Physical Sciences Section

Pak j. sci. ind. res., vol.37, no. 5, May 1994

HALO DERIVATIVES OF 1, 10-PHENANTHROLINE

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(Received November 7, 1992; revised December 5, 1993)

Halogenation of 4, 7-dihydroxy-1, 10-phenanthrolin-2, 9-dione has been studied using different halogenating agents under different conditions. The halo compounds so obtained were reacted with some chemical reagents, with the purpose of establishing their compositions. The structures of all the newly obtained compounds were confirmed by elemental analysis, IR and ^{1}H-NMR spectroscopic studies.

Key words: 1, 10-Phenanthrolines, Halogenation, Pyridocorbostyrils.

Introduction

It was reported in the literature that compounds having a carbostyril moiety have been found to be biologically active and are of industrial importance. This has led to intensive research to synthesize a number of members of this class of compounds [1-6]. We have previously reported some approaches to the synthesis such compounds [7-11]. In order to improve the biological activity and study the role of carbostyrils we had developed a new method in which carbostyril was fused to pyridone, i.e., we synthesized new starting materials for the preparation of new members of this important class of compounds, wherein a benzene ring was fused to two pyridone rings instead of one as in case of carbostyrils.

Experimental

Melting points are uncorrected and were measured on an electrical melting point apparatus MFB 590 010T (Griffin). I R spectra were recorded on a Pye Unicam SP 3-300 spectrophotometer using the KBr disc technique. The ^{1}H-NMR spectra were determined on a Varian EM-360 (60 MHz) NMR spectrometer. In all NMR experiments, the internal standard was TMS, all the chemical shifts are given in ppm are the solvent used was DMSO-ds. The physical data of new synthesized compounds are listed in Table 1.

Synthesis of 4, 7-dihydroxy-1, 10-phenanthroline-2, 9-dione 1. A solution of o-phenylenediamino (0.1 mol) in diethyl malonate (0.22 mole) was added in portions to 60 g of polyphosphoric acid (PPA) (prepared from 38.6 g of P_2O_5 and 21.4 ml of orthophosphoric acid). The deep pasty mass so obtained was heated at 170° for 30 mins and then at 200° for an additional 30 mins. The mixture was cooled poured into cold water and the resulting solution neutralized with 5% NaOH solution. The precipitate was filtered off, dried and crystallized to give (1).

3,3,8,8-Tetrachlorophenanthrolin-2,4,7,9-tetraone 2. A sloution of (1) (1 g) in a hot mixture of dioxan (7.5 ml), concentrated hydrochloric acid (5 ml), and water (1.5 ml) was cooled and treated with hydrogen peroxide (30%, 6.7 ml). The orange solution was poured into an aqueous solution of sodium carbonate to give an orange precipitate. The precipitate was filtered off, washed thoroughly with cold water, dried and crystallized to afford the tetrachloro derivative (2).

2,4,7,9-Tetrachloro-1,10-phenanthroline 3. A mixture of (1) (1 g) and phosphorus oxychloride (10 ml) was heated at 100° for 5 hrs, cooled and poured onto crushed ice. The green solid deposite was collected, washed with water, dried and crystallized to give (3).

3,8-Dibromo-4,7-dihydroxy-1,10-phenanthrolin-2,9-dione 4. Bromine (1 ml) was added dropwise to a hot solution of (1) (08 g) in formic acid (10 ml) and the mixture was diluted with cold water. The orange solid so obtained was filtered off, washed with water and crystallized to give (4).

3,5,6,8-Tetrabromo-4,7-dihydroxy-1,10-phenanthrolin-2,9-dione 5. Bromine (~0.5 ml) was added dropwise to a boiling solution of (1) (1 g) in a mixture of dioxan (4 ml) and hydrobromic acid (5 ml) until a yellow colour persisted. The mixture was then boiled for further 15 mins, cooled, diluted with cold water, and the deposited solid was filtered off. The product was dried and crystallized to give compound (5).

3,3,5,6,8,8-Hexabromo-1,10-phenanathrolin-2,4,7,9-tetraone 6. Bromine (0.4 ml) was added dropwise to a stirring solution of (1) (1 g) in aqueous dioxan (10 ml in 5 ml H_2O). The reaction mixture was warmed at 48° for 5 mins, poured into ice/cold water and the precipitate was collected. Crude (6) was washed with water, dried and purified by crystallization.

