NEW PYRROLO[1,2-a][1,10]PHENANTHROLINE DERIVATIVES[a]

F. Dumitraşcu*, C. Drăghici*, Loredana Barbu* and Christina Zălaru**

abstract: The 1,3-dipolar cycloadditions between 1-(4-chlorophenacyl)-1,10-phenantrolinium ylide **4** and dimethyl, diethyl or diisopropyl esters of acetylenedicarboxylic acid gave pyrrolo[1,2-a][1,10]phenantrolines **7a-c**. The helical chirality of ethyl (**7b**) and isopropyl esters (**7c**) was put in evidence by ^{1}H-NMR spectroscopy and the activation free energy was estimated from the coalescence. Treatment of ylide **4** with acetylenic esters at room temperature gave regio- and stereospecifically a mixture of *cis*-3,3a-dihydropyrrolophenantrolines **6** along with variable amounts of **7**..

Introduction

The monosubstituted heteroaromatic *N*-ylides obtained *in situ* by deprotonation of the corresponding cycloimmonium salts in the presence of bases are 1,3-dipoles which undergo cycloaddition with acetylenic dipolarophiles resulting in the formation of fused five membered heterocycles [1÷6].

Recently, we isolated and characterized the primary cycloadducts of monosubstituted phthalazinium and 1,10-phenanthrolinium phenacylides with dimethyl acetylene dicarboxylate [7]. Also, the rearrangement of primary cycloadducts was found to occur readily in the presence of triethylamine [7].

The present work describes the reaction of 1-(4-chlorophenacyl)-1,10-phenantrolinium ylide **4** with esters of acetylenedicarboxylic acid giving new derivatives of pyrrolo[1,2-a][1,10]phenantrolines **7b**,**c**. Compounds **7b**,**c** were found to exhibit helical chirality. Also, the NMR characterization, previously described [7] is reported.

Experimental

All meting points were recorded with a Boetius microapparatus and are uncorrected. NMR spectra were recorded with a Varian Gemini 300BB instrument, operating at 300 MHZ for ^{1}H and 75 MHz for ^{13}C, the chemical shifts being expressed in δ values relative to TMS as internal standard.

---

[a] To memory Dr. Ing. Dan Raileanu (1926-2002)

* Center of Organic Chemistry " C.D. Nenitzescu", Spl. Independentei 202B, Sect.6, Bucharest, ROMANIA.

** Faculty of Chemistry, Department of Organic Chemistry, University of Bucharest, 90-94 Şos. Panduri, Bucharest, ROMANIA

Analele Universităţii din Bucureşti – Chimie, Anul XIII (serie nouă), vol. I-II, pag. 191-195

Synthesis of diesters of 1-(4-chlorobenzoyl)-pyrrolo[1,2-a] [1,10]phenanthroline-2,3-dicarboxylate (**7a-c**) - General procedure:

2.3 g (5 mmol) phenanthrolinium salt **3** were suspended in 25 mL dichloromethane and then 5.5 mmol of dimethyl (or diethyl, diisopropyl) acetylenedicarboxylate were added. Under vigorous stirring 0.7 mL (5 mmol) of triethylamine (dissolved in 5 mL methylene chloride) were dropped. After 20 min. the reaction mixture was washed twice with water and the solvent evaporated. The residue was refluxed in ethanol for an hour and the precipitate was picked up by filtration.

Dimethyl ester, 1-(4-chlorobenzoyl)-pyrrolo[1,2-a][1,10]phenanthroline -2,3-dicarboxylate (**7a**) [7]

The product was recrystallized from nitromethane and yellow crystals were obtained. Yield 76%; m.p. 311 °C. Calcd. C 66.04; H 3.62; Cl 7.50; N 5.92. Found for $C_{26}H_{17}ClN_2O_5$: C 66.28; H 3.90; Cl 7.79; N 6.27.

