55. The Synthesis of Some 1,8-Phenanthrolines and Related Compounds

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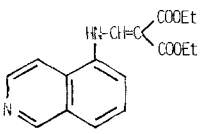
(2.VII.82)

Summary

The synthesis of ethyl 4-oxo-1,4-dihydro-1,8-phenanthroline-3-carboxylate (**2a**) and some other 1,8-phenanthrolines is reported. The ethylation of the above ester yields a thermochromic product **2b** and some ethyl 4-ethoxy-1,8-phenanthroline-3-carboxylate (**3b**). Reexamination of similar ethylations of analogous esters derived from 1,7-phenanthroline and 1,10-phenanthroline indicated formation of the *O*-ethyl derivative of the former and the *N*-ethyl derivative of the latter.

Some years ago the synthesis of benzoquinolines related to the antibacterial nalidixic acid was reported [1]. As an extension of that work the synthesis of *N*-ethyl-4-oxo-1,4-dihydro-1,8-phenanthroline-3-carboxylic acid (**2c**) and other experiments concerning related 1,7- and 1,10-phenanthrolines were carried out. Some of the compounds, *e.g.* **2d** may be anticoccidial [2].

For the synthesis of compound **2c**, 5-isoquinolinamine was condensed with diethyl ethoxymethylidenemalonate and the resulting diethyl 5-isoquinolinaminomethylidenemalonate (**1**) was thermally cyclized [3] to ethyl 4-oxo-1,4-dihydro-1,8-phenanthroline-3-carboxylate (**2a**). This ester was treated with ethyl iodide in DMF in the presence of K_2CO_3 [4] and two compounds of the elementary formula $C_{17}H_{16}N_2O_3$ were isolated. The predominant high-melting, yellow product is assumed to be ethyl *N*-ethyl-4-oxo-1,4-dihydro-1,8-phenanthroline-3-carboxylate



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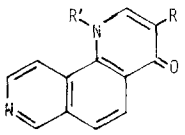

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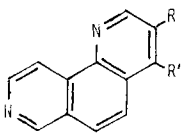
	R	R′
a	COOEt	H
b	COOEt	Et
c	COOH	Et
d	COOH	H
e	H	H



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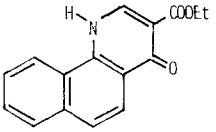
	R	R′
a	COOEt	Cl
b	COOEt	OEt
c	H	Cl
d	H	OEt



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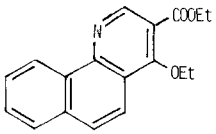

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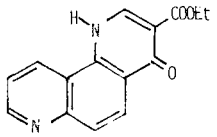

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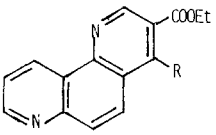

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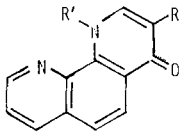
R

a Cl
b OEt



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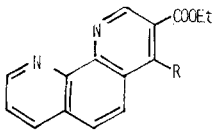
	R	R′
a	COOEt	H
b	COOEt	Et



9

R

a Cl
b OEt

(**2b**) which was saponified to the corresponding acid **2c**. The minor product of much lower m.p. and considerable solubility in solvents of moderate polarity was ethyl 4-ethoxy-1,8-phenanthroline-3-carboxylate (**3b**), the same compound being formed after conversion of ester **2a** to ethyl 4-chloro-1,8-phenanthroline-3-carboxylate (**3a**) and reaction of this compound with EtONa.

The yellow phenanthroline derivative **2b** is thermochromic [5]. In the solid state or in solution the compound changes its color reversibly from yellow to orange on temperature increase. In methyl *Cellosolve* an increase in temperature causes a decrease in absorbance between 400 nm and 430 nm, whereas between 430 and 510 nm an increase in temperature causes an increase in absorbance *(Fig. 1)*. Since there is a relatively large variation in absorbance with temperature at 470 nm, the relationship between temperature and %-transmittance was measured at this wavelength and was found to be essentially linear *(Fig. 2)*. Because of the unusual optical behavior of this compound measurements of absorbance *vs.* concentration at constant temperature were also made; these solutions obey *Beer*'s law.

