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SOME MORE 3-SUBSTITUTED-4-HYROXYCARBOSTYRILES

By

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SOME MORE 3-SUBSTITUTED-4-HYROXYCARBOSTYRILES

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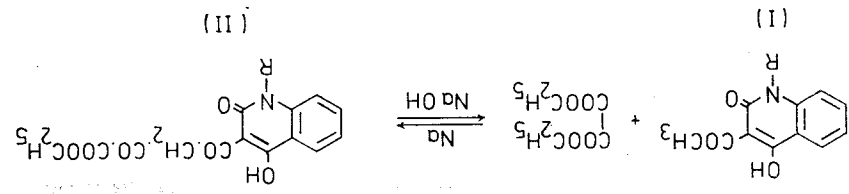
1- Alkyl (or phenyl)-3-[4'(2',4'-dioxobutyric ethyl ester)]-4-hydroxycarbostryils were synthesized and their reactions with amines, hydrazines, and hydroxylamine were investigated. Dehydration of these esters underwent cyclization to afford the pyranocarbostyrils.

3-Acetyl-6-bromo-1-ethyl (or phenyl)-4-hydroxycarbostyril were prepared and their structure were established.

The synthesis of several 3-substituted-4-hydroxycarbostyrils has been reported in the literature, the pharmacology and industrial application of some of them were also studied [1,6]. However little is known about the synthesis and pharmacology of 4-hydroxycarbostyrils with heterocyclic substituents at the 3-position. We have previously described the synthesis of some 3-heterocyclic substituted-4-hydroxycarbostyrils [7,8].

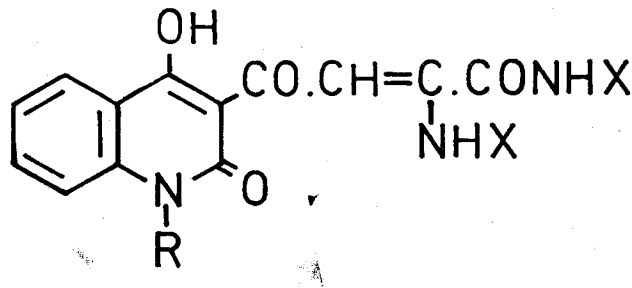
The present work is a continuation towards the synthesis of this class of compounds. Thus 3-acetyl-1-alkyl (or phenyl)-4-hydroxycarbostyrils Ia-c reacts with diethyl oxalate in the presence of metallic sodium to afford the corresponding 1-alkyl (or phenyl)-3-[4'-(2',4'-dioxobutyric ethyl ester)]-4-hydroxy-carbostyrils IIa-c. The structure of these esters was confirmed by: elemental analysis, hydroxamic acid test, ir. spectra which showed stretching frequencies at 1720 cm^{-1} (4'. C=O), 1660 cm^{-1} (C=O imide), 1630 cm^{-1} (2'. C=O), 1750 cm^{-1} (C=O esters) and 2800-2600 cm^{-1} (OH), and finally by the fact that these esters (IIa-c) regenerate the starting materials back (Ia-c) when treated with sodium hydroxide.

(II) (I)



	R
I, IIa	CH_3
b	C_2H_5
c	C_6H_5

Compounds IIa-c condense with two molecules of amines to give the enamino-amido derivatives IIIa-f.

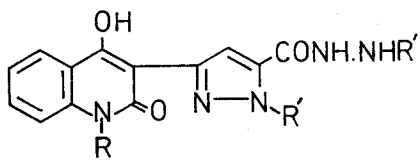


(III)

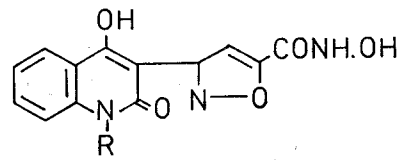
	R	X		R	X
IIIa	CH_3	C_6H_5	d	C_2H_5	C_6H_{11}
b	CH_3	C_6H_{11}	e	C_6H_5	C_6H_5
c	C_2H_5	C_6H_5	f	C_6H_5	C_6H_{11}

The substituion by the amines, as in β-diketones [7,9], occured at 4′-position in II, since the ir. spectrum of IIId reveals the absence of the bands at 1750 cm^{-1} and 1720 cm^{-1} that already present in the ir. spectrum ot the parent compound IIb.

