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Synthesis of some 1,10-Phenanthroline Derivatives

E A. MOHAMED*, A. M. TAWFIK and J. M. MORSY

Department of Chemistry, Faculty of Education, Ain-Shams University, Roxy, Cairo, A. R. Egypt

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4,7-Dihydroxy-1,10-phenanthrolin-2,9-dione (1), has been synthesised and subjected to alkylation, acylation and some other reactions. These reactions studied under different conditions gave rise to di- or tetra-, O-, N- or C-acyl or alkyl derivatives and other products.

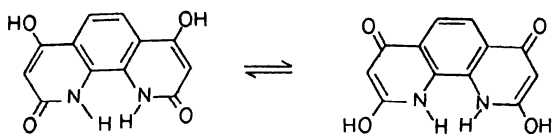
The biological activity and industrial applications of carbostyrils led to intensive research to synthesise a number of compounds[1] of this class. We reported earlier some approaches to synthesise such compounds[2]. The aim of the present work is to synthesise carbostyril moiety fused to pyridone ring, a new class of heterocyclic compounds, which may have improved pharmaceutical properties.

Results and Discussion

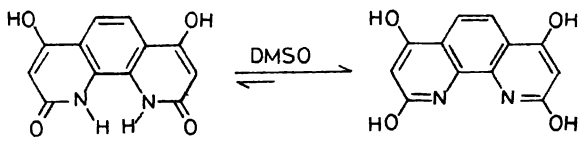
4,7-Dihydroxy-1,10-phenanthrolin-2,9-dione (**1**) (4,7-dihydroxy-9-one pyrido[3,2-*h*]carbostyril) was synthesised by heating a mixture of *o*-phenylenediamine, diethylmalonate and polyphosphoric acid. Compound **1** is a symmetric molecule, and hence in the course of the present work, it was found that each of the following pairs of centers (1,10), (2,9), (3,8), (4,7) and (5,6) are equivalent and have similar reactivity.

The ir spectrum of compound **1** (Table 1) just like that of 4-hydroxycarbostyril and related compounds[3] showed that it does not display a normal absorption peak of free OH vibration, but showed a broad band centered at ~2 600 cm^{-1} due to the formation of intermolecular OH...O and OH...N hydrogen bonds. The appearance of two peaks at 1 680 and 1 615 cm^{-1} is due to α-, γ-transannular tautomerism.

The ^1H nmr spectrum of **1** (Table 1) showed that this compound in DMSO is present mainly in the form of tetrahydroxy isomer.



The reaction of **1** with benzyl chloride was studied under different conditions and at different ratios of the reactants. When the reaction was carried out in aqueous sodium hydroxide in the ratio 1 : 2, the resulting product was the dibenzyl derivative (**2**). While at the ratio 1 : 4, the product was the tetrabenzyl derivative (**3**). Upon carrying out the reaction of **1** with benzyl chroride in presence of potassium carbonate at the ratio 1 : 2, the product was the dibenzyloxy derivative (**4**). When the latter reaction was carried out at the ratio 1 : 4 or even using excess of benzyl chloride, one and the same product (**4**)



was obtained, which can be explained by the fact that the C=O amide at positions 2 and 9 became very inactive and not able to be tautomerised to OH group for further alkylation (vide ir data of **4** shows C=O amide band and reveals the absence of OH). Similarly, ethyl chloroacetate reacted with compound **1** in presence of potassium carbonate to give **5**. 4,7-Diacetoxy-1,10-phenanthrolin-2,9-dione (**6**) was obtained by action of acetic anhydride on **1** in presence of

piperidine. Chloromethylation of the starting material took place at positions 3 and 8, when formaldehyde-hydrochloric acid mixture was used in presence of zinc chloride, affording the dichloromethyl derivative (**7**). It is of great interest to prepare acyl derivatives of the phenanthrolindione **1**. Thus, the diacetyl derivative (**8**) was obtained upon treating **1** with acetic anhydride in presence of polyphosphoric acid, whereas the diformyl derivative (**9**) was produced when **1** was reacted with dimethylformamide in presence of phosphorous oxychloride (Scheme 1).