The formation of the *N*-ethyl ester **2b** under the conditions described is somewhat surprising, since the ethylation of ethyl 4-oxo-1,4-dihydrobenzo[*h*]quinoline-3-carboxylate (**4**) under these conditions gave only ethyl 4-ethoxybenzo[*h*]quinoline-3-carboxylate (**5**) [6] suggesting prevention of *N*-ethylation by steric hindrance.

The ethylation of ethyl 4-oxo-1,4-dihydro-1,7-phenanthroline-3-carboxylate (**6**) [4] under the same conditions led to a compound with properties (m.p., solubilities) suggesting that *O*-ethylation had taken place. Indeed, the product was ethyl 4-ethoxy-1,7-phenanthroline-3-carboxylate (**7b**) since the same compound was obtained from **6** by conversion to the corresponding 4-chloroester **7a** and reaction of this compound with NaOEt. The acid prepared from ester obtained by this procedure has previously been assigned the structure of an *N*-ethyl compound and is incorrectly reported in a patent [4] as well as in a review [7] as structural analog of nalidixic acid.

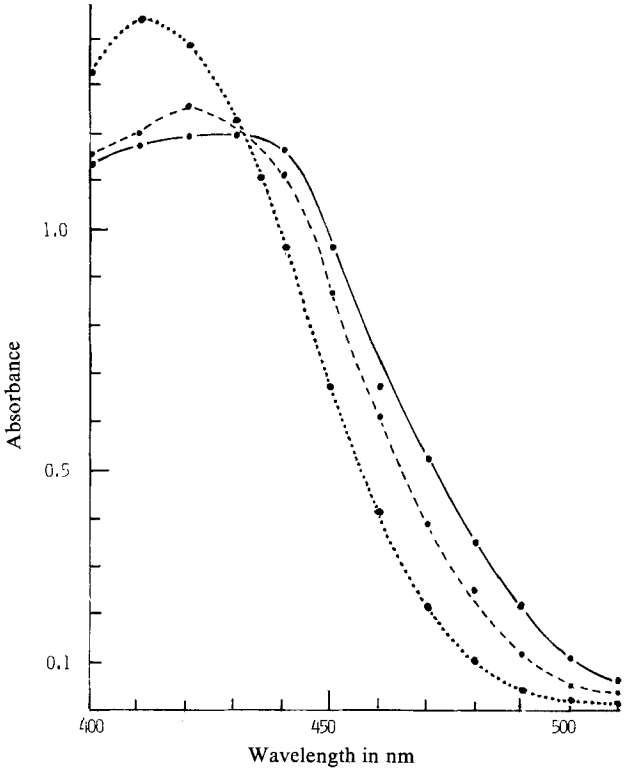


Fig. 1. *Absorbance* vs. *wavelength of a solution of compound* **2b** *in methyl* Cellosolve (conc. 108 mg/ml) *at various temperatures* (● · · · · · ● at 25°, ● - - - - - ● at 80°, and ●——● at 110°)

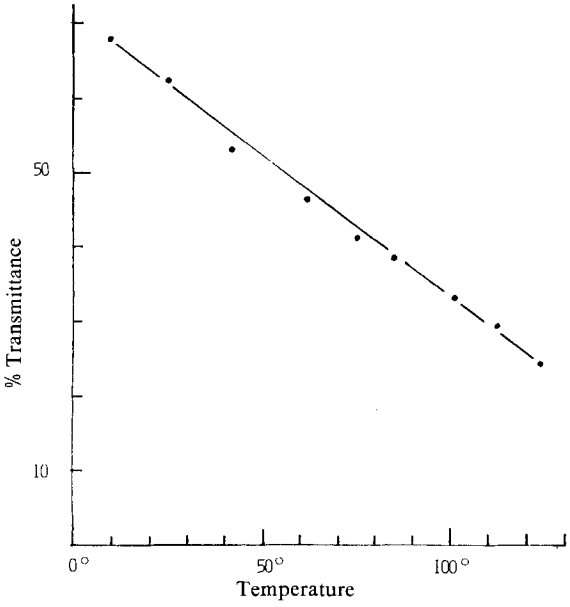


Fig. 2. *Relationship between temperature and % -transmittance of a solution of compound* **2b** *in methyl.* Cellosolve (conc. 108 mg/l) at 470 nm.