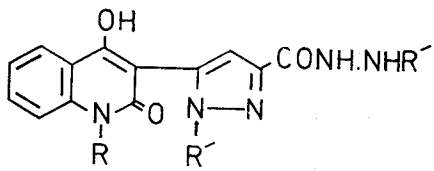
Condensation ot IIa-c with hydrazines and hydroxylamine leds to the ıormation of products resulting from the condensation of one molecule of IIa-c with two molecules of the reagent associated with the elimination of two molecules of water and one molecule of ethanol, as shown by their elemental analysis. Based on the reaction of β-diketones with hydrazines, and hydroxylamine [7,9] that gives pyrazole hydrazide and isoxazole hydroxamic acid derivatives respectively, by analogy the products that obtained from the reaction of IIa-c with these reagents may have formulae IV and V, or possibly their isomeric analogous IVi and Vi.



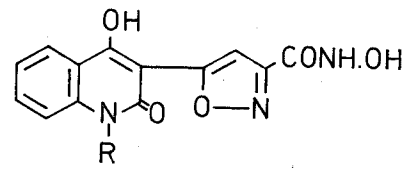
(IV)



(V)



(IVi)



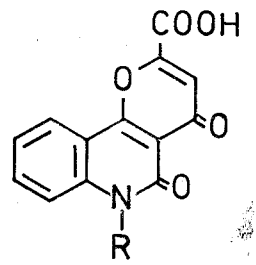
(Vi)

	R	R′
IVa	CH_3	H
b	CH_3	C_6H_5
c	C_2H_5	H
d	C_2H_5	C_6H_5
e	C_6H_5	H
f	C_6H_5	C_6H_5

	R
Va	CH_3
b	C_2H_5

The structure of compounds IV and V was confirmed by ir. which showed, for IVc, bands at 3550 cm^{-1} (NH), 3100 cm^{-1} (OH), 1620 cm^{-1} (C=N).

It is well known that o-hydroxy-β-diketones cyclized readily on dehydration to give the corresponding chromones [7,9,10]. When the dicarbonyl esters IIa-c were treated with cold conc. sulphuric acid, or with boiling ethanolic hydrochloric acid, a product was obtained having the structure VI which was confirmed by: (i) the OH group in the 4–position in analogous compounds has been reported to take part in a similar cyclization reaction [7,11,12], and the ester group has been hydrolysed to the carboxylic group.



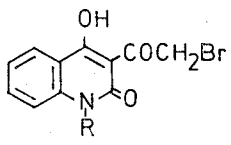
(VI)

	R
VIa	CH_3
b	C_2H_5
c	C_6H_5

(ii) Compounds VIa-c, respond positively to the known potassium hydroxide test for chromones [13], are readily hydrolysed to Ia-c on treatment with 2N sodium hydroxide solution.

(iii) The ir. spectrum of VIc reveals the presence of three carbonyl stretching frequencies at 1680, 1700, and 1780 cm^{-1} which are in agreement with the values observed for the C=O group of chromones [14], C=O of 2–quinolones [15] (fused oxygen rings in the 3,4–positions), and C=O carboxylic group respectively.

Bromination of Ib,c with bromine in acetic acid or chloroform resulted in the formation of monobromo derivatives for which the following possible structures were suggested.



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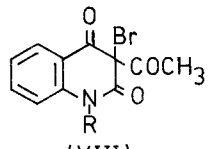
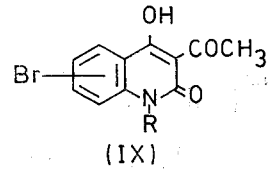


(VIII)



(IX)

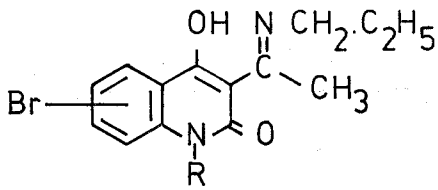
[R = C_2H_5 or C_6H_5]

Structures VII and VIII were eliminated on the ground of the following facts:

a) Refluxing the monobromo-derivatives with alcoholic potassium hydroxide left the material unchanged giving positive m-dinitrobenzene test [16].

b) The bromo derivatives condensed with one molecule of benzylamine in boiling ethanol to give a product containing bromine. The latter was readily reconverted to the starting material on boiling with dilute hydrochloric acid.