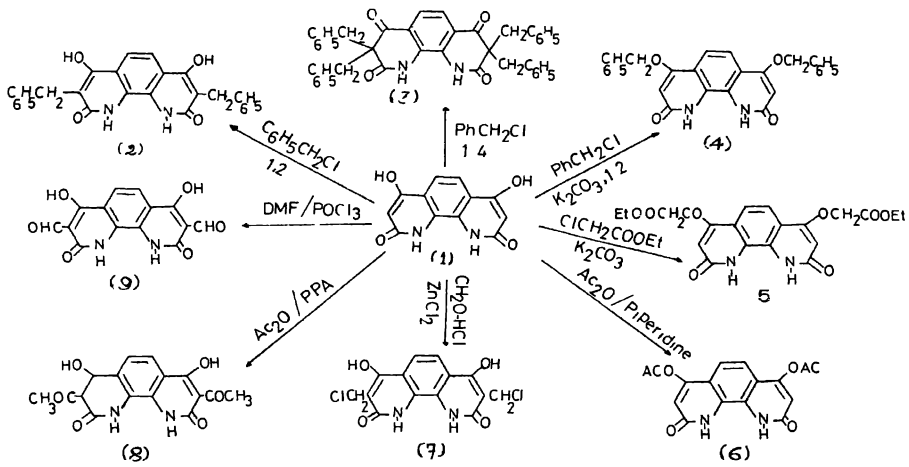
TABLE 1–SPECTRAL DATA OF COMPOUNDS **1–17***

Compd. no.	ν_{max} cm^{-1}	δ
1	3 400 (NH), 3 050 (Ar. and olefinic C-H), 2 600 (br. H-bonded OH), 1 680–1 615 (C=O), 2 000–1 700 (overtone; summation bands), 1 500–1 600 (ring vib. involving C=C), 860–730 (Ar. C-H out-of-plane deformation)	10.5 (4H, s, 4OH), 7.7–6.9 (4H, m, ArH), 4.5 (of less intensity i.e. of lower integration. of the protons at positions 3, 8)
2	3 400 (NH), 3 050 (Ar. C-H), 2 940 (C-H of CH_2 grps.), 2 740 (H-bonded OH), 1 615 (C=O)	10.9 (4H, s, 4OH), 7.8–6.8 (12H, m, ArH) and 2.6 (4H, s, $2CH_2$)
3	Absence of OH vib. peak, 3 440 (NH), 2 820 (C-H of CH_2 grps.), 1 625 (C=O)	7.6–6.7 (22H, m, ArH), 2.4 (8H, s, $4CH_2$)
4	Absence of OH vib. peak, 3 450 (NH), 3 060 (Ar. C-H), 2 920 (C-H of CH_2 grps.), 1 625 (C=O)	7.9–6.6 (12H, m, ArH), 5.2 (2H, s, at positions 3, 8), 4.45 (4H, s, 2-OCH_2 Ph.)
5	Absence of OH vib. peak, 3 405 (NH), 3 060 (Ar. C-H), 2 930 (C-H aliph.), 1 730 (C=O ester), 1 615 (C=O)	7.9–6 6 (2H, m, ArH), 5.8 (2H, s, at positions 3, 8), 3.8 (4H, q, $2CH_2$ of ester) 4.4 (4H, s, $2CH_2$ ester), 1.1 (6H, t, $2CH_3$)
6	Absence of OH vib. peak, 3 440 (NH), 3 050 (Ar. C-H), 2 940 (C-H aliph.), 1 670 (C=O ester), 1 620 (C=O)	7.9–6.7 (2H, m, ArH), 5.8 (2H s, at positions 3, 8) 2.4 (6H, s, $2CH_3$)
7	3 480 (NH), 3 040 (Ar. C-H), 2 940 (aliph. C-H), 2 760 (br, H-bonded OH), 1 625 (C=O)	7.9–6.9 (2H, m, ArH), 3.4 (4H, s, $2CH_2$)
8	3 400 (NH), 3 040 (Ar. C-H), 2 920 (C-H aliph.), 2 615 (H-bonded OH), 1 660 (C=O of the acetyl grp.), 1 615 (C=O)	7.5–7.1 (2H, m, ArH), 3.1 (6H, s, $2CH_3$)
9	3405 (NH), 3050 (Ar. C-H), 2 600 (br, H-bonded OH), 1665 (C=O of the formyl grps.), 1 615 (C=O)	9.7 (2H, s, 2CHO), 7.7–6.7 (2H m, ArH)
10	3 440 (NH), 3 050 (Ar. C-H), 1665 (C=O at positions 4,7), 1625 (C=O at positions 2, 9), 1590 (C=C conj. with two C=O)	7.8–6.9 (m, ArH and olefinic protons)
11	Absence of peak due to OH grps. at positions 4, 7, 3 320 (NH), 3 200 (OH of isonitroso grps.). 3 050 (Ar. C-H), 1 660 (C=O at positions 4, 7), 1 615 (C=O at positions 2, 9)	7.9–7.2 (m, ArH)
12	Absence of peak due to isonitroso OH grp.. 3 340 (NH), 3 040 (Ar. C-H), 1670 (C=O at positions 3, 6) 1 610 (C=O at positions 2, 7)	7.9–7.1 (m. ArH)
13	3 425 (NH), 3 050 (Ar. C-H), 2660 (br. H-bonded OH), 1 610 (C=O)	7.7–7.1 (m, ArH)
14	Absence of NH vib. peak, 3 050 (Ar. C-H). 2 985 (C-H aliph). 2 680 (br. H-bonded OH). 1 615 (C=O)	12.7 (2H, br, 2OH, exchangeable with D_2O), 7.7–6.7 (2H, m, ArH), 3.5 (6H, s, $2CH_3$)
15	Absence of NH and OH vib. peaks, 3 040 (Ar.C-H), 2 940 (C-H aliph.), 1 615 (C=O)	7.6–6.8 (2H, m, ArH), 3.6 (6H, s, $2CH_3$-O), 2.9 (OH, s, $2CH_3$-N)
16	Absence of NH vib. peak, 3 050 (Ar. C-H), 2 940 (C-H aliph.). 2 680 (br. H-bonded OH), 1 615 (C=O)	
17	3600–2200 (br. H-bonded NH and NH_2 and Ar. C-H), 1 615 (C=O)	7.7–6.8 (2H, m, ArH), 4.6 (2H, s, at positions, 3, 8), 2.5 (4H. br $2NH_2$)

