Me	Me	Et
g)	H	Me	Me
h)	Pr	Me	Et

Cyclisation of the acid (Id), as before, afforded a mixture of pyronochromanones which were separated by chromatography. Elution from benzene-light petroleum (40–60°) (1 : 1) afforded the isomer (IIb), m.p. 235–37°, ν, 1710, 1600 (coumarin), 1680 (chromanone) cm^{-1}. The structure (IIb) was assigned on the basis of an alternate synthesis. Pechmann condensation of 7-hydroxychromanone with ethyl acetoacetate could afford the pyronochromanone (IIb) or (IVb). In the actual working of the reaction only one pyronochromanone, m.p. 234–35°, eluting from benzene-light petroleum (40–60°) (1 : 1) was obtained. That the above synthesised pyronochromanone was identical with the linear isomer obtained before was established by a mixed m.p. (which was not depressed) as well as by the observation that it was different from the pyronochromanone (IVb)[2].

Elution with ether-chloroform (1 : 1) gave the isomer (IIIb), m.p. 244–46°, ν, 1720, 1620, 1580 (coumarin), 1690 (chromanone) cm^{-1}. The n.m.r. spectra of (IIb) and (IIIb) could not be taken due to their poor solubility.

The cyclisation of the acid (If) also gave a mixture which was separated by fractional crystallisation. The isomer (IIc) crystallised from light petroleum (40–60°), m.p. 132–34°. The n.m.r. spectrum is in agreement with the structure (IIc) and shows the aromatic proton signals as singlets [$\delta(CHCl_3)$ 6·88 and 8·22]. The isomer (IIIc) crystallised from ethyl acetate, m.p. 175°. The structure is confirmed by the n.m.r. spectrum which shows the aromatic protons [$\delta(CHCl_3)$ 6·92 and 7·7 (J = 9 c/sec)] as doublets.

The acid (Ih) also yielded a mixture of pyronochromanones which were separated by fractional crystallisation. The isomer (IId) crystallised from ethyl acetate-light petroleum (40–60°), m.p. 192° while the isomer (IIId) crystallised from ethyl acetate, m.p. 225°. The structures are assigned on the basis of the u.v. spectra by analogy with the u.v. spectra of similar compounds. It is observed that the linear isomers show a strong maxima at 250–255 mμ (log ϵ 4·4–4·5) while the angular isomers show a minimum at 250–255 mμ.

The acid (Ij), however, yielded only one pyronochromanone, m.p. 189° and was assigned the structure (IIIe) on the basis of the u.v. spectrum.

Similarly, the cyanoethylation of 3,4-dimethyl-6-ethyl-7-hydroxycoumarin[9]. 4,6-dimethyl-7-hydroxycoumarin[10], 6-bromo-7-hydroxy-4-methylcoumarin[11] and 6-ethyl-7-hydroxy-4-methyl-3-propylcoumarin[12] yielded the corresponding cyanoethyl derivatives (Ik), (Im), (Io) and (Iq) respectively. Hydrolysis of these cyanoethylated products with concentrated hydrochloric acid gave the acids (Il), (In), (Ip) and (Ir) respectively.

Cyclisation of the acids (Il), (In) and (Ir) gave the corresponding pyronochromanones (IIIf), (IIIg) and (IIIh), characterised by the preparation of their 2,4-dinitrophenylhydrazone derivatives. Attempts to cyclise the acid (Ip) under different experimental conditions met with failures.

9. R. D. Desai and M. Ekhlas, *Proc. Indian Acad. Sci.*, 1933, **8A**, 194.

10. Masaiti Yanagita, *Ber.*, 1938, **71**, 2269.

11. D. Chakravarti, and S. M. Mukherjee, *J. Indian Chem. Soc.*, 1937, **14**, 725.

12. R. D. Desai and C. K. Mavani, *Proc. Indian Acad. Sci.*, 1941, **14A**, 100.

As a point of interest the cyanoethylation of 6-amino-7-methylcoumarin[13] was investigated. The coumarin derivative was readily mono-cyanoethylated in the presence of acetic acid using cuprous chloride as catalyst to give (Is) which was hydrolysed to (It). Cyclisation of the acid (It), as before, afforded the pyronoquinolone derivative (V). Further work on the cyanoethylation of aminocoumarins is in progress.

EXPERIMENTAL

Cyanoethylation of Hydroxycoumarins : A mixture of the hydroxycoumarin (0.01 mole), dioxan (3.0–5.0 ml.), acrylonitrile (1.5–5.0 ml.) and aqueous sodium hydroxide (10%; 0.5–1.5 ml.) was heated under reflux for 20 hr. Aqueous alkali (10%; 100.0 ml.) was then added and the mixture was extracted thoroughly with chloroform. The extract was repeatedly washed with alkali, then water and dried. Removal of the solvent left the cyanoethyl derivative. (Table I).