The ethylation of ethyl 4-oxo-1,4-dihydro-1,10-phenanthroline-3-carboxylate (**8a**) under the same conditions gave an ethyl derivative different from ethyl 4-ethoxy-1,10-phenanthroline-3-carboxylate (**9b**) prepared by the same unambiguous method as the other ethoxy-esters **3b** and **7b**. Therefore this compound is ethyl *N*-ethyl-4-oxo-1,4-dihydro-1,10-phenanthroline-3-carboxylate (**8b**) as reported [8]. It is colorless and thermochromism was not observed. The description of this compound in the patent is somewhat limited and some information about it is included in this report.

Since relatively little is known about 1,8-phenanthroline derivatives a few additional compounds with this system were prepared. Saponification of ester **2a** gave the acid **2d** which was decarboxylated to 1,4-dihydro-1,8-phenanthrolin-4-one (**2e**). Reaction of **2e** with $POCl_3$ gave the corresponding 4-chloro-1,8-phenanthroline (**3c**), converted by treatment with EtONa to 4-ethoxy-1,8-phenanthroline (**3d**), which was expected to aid in deciding in which tautomeric form compound **2e** exists.

The IR. spectra of the esters **2a**, **3a** and **3b** contain bands at wavenumbers (*ca.* 1700 cm^{-1}) expected for C=O absorption. They are presumably due to the carbonyl part of the ester group. The absence of a band in the same region of the spectrum of ester **2b**, as well as its thermochromism, high m.p. and insolubility in non-polar solvents may be explained by assuming this compound exists in an associated form.

Comparison of the IR. spectra of compounds **2e** and **3d** suggests that **2e** exists, as expected, at least predominantly in the oxo-form. The absorption at 1623 cm^{-1} is in the range of C=O absorption of 4-quinolones [9] and there is some absorption between 3175 cm^{-1} and 3000 cm^{-1} which is not present in the spectrum of **3d** and which could be due to NH-stretching. The UV. spectra of these two compounds are close and did not permit a structural assignment.

A biological evaluation[1]) of compounds **2b** and **2c** indicated no antibacterial or antifungal activity.

Experimental Part

General remarks. Melting points (m.p.) were taken on a *Mel-Temp* apparatus and are uncorrected. The UV. spectra were recorded on a *Beckman DB-GT* instrument and are reported as λ_{max} in nm and $\log\varepsilon_{max}$, the IR. spectra were taken on a *Beckman IR 8* instrument and the wavenumbers in cm^{-1} of the most important absorptions are listed. The NMR. spectra were recorded on a *Hitachi-Perkin-Elmer R 24A* instrument: δ-value with respect to TMS as internal standard, type of signal (*s* = singlet, *d* = doublet, *t* = triplet, *qa* = quartet, *m* = multiplet), coupling constant *J* in Hz, number of H-nuclei represented. Absorption measurements in the visible range were made with a *Bausch & Lomb Spectronic 20* instrument. The microanalyses were carried out by *Baron Consulting Co.*, Analytical Services, Orange, Conn. 06477.

Diethyl 5-isoquinolinaminomethylidenemalonate (**1**). A mixture of 11.5 g of 5-isoquinolinamine, 17.5 g of diethyl ethoxymethylidenemalonate and 50 ml of EtOH was refluxed for 1.5 h. The product which crystallized on cooling was collected, yield 18.7 g (75%), m.p. 123–125° (from EtOH).