*All compounds gave satisfactory elemental analysis : C, H, N and also S and/or Cl if present.

The extent of the reactivity of the methylene groups of compound **1** at positions 3 and 8 was examined by testing the action of benzaldehyde of **1**, which readily afforded the dibenzal derivative (**10**).

This high reactivity of the methylene groups prompted us to react compound **1** with nitrous acid to obtain the di-isonitroso derivative (**11**). The latter compound when treated with 30% sulphuric acid underwent ring-opening and closure to produce the azolineisatine derivative (**12**). A polysulphide compound (**13**) was obtained from the reaction of **1** with thionyl chloride in dioxane. Methylation of compound **1** with different methylating agents yielded different products Using dimethysulphate, methylation took place at NH centers only, giving rise to *N,N*-dimethyl derivative (**14**). But when methyl iodide was used as a



Scheme 1

methylating agent, both NH and OH centers were affected leading to the formation of the tetramethyl derivative (**15**), which was readily hydrolysed to compound **14** by hydrochloric acid. Whereas the *N,N*-diethyl derivative (**16**) was obtained by action of triethylphosphate on the starting compound **1**.

Finally, the two hydroxy groups at positions 4 and 7 of compound **1** could be replaced by hydrazino groups by reacting **1** with hydrazine hydrate to give compound **17** (Scheme 2).

Experimental

Melting points are uncorrected and were measured on a MFB 590 010T (Griffin) apparatus. Ir spectra (KBr) were recorded on a Pye-Unicam SP 3-300 spectrophotometer and ^{1}H nmr spectra (DMSO-d_6) on a Varian EM-360 (60 MHz) spectrometer using TMS as internal standard.

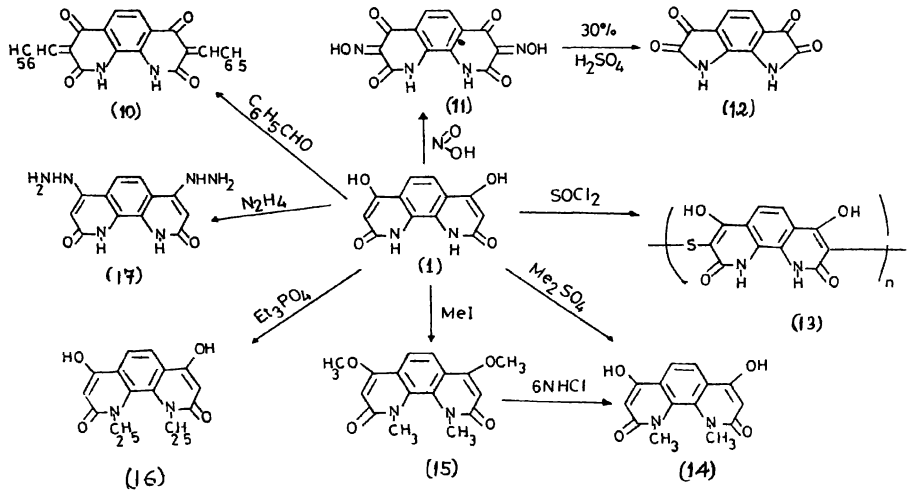
4,7-Dihydroxy-1,10 phenanthrolin-2,9-dione (**1**) : A solution of *o*-phenylenediamine (0.1 mol) in diethylmalonate (0.22 mol) was added portionwise to PPA (polyphosphoric acid, 60 g; prepared from 38.6 g of P_2O_5 and 21.4 ml of orthophosphoric acid). The deep green pasty mass so obtained was heated at 170° for 30 min and then at 200° for an additional 30 min. The reaction mixture was left to cool and poured into cold water. The solution obtained was neutralised by 5% NaOH solution, and the resulting solid was dried and crystallised (85%), m.p. 315–16°(EtOH).