Conversion of 5 into 6. Bromine was added dropwise (0.5 ml) to a solution of (5) (0.4 g) in aqueous dioxan until a yellow colour persisted. The mixture was warmed at 48° for 5 min, poured onto ice/cold water, and the product dried and crystallized from acetic acid to gives (6) (m.p. and mixed m.p.).

TABLE 1. PHYSICAL AND SPECTROSCOPIC DATA OF THE NEWLY SYNTHESIZED COMPOUND.

Comp.	Yield %	M.P. °C	Srystn. solvent	Molecular formula Molecular wieght	IR (KBr) υ cm^{-2}	^{1}H-NMR (DMSO-ds/TMSint.), δ ppm.
1.	85	315-6	EtOH	$C_{12}H_8N_2O_4$ (244)	3400 (NH), 3050 (Ar & olefinic C-H), 2600 (br, H-bonded OH) & 1680-1615 (C=O)	10.5 (s 4H 4OH), 7.7-6.9 (m, 4H Ar.) and 4.5 (of less intensity, i.e. lower integration; protons at positions 3 and 8
2.	70	>350	aq.DMF	$C_{12}H_4N_2O_4Cl_4$ (382)	3400 (N), 1650 & 1615 (C=O) and 1220 (st, C-Cl)	
3.	40	284-6	Benzene	$C_{12}H_4N_2Cl_4$ (318)	3040 (Ar C-H) & 1035 (st., C-Cl)	
4.	59	255-6	Benzene	$C_{12}H_6N_2O_4Br_2$ (402)	3400 (NH), 3050 (Ar C-H), 2600 (br H-Bonded OH), 1650 (C=O) & 1220 (st, C-Br)	
5.	61	>350	aq.DMF	$C_{12}H_4N_2O_4Br_4$ (560)	3360 (NH), 2660 (br H-bonded OH), 1640 (C=O) & 1210 (st., C-Br).	
6.	75	>350	AcOH	$C_{12}H_2N_2O_4Br_5$ (718)	3400 (NH), 1615 (C=O) & 1220 (C-Br)	
7.	74	282-4	aqEtOH	$C_{12}H_6N_2O_4I_2$ (496)	3360 (NH), 3030 (Ar C-H), 2660 (H-bonded OH) & 1615 (C=O)	7.7-6.9 (m, Ar. protons at positions 5 & 6)
8.	50	>350	EtOH	$C_{20}H_{24}N_2O_8$ (420)	3440 (NH), 3060 (Ar C-H), 1665 &1635 (C=O)	
9.	63	>350	EtOH	$C_{36}H_{24}N_2O_8$ (612)	3400 (NH), 3040 (Ar C-H), 1670 & 1640 (C=O)	
10.	75	>350	EtOH	$C_{16}H_{16}N_6O_4$ (356)	3600-2600 (grp. of br bands (NH), 3050 (Ar C-H), 2940 (aliph C-H), 1660 & 1615 (C=O)	7.9-7.2 (m, 2H, Ar.), 3.5(t, 8H, 4 CH_2 grps. of the two imidazolidine rings), 2.3 (t , 4H, 4NH)
11.	60	>350	aq.AcOH	$C_{20}H_{32}N_{10}O_4$ (476)	3600-2400 (br NH_2, NH, Ar. C-H & aliph. C-H), 1665 & 1630 (C=O)	7.9-7.3 (m, 2H, Ar.), 3.3 (t, 16H, 8 CH_2 grps) & 2.4 (t, 12H, NH_2 & NH of the amino grps.)
12.	50	>350	aq.EtOH	$C_{26}H_{28}N_4O_4$ (450)	3400 (NH), 3050 (Ar C-H), 2960 (aliph, C-H), 1655 & 1635 (C=O) & 1585 (C=N of the dianil grp.)	
13.	50	237-9	MeOH	$C_{26}H_{20}N_4O_4Cl_2$ (523)	3410 (NH), 3065 (Ar C-H), 2920 (aliph C-H), 1660 & 1630 (C=O)	
14.	50	>350	AcOH	$C_{18}H_{20}N_4O_4Cl_2$ (427)	3600-2800 (br, NH grps. Ar & aliph C-H), 1660 & 1615 (C=O)	
15.	88	>350	DMF	$C_{12}H_8N_6O_4$ (300)	3600-2800 (br, NH_2, NH & C-H), 1665 & 1640 (C=O) & 1590 (Oxocyclic C=N)	
16.	87	>350	AcOH	$C_{24}H_{16}N_6O_4$ (452)	3600-2800 (br. NH &Ar C-H), 1660 & 1635 (C=O) & 1590 (Oxocyclic C=N)	7.9-7.2 (m, 2H, Ar.), 2.8 (s, 2H, 2NH) & 2.5 (s, 4H, 2 NH_2)
17.	45	270-2	aq.AcOH	$C_{12}H_6N_2O_4Cl_2$ (313)	3600-2400 (br NH, Ar C-H &H-bonded OH) & 1645 (C=O)	
18.	83	256-7	aq.EtOH	$C_{10}H_4N_2O_4$ (216)	3340 (NH), 3040 (Ar C-H), 1670 & 1610 (C=O)	7.9-7.1 (m, 2H, Ar-protons)
19.	90	300-2	aq.DMF	$C_{12}H_6N_4O_5$ (302)	3320 (NH), 3200 (OH of nitroso), 3050 (Ar C-H), 1660 & 1615 (C=O)	8-7.3 (m, 2H, Ar-protons)