$C_{17}H_{18}N_2O_4$ (314.3) Calc. C 64.96 H 5.77 N 8.91% Found C 64.78 H 6.00 N 9.12%

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[1]) I thank Dr. *H. W. Gschwend* of the Pharmaceuticals Division of *Ciba-Geigy Corp.*, Summit, N.J. 07901 for this information.

Ethyl 4-oxo-1,4-dihydro-1,8-phenanthroline-3-carboxylate (**2a**). Compound **1** (7.5 g) was added to 40 ml of boiling diphenyl ether at such a rate that boiling did not stop. Heating was continued for a few minutes after the addition was complete, then the mixture was cooled and diluted with low-boiling petroleum ether. The solid was collected and washed with warm petroleum ether, yield 5.5 g (86%), m.p. 270–272° (dec.) (from acetic acid). – IR. (Nujol): 3175–3030 several shoulders, 1712, 1613, 1592, 1543, 1314, 1285, 1235, 1217, 1177, 1134, 1090, 846, 812, 705.

$C_{15}H_{12}N_2O_3$ (268.3) Calc. C 67.16 H 4.51 N 10.44% Found C 66.94 H 4.44 N 10.17%

Reaction of **2a** *with ethyl iodide.* A mixture of 2.7 g of **2a**, 2.0 g of anh. K_2CO_3, and 15 ml of DMF was stirred and warmed on a steam bath until an essentially clear, dark solution formed. Ethyl iodide (1 ml) was added and stirring and heating was continued for about 3 h. After cooling overnight the mixture was diluted with H_2O to a total volume of about 80 ml. The yellow solid which formed on standing was collected (1.6 g), washed with ether and recrystallized repeatedly from H_2O once with charcoal. The bright yellow crystals of **2b** *(ethyl N-ethyl-4-oxo-1,4-dihydro-1,8-phenanthroline-3-carboxylate)* melted above 300° after drying at 78°/1.5 Torr. – IR. (Nujol): 3030, 1653, 1587, 1550, 1520, 1504 sh., 1418, 1290, 1211, 1149, 866, 826, 797, 775, 725.

$C_{17}H_{16}N_2O_3$ (296.3) Calc. C 68.91 H 5.44 N 9.45% Found C 69.02 H 5.25 N 9.37%

This compound exhibits thermochromism. Curves of its absorbance between 400 and 510 nm at 25°, 80° and 110° (in methyl *Cellosolve*) are presented in *Figure 1*. The essentially linear relationship between %-transmittance and temperature at 470 nm is shown in *Figure 2*.

The aqueous mother liquor obtained above was extracted with Et_2O and the extracts were combined with some solid which had separated on further standing of the original mother liquor. The extract was washed with H_2O, dried (Na_2SO_4), then the solvent was evaporated, leaving 0.5 g of ethyl 4-ethoxy-1,8-phenanthroline-3-carboxylate (**3b**) (IR. and mixed m.p.), m.p. 103–105° (from heptane).

The analogous esters **4**, **6** and **8a** derived from benzo[*h*]quinoline, 1,7-phenanthroline and 1,10-phenanthroline, respectively, were subjected to ethylation under the same conditions (see the *Table*).

N-Ethyl-4-oxo-1,4-dihydro-1,8-phenanthroline-3-carboxylic acid (**2c**). Saponification of 1.2 g of **2b** by refluxing with 12 ml of 5% NaOH-solution, followed by neutralization with CH_3COOH gave 0.4 g of crude product. Recrystallization from H_2O, once with charcoal gave pale yellow crystals, m.p. above 310° (dec.).