^{1}H-NMR ($CDCl_3$+TFA; δ, ppm; *J*, Hz): 3.77; 4.01 (2s, 6H, CH_3); 7.38 (d, 2H, 8.6, H-3', H-5'); 7,41 (d, 2H, 8.6, H-2', H-6'); 7.99 (d, 1H, 9.6, H-5); 8.23 (dd, 1H, 8.2; 6.3, H-9); 8.32 (d, 1H, 8.9, H-7); 8.39 (d, 1H, 9.6, H-6); 8.59 (d, 1H, 9.6, H-4); 9.17 (dd, 8.2; 1.2, H-8); 9.36 (dd, 6.3, 1.2, H-10).

^{13}C-NMR ($CDCl_3$+TFA; δ, ppm): 53.2; 54,1 ($2CH_3$); 94.9 (C-3); 117.7; 118.8; 122.3; 126.3; 127.0; 128.5; 130.6 (C-1, C-2, C-3a, C-5a, C-7a, C-11a, C-11b); 124.7 (C-4, C-5, C-9); 126.1 (C-6); 126.9 (C-2', C-6'); 129.6 (C-3', C-5'); 130.3 (C-7); 138.0 (C-1'); 139.1 (C-4'); 144.4 (C-10); 147.4 (C-8); 164.4; 166.9 (CO_2CH_3); 183.5 (COAr).

Diethyl ester, 1-(4-chlorobenzoyl)-pyrrolo[1,2-a] [1,10]phenanthroline-2,3-dicarboxylate (**7b**)

The product was recrystallized from ethanol and yellow crystals were obtained. Yield 76%, m.p. 248-9 °C. Anal. Calcd. C 67.14; H 4.23; Cl 7.08; N 5.59. Found for $C_{28}H_{21}ClN_2O_5$: C 67.37; H 4.51, Cl 7.39; N, 5.87

^{1}H-NMR ($CDCl_3$; δ, ppm; *J*, Hz): 1.10 (t, 3H, 7.1, 2-$CH_2C\mathbf{H_3}$); 1.38 (t, 3H, 7.2, 3-$CH_2C\mathbf{H_3}$); 3.76-4.02 (m, 2H, 7.1, 14.2, 2-$C\mathbf{H_2}CH_3$, system ABX_3); 4.32-4.47 (m, 2H, 7.2, 14.4, 3-$C\mathbf{H_2}CH_3$, system ABX_3); 7.35 (dd, 1H, 8.2, 4.3, H-9); 7.49 (d, 2H, 8.5, H-3', H-5'); 7.68 (d, 1H, 9.2, H-5); 7.79 (d, 1H, 8.6, H-7); 7.85 (d, 1H, 8.6, H-6); 8.02 (dd, 1H, 4.3, 1.7, H-10); 8.10 (d, 2H, 8.5, H-2', H-6'); 8.17 (dd, 1H, 8.3, 1.7, H-8); 8.55 (d, 1H, 9.2; H-4).

^{13}C-NMR ($CDCl_3$; δ, ppm): 13.7; 14.3 ($2CH_3$); 60.4; 61,5 ($2CH_2$); 104.2 (C-3); 120.3 (C-4); 122,5 (C-9); 138.4 (C-4'); 125.3 (C-7); 125.9 (C-5); 126.7 (C-6); 136.5 (C-1'); 131.3 (C-2', C-6'); 128.3 (C-3', C-5'); 136.1 (C-8); 125.7; 125.9; 127.7; 128.9; 130.1; 137.3; 137.4 (C-1, C-2, C-3a, C-5a, C-7a, C-11a, C-11b); 145.5 (C-10); 163.4; 165.4 ($CO_2CH_2CH_3$); 182.9 (COAr).

Diisopropyl ester, 1-(4-chlorobenzoyl)-pyrrolo[1,2-a] [1,10]phenanthroline-2,3-dicarboxylate (**7c**)

The product was recrystallized from nitromethane and yellow crystals were obtained. Yield 78%, m.p. 231-2 °C. Anal. Calcd. C 68.12; H 4.76; Cl, 6.70; N 5.30. Found for $C_{30}H_{25}ClN_2O_5$: C 68.43; H 4.97; Cl 7.01; N 5.55.