3,8-Dibenzyl-4,7-dihydroxy-1,10-phenanthrolin-2,9-dione (**2**) : A mixture of compound **1** (0.004 mol), benzyl chloride (0.008 mol) and aqueous NaOH (4%; 2 ml) was heated at 100° for 3 h, then cooled and acidified by dilute HCl. The aqueous layer was decanted and the residual oily material was dissolved in methanol (3 ml) and left overnight in a refrigerator. The resulting solid was crystallised (43%), m.p. 242–43°(EtOH).

3,3,8,8-Tetrabenzyl-1,10-phenanthrolin-2,4,7,9-tetraone (**3**) : The same technique used in synthesis of **2**, was applied at the ratio of 1 : 4 of reactants to yield the product which was crystallised from MeOH, (47%), m.p. > 350°.

4,7-Dibenzyloxy-1,10-phenanthrolin-2,9-dione (**4**) : A mixture of compound **1** (0.004 mol), benzyl chloride (0.008 mol), anhydrous K_2CO_3 (0.2 g) and DMF (5 ml) was heated on a water-bath for 3 h. The reaction mixture was then cooled and poured into cold water. The aqueous layer was decanted and the residue was dissolved in methanol (5 ml) and kept overnight in a refrigerator and the resulting solid was crystallised from aqueous DMF, (30%), m.p. >350°.

4,7-Di(methylenoxycarboxylic ethyl ester)-1,10-phenanthrolin-2,9-dione (**5**) : A mixture of com-



Scheme 2

pound **1** (0.004 mol), ethyl chloroacetate (0.008 mol) and anhydrous K_2CO_3 (2 g) in dry acetone (50 ml) was refluxed on a water-bath for 36 h. Most of the solvent was then distilled off and the residual oil was dissolved in methanol and left overnight in a refrigerator and the resulting solid was crystallised from aqueous MeOH, (56%), m.p. 202–03°.

4,7-Diacetoxy-1,10-phenanthrolin-2,9-dione (**6**) : A mixture of the 1,10-phenanthroline derivative (**1**; 1 g) and acetic anhydride (10 ml) was refluxed for 3 h in presence of a few drops of piperidine. The solution obtained was cooled and poured into cold water. The solid product formed was crystallised to afford the titled compound (63%), m.p. >350 (aq. DMF).

3,8-Di(chloromethylenel)-4,7-dihydroxy-1,10-phyenanthrolin-2,9-dione (**7**) : To a mxiture of compound **1** (0.8 g), formaline (30%; 0.4 ml) and concentrated hydrochloric acid (2 ml), zinc chloride (1.2 g) was added with stirring at room temperature during a period of 30 min. The reaction mixture was then refluxed for 4 h, cooled and neutralised with aqueous NaOH (5%) solution to yield the chloromethylated product (74%), m.p. >350° (aq. AcOH).

3,8-Diacetyl-4,7-dihydroxy-1,10-phenanthrolin-2,9-dione (**8**) : A mixture of **1** (1 g), glacial acetic acid (5 ml) and polyphosphoric acid (31.5 g) (from 20 g phosphorous pentaoxide and 11.5 ml orthophosphoric acid) was heated at 100° for 2.5 h. The reaction mixture was then cooled, poured into ice-cold water and neutralised by aqueous sodium hydroxide (5%). The resulting solid was washed with water and crystallised (70%), m.p. 306–08° (MeOH).