$C_{15}H_{12}N_2O_3$ (268.3) Calc. C 67.17 H 4.59 N 10.44% Found C 66.95 H 4.60 N 10.19%

Ethyl 4-chloro-1,8-phenanthroline-3-carboxylate (**3a**). A mixture of 3.6 g of **2a** and 14 ml of $POCl_3$ was refluxed for 18 h. Excess $POCl_3$ was then removed at reduced pressure and the residue

Table. *Data regarding the esters* **5**, **7a**, **7b**, **8b**, **9a** *and* **9b**

Starting ester	Reactant	Product	M.p. [°C]	Yield %	Recryst. solvent	M.w.	Calc. % C	Calc. % H	Calc. % N	Found % C	Found % H	Found % N
4	EtI	**5**	60–61[a])	50[b])	EtOH/H_2O	295.3	[c])	[c])	[c])			
6	EtI	**7b**	80–81	38	Heptane	296.3	68.91	5.44	9.45	68.68	5.31	9.71
8a	EtI	**8b**	158–160	74[b])	C_6H_6/Heptane	296.3	68.91	5.44	9.45	69.22	5.44	9.21
6	$POCl_3$	**7a**	135–135.5	95	EtOH	286.5	62.84	3.87	9.77	62.68	3.81	9.49
8a	$POCl_3$	**9a**	130–132.5	65	Heptane	286.5	62.84	3.87	9.77	63.13	4.09	10.02
7a	EtONa	**7b**	80–81	87	Et_2O	296.3	68.91	5.44	9.45	68.69	5.70	9.77
9a	EtONa	**9b**	69–71	75	EtOH/H_2O	296.3	68.91	5.44	9.45	68.92	5.52	9.63

[a]) [6]: 60–60.5°. [b]) Some unreacted starting material was also isolated. [c]) Identified by mixed m.p. and IR.

was mixed with water and ice and neutralized with dilute NaOH. The solid which formed was collected and dried, yield 3.0 g (78%), m.p. 159–159.5° (from EtOH). – IR. (Nujol): 1727, 1701, 1563, 1318, 1238, 1179, 1139, 1065, 847, 812, 769, 726. – ^{1}H-NMR. ($CDCl_3$): 9.7–8.8 (br., *s* at 9.30, 4 H); 8.36 (*d*, *J* = 9.0, 1 H); 8.00 (*d*, *J* = 9.0, 1 H); 4.54 (*qa*, *J* = 7.0, 2 H); 1.50 (*t*, *J* = 7.0, 3 H).

$C_{15}H_{11}ClN_2O_2$	Calc.	C 62.84	H 3.87	Cl 12.36	N 9.77%
(286.7)	Found	„ 62.64	„ 4.07	„ 12.57	„ 9.83%

Ethyl 4-chloro-1,7-phenanthroline-3-carboxylate (**7a**) *and ethyl 4-chloro-1,10-phenanthroline-3-carboxylate* (**9a**) were prepared by the same method. Additional information is contained in the *Table.*

Ethyl 4-ethoxy-1,8-phenanthroline-3-carboxylate (**3b**). A solution of 0.1 g of Na in 5 ml of dry EtOH was added to a boiling suspension of 1.2 g of **3a** in 20 ml of dry EtOH. The mixture was refluxed for 1 h and formed a neutral, clear solution. After most of the EtOH had been removed H_2O was added. The oil which formed solidified and was recrystallized from heptane, m.p. 104–105°. – IR. (Nujol): 1724, 1709 shoulder, 1590, 1572, 1312, 1238, 1217, 1179, 1154, 1022, 1022, 842, 822, 776, 673. – ^{1}H-NMR. ($CDCl_3$): 9.6–8.7 (br., *s* at 9.32, 4 H); 8.23 (*d*, *J* = 9.5, 1 H); 7.90 (*d*, *J* = 9.5, 1 H); 4.51 (*qa*, *J* = 7.2, 2 H); 4.35 (*qa*, *J* = 7.2, 2 H); 1.5 (*t*, *J* = 7.2, 3 H); 1.4 (*t*, *J* = 7.2, 3 H).