^{1}H-NMR ($CDCl_3$; δ, ppm; *J*, Hz): 0.93; 1.14 (2d, 6H, 6.3, CH_3); 1.37; 1,40 (2d, 6H, 6.3, CH_3); 4.80 (sep, 1H, 6.3, C**H**Me_2); 5.32 (sep, 1H, 6.3, C**H**Me_2); 7.34 (dd, 1H, 8.2, 4.3, H-9); 7.50 (d, 2H, 8.5, H-3', H-5'); 7.68 (d, 1H, 9.2, H-5); 7.79 (d, 1H, 8.6, H-7); 7.86 (d, 1H, 8.6, H-6); 7.96 (dd, 1H, 4.3, 1.7, H-10); 8.14 (d, 2H, 8.5 , H-2', H-6'); 8.17 (dd, 1H, 8.2; 1.7, H-8); 8.59 (d, 1H, 9.2, H-4).

^{13}C-NMR ($CDCl_3$; δ, ppm): 21.0; 21.5; 21.9; 22,1 ($4CH_3$); 67.9; 69.7 (2**C**HMe_2); 104.6 (C-3); 120.3 (C-4); 122.4 (C-9); 125.2 (C-7); 125.7 (C-5); 125.7; 125.8; 127.7; 129.0; 129.6; 137.2; 138.5 (C-1, C-2, C-3a, C-5a, C-7a, C-11a, C-11b); 126.7 (C-6); 128.4 (C-3', C-5'); 131.5 (C-2', C-6'); 136.5 (C-8); 136.6 (C-1'); 138.5 (C-4'); 145.5 (C-10); 162.9; 165.1 ($CO_2CH(CH_3)_2$); 182.8 (COAr).

Results and Discussion

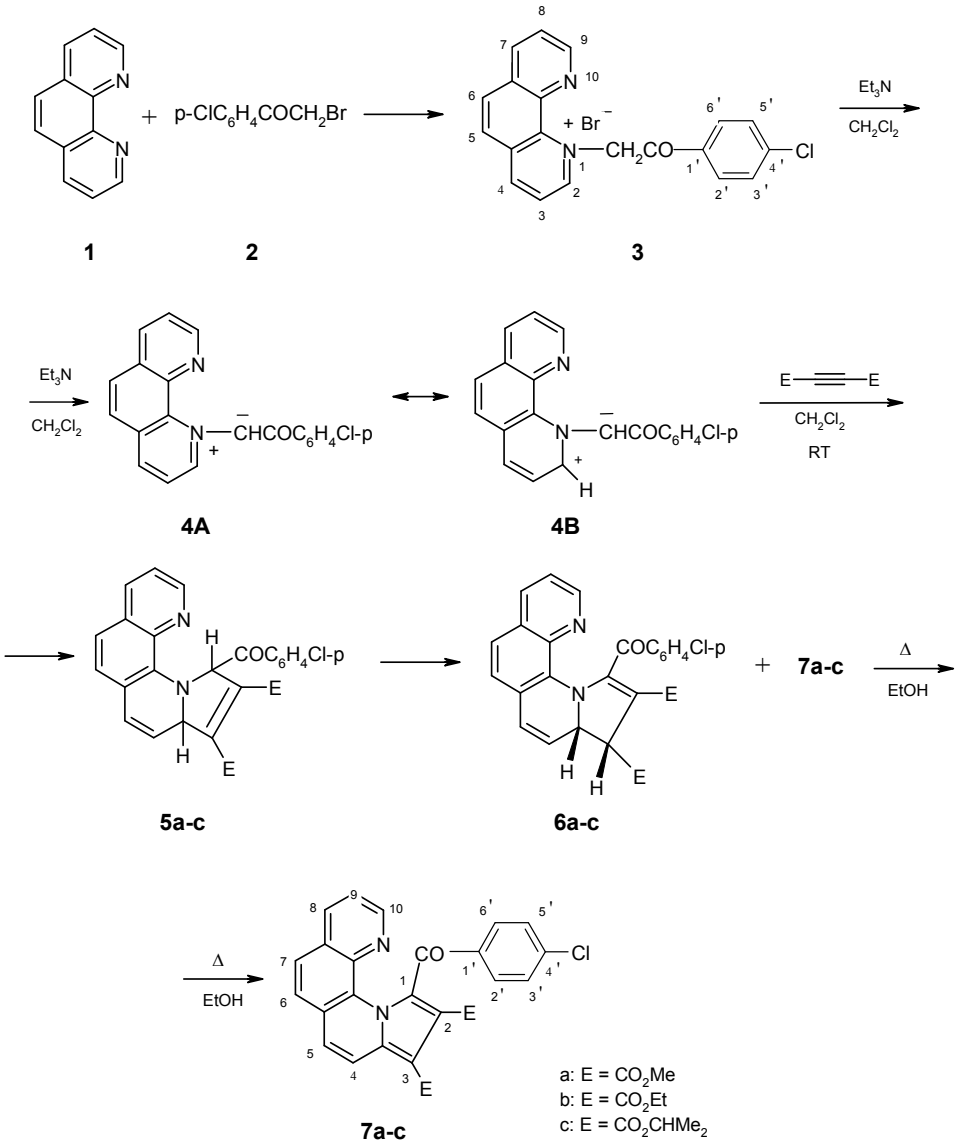
1-(4-Chlorophenacyl)-1,10-phenanthrolinium bromide (**3**) was obtained by reaction between 1,10-phenanthroline monohydrate(**1**) and 2-bromo-4'-chloroacetophenone(**2**), in acetone at reflux, similarly to previous literature procedure [8÷9].