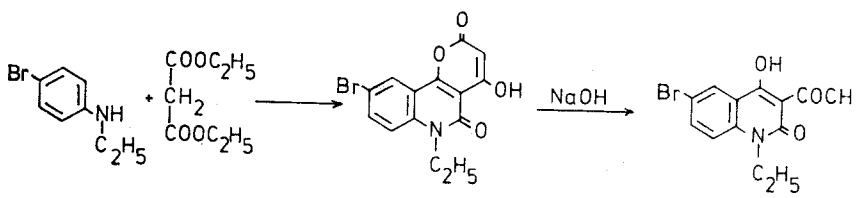
These evidences supports that substitution by the bromine atom took place in the aromatic ring and that the product obtained from the reaction of the monobromo derivatives with benzylamine was Schiff's base having structure Xa,b [17].



(X)

[R = (a) C_2H_5 or (b) C_6H_5]

The bromine atom in the bromo derivative IXa,b was proved to be in the 6–position. This was established through synthesis [11,17] by reacting p-bromo-N-ethylaniline with diethylmalonate in nitrogen atmosphere at the boiling point of the reaction mixture where XI was isolated, which upon hydrolysis with 2N sodium hydroxide gave IX (m.p. and m.m.p.).



(XI) (IXa)

EXPERIMENTAL

Melting points are uncorrected. The ir. spectra were obtained with a Perkin-Elmer Infracord Spectrophotometer model 1378 using KBr wafer technique.

1–Alkyl (or phenyl)–3–[4′(2′,4′–dioxobutyric ethyl ester)]–4–hydroxy carbostyrils; IIa-c:

Finally divided sodium (0 .25 mol.) was added portionwise, over a period of one hour, to a mixture of Ia-c (0 .05 mol) and dry diethyl oxalate (1 .15 mol.) previously heated to 150°C. The reaction mixture was kept at room temperature overnight, triturated with little ethanol and then poured into dilute hydrochloric acid. The solid product IIa-c was filtered, washed throughly with water and recrystallized from the proper solvent as a golden yelow crystals (cf. Table 1).

Table (1)

1–Alkyl (or phenyl)–3–*k*4′(2′,4′–dioxobutyric ethyl ester)]–4–hydroxy-carbostyrils

Compound	M.p. °C	Crystallization solvent	Yield %	Formula	Analysis (Required/Found)		
					C	H	N
IIa	130	Methanol	66	$C_{16}H_{15}NO_6$	60.56 60.50	4.73 5.00	4.41 4.70
IIb	131	Methanol	70	$C_{17}H_{17}NO_6$	61.63 61.63	5.13 5.00	4.23 4.71
IIc	186	Ethanol	73	$C_{21}H_{17}NO_6$	66.49 66.60	4.48 4.70	3.68 3.51

Action of sodium hydroxide on IIa-c

A solution of 0 .5 gm of IIa-c in 2N sodium hydroxide (5 ml) was allowed to stand at room temperature for 48 hr., acidified with dilute hydrochloric acid and the solid which formed was filtered off and crystallized from methanol to give Ia-c in 93 % yield (m.p. and m.m.p.).

3-(β-alkyl- or arylaminofumarylamide)-1-alkyl (or phenyl)-4-hydroxy-carbostyrils; IIIa-f: General procedure:

A solution of IIa-c (0 .002 mol.) in ethanol (10 ml) was treated with excess of the requisite amine (0 .005) mol.. The reaction mixture was refluxed for 4 hr., cooled, the crystalline product formed was filtered off and recrystallized from the proper solvent to give IIIa-f as yellow crystals (cf. Table 2).

Table (2)

3-((-Alkyl- or arylaminofumarylamide)-1-alkyl- (or phenyl)-4-hydroxy-carbostyrils

Compound	M.p. °C	Crystallization solvent	Yield %	Formula	Analysis (Required/Found) C	H	N
IIIa	151–152	Methanol	80	$C_{26}H_{21}N_3O_4$	71.07 70.86	4.78 4.92	9.56 9.29
IIIb	164	Methanol	71	$C_{26}H_{33}N_3O_4$	69.18 69.43	7.31 7.00	9.31 9.52
IIIc	167–168	Ethanol	76	$C_{27}H_{23}N_3O_4$	71.52 71.62	5.08 4.77	9.27 8.91
IIId	142.143	Ethanol	92	$C_{27}H_{35}N_3O_4$	69.67 69.76	7.52 7.38	9.03 9.25
IIIe	256	Dioxane	69	$C_{31}H_{23}N_3O_4$	74.25 74.00	4.59 4.93	8.38 8.11
IIIf	241	Dioxane	73	$C_{31}H_{35}N_3O_4$	72.51 72.30	6.82 7.02	8.19 8.42