3,8-Diformyl-4,7-dihydroxy-1,10-phenanthrolin-2,9-dione (**9**) : To a cooled stirred solution of **1** (0.004 mol) in DMF (30 ml), phosphorous oxychloride (0.01 mol) was added for a period of 1 h. The temperature was kept below 10° during addition with continuous stirring. The reaction mixture was then heated at 100° for 5 h, cooled and poured into ice-cold water. The resultingsolid wascrystallised (22%), m.p. > 350° (C_6H_6).

3,8-Dibenzal-1,10-phenanthrolin-3,8-diyliden-2,4,7,9-tetraone (**10**) : A mixture of 1,10-phenanthroline derivative **1** (0.004 mol) and benzaldehyde (1 ml) was fused at 150° for 4 h. The oily product was triturated with light petroleum ether, and the solid obtained was crystallised (41%), m.p. 294–96° (C_6H_6-pet. ether).

1,10-Phenanthrolin-3,8-diylidene-2,4,7,8-tetraone-3,8-dioxime(3,8-diisonitroso-1,10-phenanthrolin-3,8-diyliden-2,4,7,8-tetraone) (**11**) : A solution of compound **1** (0.5 g) in ethanol (10 ml) was treated with sulphuric acid (20%; 10 ml) and

cooled to 0.5%. A solution of sodium nitrile (0.5 g in 12 ml water) was added to it and the reaction mixture was left at room temperature for 2 h. The resulting brown solid was washed with water and crystallised (90%), m.p. 300–02° (aq. DMF).

Azoline(3, 2 g)isatin-6,7-dione(azoline-(3, 2 g)indolin-2,3,6,7-tetraone) (**12**) : The diisonitroso derivative (**11**; 0.5 g) was dissolved in H_2SO_4 (30%; 20 ml) and boiled for 10 min. The reaction mixture was then cooled to about 4° and the resulting solid was washed with cold water, dried and crystallised (83%), m.p. 265–67° (aq. EtOH).

Poly(4,7-dihydroxy-1,10-phenanthrolin-2,9-dione-3,8-di-yl)sulphide (**13**) : To a solution of **1** (1 g) in dioxane (5 ml), thionyl chloride (10 ml) was added, and the solution obtained was heated at 100° for 2 h. The excess $SOCl_2$ was then distilled off, the residue dissolved in methanol and left in a refrigerator to yield a reddish brown solid which was crystallised (91%), m.p. >350° (aq. MeOH).

4,7-Dihydroxy-1,10-dimethyl-1,10-phenanthrolin-2,9-dione (**14**) : To a stirred solution of compound **1** (1 g) in methanolic NaOH solution (1%; 10 ml), dimethylsulphate (0.1 ml) was added and the reaction mixture was then refluxed for 1 h. The resulting methanolic solution was concentrated, diluted with water and neutralised. The solid obtained was washed with water, dried and crystallised (84%), m.p. 332–34° (aq. MeOH).

4,7-Dimethoxy-1,10-dimethyl-1,10-phenanthrolin-2,9-dione (**15**) : A mixture of compound **1** (0.5 g), aqueous NaOH (20%; 2 ml), methanol (5 ml) and methyl iodide (2 g) was refluxed for 1 h. Additional amounts of MeI (1 ml) and aqueous NaOH (30%; 0.5 ml) were added and the refluxing was continued for further 1 h. After cooling, the crude product was filtered off, washed well with water, dried and crystallised (75%), m.p. 204–05° (C_6H_6).

Effect of 6N HCl on **15** : A solution of **15** (1 g) in 6*N* HCl (10 ml) was boiled for 3 h. The resulting solid was washed with water and crystallised to yield **14** (m.p., m.m.p.).

1,10-Diethyl-4,7-dihydroxy-1,10-phenanthrolin-2,9-dione (**16**) : Triethylphosphate (10 ml) was added to a solution of **1** (1 g) in DMF (10 ml) and the reaction mixture was refluxed for 3 h. The resulting solution was cooled, diluted with excess of water (20 ml), neutralised with $NaHCO_3$ solution and the resulting solid was crystallised (60%), m.p. 342–44° (C_6H_6-pet. ether).

4,7-Dihydrazino-1,10-phenanthrolin-2,9-dione (**17**) : A mixture of **1** (0.004 mol) and hydrazine hydrate (0.01 mol), in 1-butanol (20 ml) was refluxed for 6 h. The solid formed was washed with light petroleum ether, dried and crystallised (55%), m.p. 318–20° (C_6H_6).

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