$C_{17}H_{16}N_2O_3$ (296.3) Calc. C 68.91 H 5.44 N 9.45% Found C 68.69 H 5.36 N 9.20%

Ethyl 4-ethoxy-1,7-phenanthroline-3-carboxylate (**7b**) *and ethyl 4-ethoxy-1,10-phenanthroline-3-carboxylate* (**9b**) were prepared by the same method. More information is contained in the *Table.*

4-Oxo-1,4-dihydro-1,8-phenanthroline-3-carboxylic acid (**2d**). A 1.0 g-sample of **2a** was refluxed with 40 ml of 0.1N NaOH. The dark solution which formed was treated with charcoal and then poured into 100 ml of 0.1N HCl. The final pH was about 2 and 0.4 g of crude product was collected. Recrystallization from methyl *Cellosolve* gave very pale greenish needles, m.p. 285–287°.

$C_{13}H_8N_2O_3$ (240.2) Calc. C 65.00 H 3.36 N 11.66% Found C 65.23 H 3.47 N 11.92%

1,4-Dihydro-1,8-phenanthrolin-4-one (**2e**). A sample of **2d** (0.6 g) was decarboxylated at 290–295°. Vacuum sublimation at 280–310°/1.1 Torr, gave 0.25 g (51%) of pale yellow product, m.p. 325–328° (from EtOH/H_2O). – UV. (EtOH): 210 (4.35); 229 (sh., 4.38); 241 (4.44); 247 (sh., 4.39); 317 (3.97); 342 (3.83). – IR. (Nujol): 3175 to 3030 several shoulders, 1623, 1572, 1534, 1255, 1174, 830, 725.

$C_{12}H_8N_2O$ (196.2) Calc. C 73.46 H 4.11 N 14.28% Found C 73.43 H 4.27 N 14.54%

4-Chloro-1,8-phenanthroline (**3c**). The crude decarboxylation product from 1.7 g of **2d** was refluxed with 6 ml of $POCl_3$ for 4 h. After standing overnight the excess $POCl_3$ was distilled off at reduced pressure, water was added and some dark impurities were removed by filtration. The filtrate was neutralized and the yellowish precipitate collected and dried (0.8 g, 53%). Recrystallization from heptane gave the analytical sample, m.p. 174–174.5°. – UV. (EtOH): 213 (sh., 4.24); 237 (4.53); 246 (sh., 4.52); 285 (sh., 3.94); 297 (3.94); 334 (3.22); 350 (3.31). – IR. (Nujol): 1580, 1557, 1495, 1269, 1062, 1033, 833, 800, 723, 648. – ^{1}H-NMR. ($CDCl_3$): 9.35 (*s*, 1 H); 9.1–8.7 (*m*, 3 H); 8.32 (*d*, *J* = 9, 1 H); 7.98 (*d*, *J* = 9, 1 H); 7.7 (*d*, *J* = 4, 1 H).

$C_{12}H_7ClN_2$ (214.7) Calc. C 67.15 H 3.29 N 13.05% Found C 67.04 H 3.51 N 13.27%

4-Ethoxy-1,8-phenanthroline (**3d**). A solution of 1.0 g of **3c** in 20 ml of warm dry EtOH was added to a solution of 0.3 g of Na in 10 ml of dry EtOH. Some crystalline material formed on refluxing the mixture for 1.5 h. EtOH was distilled and the residue (0.9 g, 86%) was washed with H_2O and recrystallized from EtOH/H_2O and then from cyclohexane. The colorless crystals melted at 112–114°. – UV. (EtOH): 209 (4.35); 217 (sh., 4.28); 247 (4.60); 289 (4.04); 300 (4.10); 330 (3.26); 346 (3.36). – IR. (Nujol): 1582, 1508, 1344, 1294, 1266, 1109, 1100, 1042, 1033, 843, 830, 729. – ^{1}H-NMR. ($CDCl_3$): 9.35 (br., *s*, 1 H); 9.1–8.7 (*m*, 3 H); 8.26 (*d*, *J* = 9.2, 1 H); 7.83 (*d*, *J* = 9.2, 1 H); 6.95 (*d*, *J* = 5.5, 1 H); 4.30 (*qa*, *J* = 7.1, 2 H); 1.58 (*t*, *J* = 7.1, 3 H).

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