* All the synthesized compounds 1-19 gave satisfactory elemental analysis, C, H & N and also halogen if present.

4,7-Dihydroxy-3, 8-diiodo-1, 10-phenanthrolin-2, 9-dione 7. A solution of (I_2) (1.7 g) in dioxan (10 ml) was added dropwise with stirring to a boiling solution of compound (1) (0.5 g) in aqueous sodium carbonate solution (0.6 g in 12.5 ml H_2O) until a yellow colour persisted in the solution. The solution was then acidified with acetic acid at 5° and the solid was filtered off, washed with water, dried and crystallized to give (7).

3, 3, 8, 8-Tetraethoxy-1, 10-phenanthrolin-2, 4, 7, 9-tetraone 8. An alcoholic solution of sodium ethoxide (sodium, 0.28 g and ethanol, 5 ml) was added to a suspension of 2 (1 g) in absolute ethanol (10 ml) and the mixture was warmed at 60° for 30 mins. Acidification of the reaction mixture at 0° with dilute hydrochloric acid (6N, 5 ml) yielded a brown solid which was filtered and crystallized to give 8.

3, 3, 8, 8-Tetraphenoxy-1, 10-phenanthrolin-2, 4, 7, 9-tetraone 9. An alcoholic solution of sodium methoxide (sodium (0.3 g) and methanol (12 ml) was added to a mixture of compound 2 (1 g), phenol (3 g) and dry toluene (12 ml), and the mixture was heated on a water bath for 30 mins, cooled and treated with concentrated HCl (1.5 ml) and ethanol (7 ml). The solid which separated was filtered off and crystallized to give (9).

Spiro [1, 10-phenanthrolin-2, 4, 7, 9-tetraone-3, 2'-8, 2"-diimidazolidine] 10. A mixture of (2) (0.001 mol) and ethylenediamine (0.002 mol) was heated at 100° for 30 mins. The

mixture was triturated with cold dil. HCl and the crude product filtered off, washed with water, and crystallized to give (10).

3, 3, 8, 8-Tetra (aminoethyleneamino)-1, 10-phenanthrolin-2,4,7,9-tetraone 11. Amixture of (2) (0.001 mol) and ethylenediamine (0.004 mol) was heated at 100° for 30 mins. The solid product obtained after trituration with dilute hydrochloric aid was filtered off, washed with water and crystallized to give (11).

3, 8-(Diaminobenzyl)-1, 10-phenantholin-2, 4, 7, 9-tetraone 12. The tetrachloro compound (2) (0.007 mol) was fused with benzylamino (0.002 mol) at 100° for 30 mins. The mixture was cooled, triturated with cold diluted hydrochloric acid to yield a solid which was filtered off, washed with water, dried and crystallized to give (12).

3, 8-Dichloro-3, 8-dimethylanilino-1, 10-phenanthrolin-2,4,7,9-tetraone 13. A mixture of (2) (0.001 mol) and *N*-methylaniline (0.002 mol) in ethanol (15 ml) was refluxed for 2 hrs. Concentration of the solution afforded a solid which was collected and crystallized from methanol to yield (13).

3,8-Dichloro-3,8-dipropylamino-1,10-phenanthrolin-2,4,7,9-tetraone 14. A mixture of (12) (0.002 mol) and *n*-propylamine in ethanol (15 ml) was refluxed for 2 hrs. The solid obtained, upon cooling, was collected and crystallized to yield (14).