1-Alkyl (or phenyl)-3-[5 (or 3)-formylhydrazide pyrazol-3 (or 5)-yl]-4-hydroxycarbostyrils, and 1-alkyl (or phenyl)-3-[5 (or 3)-formylphenyl-hydrazide-1-phenylpyrazol-3 (or 5)-yl]-4-hydroxycarbostyrils; IVa-f:

IIa-c (0 .002 mol.) was treated with hydrazine hydrate (or phenyl-hydrazine) (0 .004 mol.) in (10 ml) ethanol. The reaction mixture was refluxed for 4 hr., cooled, the solid which deposited was filtered off and recrystallized from the proper solvent to give IVa-f as colourless crystals (cf. Table 3).

1-Alkyl (or phenyl)-3-[5 (or 3)-hydroxamic formylisooxazol-3 (or 5)-yl]-4-hydroxycarbostyrils; Va-c:

To a solution of IIa-c (0 .002 mol.) in ethanol (10 ml.), hydroxylamine hydrochloride (0 .004 mol.) was added, and the reaction mixture was refluxed for 5 hr. The solid which separated on cooling was filtered off and crystallized from the proper solvent to give Va-c as colourless crystals (cf.Table 4).

Table (3)

1–Alkyl (or phenyl)–3–[5 (or 3–) formylhydrazide (or formylphenyl–hydrazide)–1–H (or phenyl) pyrazol–3– (or 5)–yl]–4–hydroxycarbostyrils.

Compound	M.p. °C	Cyrstallization solvent	Yield %	Formula	Analysis (Required/Found) C	H	N
IVa	227	Ethanol	69	$C_{14}H_{13}N_5O_3$	56.19 56.42	4.34 4.62	23.41 23.28
IVb	246–247	Dioxane	74	$C_{26}H_{21}N_5O_3$	69.18 69.54	4.65 5.00	15.52 15.73
IVc	214–215	Toluene	78	$C_{15}H_{15}N_5O_3$	57.51 57.77	4.79 4.92	22.36 22.45
IVd	234	Anisole	81	$C_{27}H_{23}N_5O_3$	69.68 69.96	4.94 4.59	15.05 15.00
IVe	301–302	DMF	65	$C_{19}H_{15}N_5O_3$	63.16 63.38	4.15 4.20	19.39 19.64
IVf	289–291	DMF	66	$C_{31}H_{23}N_5O_3$	72.51 72.55	4.48 4.54	13.64 13.49

Table (4)

1–Alkyl (or phenyl)–3–[5 (or 3–) hydroxamic formylisooxazol–3– (or 5)–yl]–4–hydroxycarbostyrils.

Compound	M.p. °C	Crystallization solvent	Yield %	Formula	Analysis (Required/Found) C	H	N
Va	227–228	Ethanol	73	$C_{14}H_{11}N_3O_5$	55.81 56.01	3.65 3.66	13.95 14.00
Vb	167–168	Ethanol	69	$C_{15}H_{13}N_3O_5$	57.14 56.99	4.13 4.25	13.33 13.31
Vc	283–284	Anisole	82	$C_{19}H_{13}N_3O_5$	62.81 62.62	3.58 3.54	11.57 11.30

6–Alkyl (or phenyl)–2–carboxylic–4–oxo [4H]—pyrano [3,2–c]–carbostyrils; VIa-c;:

General procedure: IIa-c (0.5 g.) was shaked with conc. sulphuric acid (6 ml.) for 15 min. The reaction mixture was poured into ice-cold water, and the solid which formed was filtered off and crystallized from the proper solvent to give VIa-c (cf. Table 5). Cyclization was also achieved in good yield when IIa-c was refluxed with ethanol-hydrochloric acid mixture for 1.5 hr.