TABLE I

Coumarin (g.)	Acrylonitrile used (ml)	Cyanoethylated coumarin (mg.)	M.P. °C	Solvent*	Required %			Found %		
					C	H	N	C	H	N
1.6	1.5	(Ia) 200	167–69	A—B	67.0	4 2	6.5	67 3	4.4	6.9
5.0	5.0	(Ic) 150–210	128–30	C—B	68.1	4.8	6.1	68.4	5.0	6.0
2.0	4.0	(Ie) 380	138	A	70.0	5.8	5.4	70.2	5.9	5.5
1.9	3.0	(Ig) 100	147	A—B	69.1	5.3	5.8	69.1	5.0	5.6
2.0	5.0	(Ii) 180	110–12	A	70.8	6.3	5.1	70.6	6.1	5.0
2.1	3 0	(Ik) 100	155	A	70.8	6.3	5.1	70.5	6.2	5.1
2.4	4.0	(Im)255	193	A—B	69.1	5.4	5.8	69.3	5.2	5.7
2.5	4.0	(Io) 100	200	A	50.7	3.2	4.5	50.8	3.3	4.2
2.0	5.0	(Iq) 200	128	A	72.2	7.0	4.6	72.4	7.3	4.3
0.9	0.5	(Is)	190–91	A	68.4	5.3	12.3	68.0	5.3	12.1

*All products obtained as needles. Solvents : A, ethyl acetate; B light petroleum (b.p. 40–60°); C, benzene.

Hydrolysis of Cyanoethylated Coumarins : The cyanoethyl derivative was heated under reflux with concentrated hydrochloric acid (10.0 ml. for 100 mg. of solid) for 1 hr. The solid which separated from the cooled solution was filtered off and dissolved in the minimum amount of sodium bicarbonate solution. The solution was filtered, and the filtrate on acidification gave the required acid (Table II).

Cyclisation of the 2-Carboxyethoxycoumarins : The acid was added to a mixture of phosphorus pentoxide (10.0 g. for 300 mg. acid) and phosphoric acid (4.0 ml.) preheated to 100° (30 min.) and kept at 100° for 2 hr. with occasional shaking. Water was added and the

13. A. Clayton, *J. Chem. Soc.*, 1910, 1352.

TABLE II

Cyanoethylated coumarin (mg.)	Acid (mg.)	M.P. °C	Solvent*	Required % C	Required % H	Required % N	Found % C	Found % H	Found % N
(Ia) 520	(Ib) 400	164–66	A—B	61.5	4.3		61.8	4.6	
(Ic) 250	(Id) 190	197–99	A	62.9	4.9		63.3	4.9	
(Ie) 380	(If) 280	173	A	65.2	5,8		65.2	5.6	
(Ig) 250	(Ih) 190	195–96	A	64.1	5.3		64.0	5.2	
(Ii) 385	(Ij) 200	140	A	66.2	6.2		65.9	6 0	
(Ik) 250	(Il) 180	165–68	A	66.2	6.2		66.1	6.1	
(Im) 250	(In) 190	185	A	64 1	5.3		64.1	5.6	
(Io) 250	(Ip) 100	230	A	47.6	3.3		48.0	3.6	
(Iq) 300	(Ir) 180	135	A	67.9	6.9		67.5	6.4	
(Is) 135	(It) 90	164–66	A	63.2	5.3	5.7	63.4	5.5	5.7

* All products obtained as needles except (If) as prisms. Solvents : See Table I.

solid which separated was filtered off, washed with water, sodium bicarbonate solution, and then water again to give the pyronochromanones (Table III).

TABLE III

Acid (mg.)	Chromanone (mg,)	M.P. °C	Solvents*	Required % C	Required % H	Required % N	Found % C	Found % H	Found % N	M.P. of DNP	Reqd. % N	Found % N
(Ib) 400	(IIa) 200	207–09	A–B	66.7	3.7		67.0	3.6		291–92′	14.1	14.4
	(IIIa)	217–19	A–B	66.7	3.7		67.0	3.5		286–88′	14.1	14.2
(Id) 150	(IIb) 100	235–37	C–B	67.8	4.4		67.7	4.3		297–98′	13.7	13.5
	(IIIb)	244–46	D	67.8	4.4		67.5	4.2		292′	13.7	13.8
(If) 150	(IIc) 100	132–34	B	69.7	5.4		70.0	5.6		281	12.7	12 5
	(IIIc)	175	A	69.7	5.4		69.9	5.6		270	12.7	12.9
(Ih) 150	(IId) 100	192	A–B	68.7	5.0		68.9	4.9		269	13.1	12.9
	(IIId)	225	A	68.7	5.0		68.5	5.3		293	13.1	13.3
(Ij) 200	(IIIe) 100	189	A	70.5	5.9		70.2	6.0		244	12.4	12.6
(Il) 150	(IIIf) 100	125	A–B	70.5	5.9		70.1	5.8		273	12.4	12.3
(In) 150	(IIIg) 100	212	A	68.8	4.9		68.5	5.0		288	13.2	13.3
(Ir) 150	(IIIh) 80	145	A	71.9	6.7		71.9	6.9		262	11.6	11.3
(It) 100	(V) 40	227–28	C	68.1	4.8	6.1	68.4	5.0	6.0	286–87′	17 1	17.0

* As in Table I and D, acetone. ′Decomp.