3,8-Dihydrazone-1,10-phenanthrolin-2,4,7,9-tetraone 15. A mixture of (2) (0.001 mol) and hydrazine hydrate (0.002 mol) and ethanol (15 ml) was refluxed for 2.5 hrs. The solid product obtained was filtered off, and crystallized to yield (15).

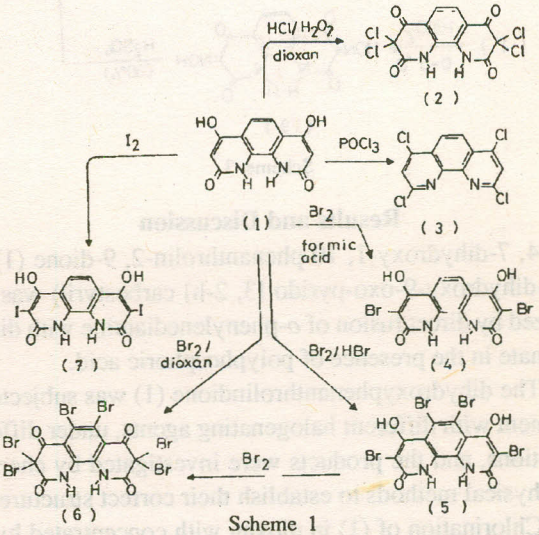
3,8-Diphenylhydrazone-1,10-phenanthrolin-2,4,7,9-tetraone 16. A mixture of compound (2) (0.001 mol) and phenylhydrazine (0.002 mol) in ethanol (15 ml) was refluxed for 2 hrs. The mixture was concentrated to afford a solid, which was collected, and crystallized to give (16).

Effect of sodium hydroxide on 2. A stirred mixture of compound (2) (1.4 g) and aqueous sodium hydroxide (2N, 22.1 ml) was heated at a temperature lower than the boiling point, for 30 mins. The hot mixture was filtered and the insoluble solid was identified as the tetrachloro compound (2). The pale brown filtrate was neutralized with acetic acid to give a yellow solid which was filtered off, washed with cold water, dried, and crystallized to afford (17).

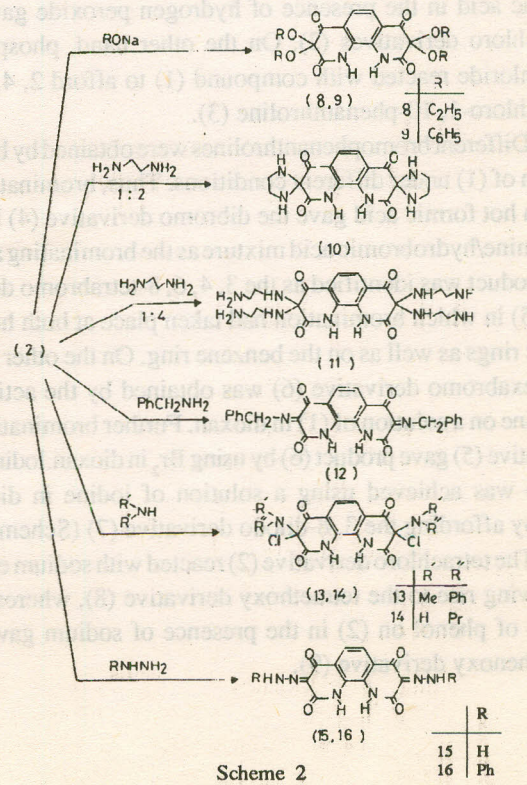
A mixture of (2) (1.2 g) and aqueous sodium hydroxide (2N, 9.8 ml) was refluxed for 2.5 hrs. The solution was cooled and the solid was collected by filtration, washed throughly with water, dried and crystallized to yield (18) (m. p. and mixed m.p.). The mother liquor was neutralized with acetic acid to give (17).

3, 8-diisonitroso-1, 10-phenanthrolin-3, 8-diylidene-2, 4, 7, 8-tetraone 19. A solution of compound (1) (0.5 g) in ethanol (10 ml) treated with sulphuric acid (20%; 10 ml) and cooled to 0-5°. A solution of sodium nitrate (0.5 g in 12 ml water) was added, the reaction mixture was left at room temperature for 2 hrs. The brown solid deposited was filtered off, washed with water and crystallized to give (19).