Action of sodium hydroxide on VIa-c

VIa-c (0.2 gm) was refluxed with 2N sodium hydroxide (5 ml) for 30 min., the reaction mixture was then cooled, acidified with dilute

Table (5)

6-Alkyl (or phenyl)-2-carboxylic-4-oxo [4H]-pyrano [3,2-c] carbostyrils

Compound	M.p. °C	Crystallization solvent	Yield %	Formula	Analysis (Required/Found) C	H	N
VIa	237	Acetic acid	75	$C_{14}H_9NO_5$	61.99 62.14	3.32 3.44	5.17 5.00
VIb	209	Acetic acid	76	$C_{15}H_{11}NO_5$	63.16 63.25	3.86 3.59	4.91 5.21
VIc	280	Acetic acid	69	$C_{19}H_{11}NO_5$	68.47 68.46	3.30 3.44	4.20 4.13

hydrochloric acid and the product which separated was filtered off to give Ia-c in 90–92 % yield (m.p. and m.m.p.).

Preparation of 3-acetyl-6-bromo--1-ethyl (or phenyl)-4-hydroxy-carbostyrils; IXa,b:

a) **Through bromination of Ib and c**

To a solution of Ib,c (0 .005 mol.) in glacial acetic acid (5 ml.), bromine (0 .005 mol.) was added dropwise with shaking. The reaction mixture was left at room temperature overnight, and the yellow crystals which formed were collected, washed with ethanol and recrystallized from the proper solvent to give the titled compounds (IXa,b) (cf. Table 6).

Table (6)

3-Acetyl-6-bromo-1-ethyl (or phenyl)-4-hydroxycarbostyrils

Compound	M.p. °C°	Crystallization solvent	Yield %	Formula	Analysis (Required/Found) C	H	Br	N
IXa	163	dioxane	82	$C_{13}H_{12}BrNO_3$	50.32 50.55	3.87 3.82	25.80 25.77	4.52 4.73
IXb	256	Acetic acid	86	$C_{17}H_{12}BrNO_3$	56.98 56.73	3.35 3.34	22.35 22.51	3.91 4.00

b) **From p-bromo-N-ethylaniline**

A mixture of p-bromo-N-ethylaniline (5 ml) and diethylmalonate (25 ml) was heated in nitrogen atmosphere for 6 hr., the ethanol formed was allowed to escape freely through a short column. The reaction mixture was cooled and the solid precipitated was washed with petroleum ether, it was then stirred in boiling ethanol (20 ml.) and the insoluble

material was separated by filtration and crystallized from anisole to give 9–bromo–5, 6–dihydro–4–hydroxy–2, 5–dioxo–6–ethyl–[2H]–pyrano–[3,2–c] quinoline; XIa as yellow crystals, yield %, m.p. 289–291°C. Anal. Calcd. for $C_{14}H_{10}BrNO_4$: C, 50.00; H,2.98; Br, 23.81; N, 4.16. Found: C, 49.95; H, 2.87; Br, 23.74; N, 4.16.

XIa (1 gm) was refluxed with 10 ml of 2N sodium hydroxied solution for 2 hr. After cooling, the reaction mixture was filtered and the filtrate was acidified with dilute hydrochloric acid. The solid formed was collected and crystallized from dioxane to give IXa (m.p. and m.m.p.).

Formation of 3–(1–*benzylimincethyl*)–6–*bromo*–1–*ethyl* (*or phenyl*)–4–*hydroxycarbostyrils; Xa,b:*

A mixture of IXa,b (0.002 mol), benzylamine (0.0025 mol), and ethanol (5 ml) was heated until it became clear then allowed to stand at room temperature overnight. The pale-yellow crystals formed were filtered off and recrystallized from the proper solvent to give the titled compounds; Xa, b as pale yellow needles (cf. Table 7). On refluxing Xa,b in ethanol (7 ml) and conc. hydrochloric acid (3 ml) for 4 hr., the product obtained after crystallization was identified as IXa,b (m.p. and m.m.p.); yield 94 %.

Table (7)

3–(1–Benzyliminoethyl)–6–bromo–1–ethyl (or phenyl)–4–hydroxycarbostyrils

Compound	M.p. °C	Crystallization solvent	Yield %	Formula	Analysis (Required/Found)			
					C	H	Br	N
Xa	182	Methanol	79	$C_{20}H_{19}BrN_2O_2$	60.15 60.23	4.76 4.64	20.05 20.18	7.02 6.98
Xb	264–265	Ethanol	80	$C_{24}H_{19}BrN_2O_2$	64.43 64.80	4.25 4.00	17.90 17.88	6.26 6.32

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