λmax values (log ε) for solutions in MeOH : (IIa) 225 (4.17), 255 (4.50), 305 (4.07), 330 (4.07) and 340 (4.08) mμ; (IIIa) 215 (4.08), 240 (4.02), 265 (3.95), 310(4.02), 335 (3.98) and 345 (3.98) mμ; (IIb) 250 (4.48), 290 (4.02) and 340 (4.08) mμ; (IIIb) 270 (3.99), 295 (3.98), 305 (3.98), 335 (4.01) and 345 (4.03) mμ; (IIc) 255 (4.43), 290 (4.04) and 345 (4.06) mμ; (IIIc) 240 (4.09), 275 (4.03), 300 (4.05) and 350 (4.01) mμ; (IId) 255 (4.45), 300 (3.98) and 345 (3.95) mμ; (IIId) 235 (3.94), 275 (4.08), 300 (3.86) and 345 (3.87) mμ; (IIIe) 275 (3.99), 300 (4.06) and 350 (4.00) mμ; (IIIf) 275 (4.03), 305 (4.00) and 350 4.01) mμ; (IIIg) 272 (3.94), 308 (3.88) and 344 (3.91) mμ; (IIIh) 275 (4.06), 305 (4.03), and 350 (4.09) mμ.

Pechmann condensation of 7-hydroxychromanone with malic acid : A mixture of 7-hydroxychromanone (500 mg.), malic acid (500 mg.) and concentrated sulphuric acid (10.0 ml.) was heated at 130° for 3 hr. The cold solution was poured over ice and extracted with chloroform. The extract was washed with water, alkali, water again and dried. Removal of the solvent gave 115 mg. of a solid which was chromatographed over alumina. Only (IVa) eluting from light-petroleum (40–60°)-benzene (1 : 1) was obtained. (Found : C, 66·7, H, 3·7; $C_{12}H_8O_4$ requires C, 67·0; H, 4·0%); 2,4-DNP, m.p., 285–86° decomp. (Found : N, 14·3; $C_{18}H_{12}N_4O_7$ requires N, 14·1%).

Pechmann condensation of 7-hydroxychromanone with ethyl acetoacetate : To a solution of anhydrous aluminium chloride (800 mg.) in dry nitrobenzene (4.0 ml.) was added 7-hydroxychromanone (500 mg.) and ethyl acetoacetate (1·2 ml.) and heated at 130° for 4 hr. Ice and hydrochloric acid were added and the nitrobenzene removed by steam distillation. The residual sticky solid was extracted with chloroform. The extract was washed thoroughly with aqueous alkali, water and dried. Removal of the solvent gave 126 mg. of an oil which was chromatographed over alumina. The oil obtained on elution with light petroleum (40–60°)-benzene (1 : 1) was crystallised from the same mixture and then from ethyl acetate-light petroleum (40–60°) to give a solid m.p. 234–35°. A mixed m.p. with (IIb) obtained before was undepressed.

Cyanoethylation of 6-amino-7-methylcoumarin : A mixture of the aminocoumarin (900 mg.), acrylonitrile (0.5 ml.), glacial acetic acid (2.0 ml.) and cuprous chloride (50 mg.) was heated under reflux for 6 hr. and then neutralised with ammonia solution and left overnight. The brown mass (700 mg.) was filtered and chromatographed over alumina. The yellow solid eluted with ether-chloroform (1 : 1) gave (Is). The solid obtained from benzene-ether (1 : 1) was the unchanged coumarin derivative (m.m.p.).

Hydrolysis of (Is) to (It) : The cyanoethyl derivative (Is) (135 mg.) was heated under reflux with concentrated hydrochloric acid (13.5 ml.) for 1 hr. The solution was cooled and neutralised with ammonia solution to about *p*H 5.2 when the acid (It) separated.

We thank Miss J. Pradhan and Mr. D. V. Rege for the microanalyses, the CIBA Research Centre, Bombay, for i.r. and n.m.r. spectra and also the Central Drug Research Institute. Lucknow for n.m.r. spectra and the U.G.C. for a junior research fellowship (to J.R.P.).

Organic Chemistry Research Laboratories,
Institute of Science,
15, Madame Cama Road,
Bombay-32.

Received July 1, 1970