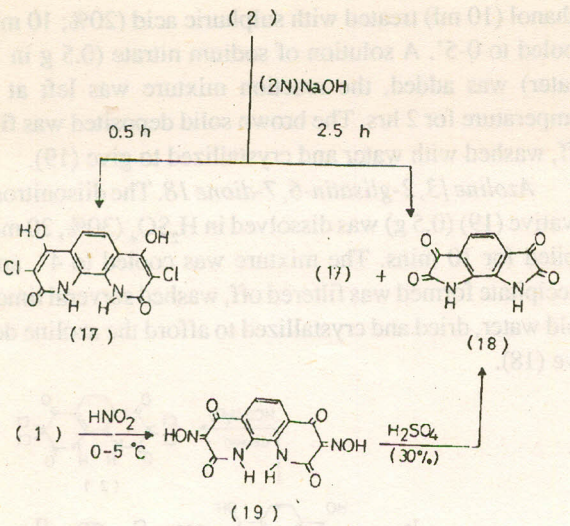
Azoline [3,2-glisatin-6,7-dione 18. The diisonitroso derivative (19) (0.5 g) was dissolved in H_2SO_4 (30%, 20 ml) and boiled for 10 mins. The mixture was cooled to 4°, and the precipitate formed was filtered off, washed serveral times and cold water, dried and crystallized to afford the azoline derivative (18).



Scheme 1



Scheme 2



Scheme 3

Results and Discussion

4, 7-dihydroxy-1, 10-phenanthrolin-2, 9-dione (1) and (4, 7-dihydroxy-9-oxo-pyrido [3, 2-h] carbostyril) was synthesized by direct fusion of *o*-phenylenediamine with diethyl malonate in the presence of polyphosphoric acid.

The dihydroxyphenanthrolindione (1) was subjected to treatment with different halogenating agents, under different conditions, and the products were investigated by chemical and physical methods to establish their correct structures.

Chlorination of (1) in dioxan with concentrated hydrochloric acid in the presence of hydrogen peroxide gave the tetrachloro derivatives (2). On the other hand, phosphorus oxychloride reacted with compound (1) to afford 2, 4, 7, 9-tetrachloro-1, 10-phenanthroline (3).

Different bromophenanthrolines were obtained by bromination of (1) under different conditions. Thus, bromination of (1) in hot formic acid gave the dibromo derivative (4) Using a bromine/hydrobromic acid mixture as the brominating agent, the product was identified as the 3, 4, 6, 8-tetrabromo derivative (5) in which bromination had taken place at both heterocyclic rings as well as on the benzene ring. On the other hand, the hexabromo derivative (6) was obtained by the action of bromine on a solution of (1) in dioxan. Further bromination of derivative (5) gave product (6) by using Br_2 in dioxan.Iodination of (1) was achieved using a solution of iodine in dioxan, thereby affording the 3, 8-diiodo derivative (7) (Scheme1).

The tetrachloro derivative (2) reacted with sodium ethoxide giving rise to the tetraethoxy derivative (8), whereas the action of phenol on (2) in the presence of sodium gave the tetraphenoxy derivative (9).

When the reaction of (2) with ethylenediamine was carried out using a ratio of 1:2, the product was the spiro compound (10), whereas when the reaction was carried out using a ratio of 1:4, the product was the tetra-amino derivative (11). Heating of the tetrachloro derivative (2) with benzylamine give the dianil derivative (12).

N-Methylaniline reacted with the tetrachloro compound (2) to give the 3, 8-dichloro-3, 8-diamino derivative (13). Substitution of only two chlorine atoms by two amino groups may be attributed to steric hindrance of the bulky $-N(CH_3)C_6H_5$ group which prevents attack of a second molecule of the amine, at each reactive sites. Similarly, reaction of (2) with *n*-propylamine in ethanol using a ratio of 1:2 afforded the dichloro-diamino derivatives (14).

Reactions of (2) with hydrazine hydrate and phenylhydrazine gave rise to the dihydrazone and the diphenylhydrazone derivatives (15) and (16), respectively (Scheme 2).

Heating of (2) with a 2N solution of sodium hydroxide for 0.5 hrs. gave rise to the dichloro compound (17) while refluxing for a longer time afforded a mixture of (17) and the isatin derivative (18). Compound (18) was also obtained by reacting (1) with nitrous acid and treating the oxime (isonitroso) (19) with 30% sulphuric acid (Scheme 3).

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