The cycloimmonium ylide **4**, being unstable was generated in situ by reaction between quaternary salt **3** and triethylamine. Ylide **4** has an amphionic structure and can act as 1,3-dipole, according to the structure **4B** (Scheme 1), in reaction with acetylenic dipolarophiles,

Treatment of 1-(4-chlorophenacyl)-1,10-phenantrolinium ylide (**4**) with dimethyl, diethyl or diisopropyl esters of acetylenedicarboxylic in dichloromethane at room temperature gave a mixture consisting *cis* **6a-c** and **7a-c**. When the above mixture was heated in ethanol at reflux, pyrrolo[1,2-a][1,10]phenanthrolines **7a-c** were obtained in good yields (Scheme 1). The structure proof for *cis* stereochemistry was assigned by ^{1}H-NMR spectroscopy. The H-3 atom appeared as doublet with coupling constant J = 13.8 Hz, whereas H-3a gave a double triplet with coupling constants of 13.8, 2.6 and 2.1 Hz, the last two values corresponding to the coupling with H-4 and H-5 protons. The large value of the vicinal coupling constant between H-3 and H-3a indicated a *cis* configuration, in agreement similar values for other dihydroderivates [10-13].

The ^{1}H- and ^{13}C-NMR data for the compounds **7a-c** were also in agreement with the structure assignment. Supplementary evidence was given by COSY, HETCOR and NOE experiments.

The most characteristic feature of ^{1}H-NMR spectrum of the compound **7b** is two distinct patterns ABX_3 for the two methylenic protons in the ester groups. This behaviour can be explained by non-coplanarity between pyrrolic and pyridinc moieties, rendering helical [14] conformation to the molecule 7**b**. A similar observation was made for compound **7c**. At room temperature the methyl protons of each isopropyl radical appeared in the ^{1}H-NMR spectrum as two doublets (Fig 1).


p-ClC6H4COCH2Br
Et3N
CH2Cl2
+ Br−
CH2CO
Cl
1
2
3
4A
4B
CHCOC6H4Cl-p
E
RT
COC6H4Cl-p
5a-c
6a-c
7a-c
Δ
EtOH
CO
a: E = CO2Me
b: E = CO2Et
c: E = CO2CHMe2

Scheme 1

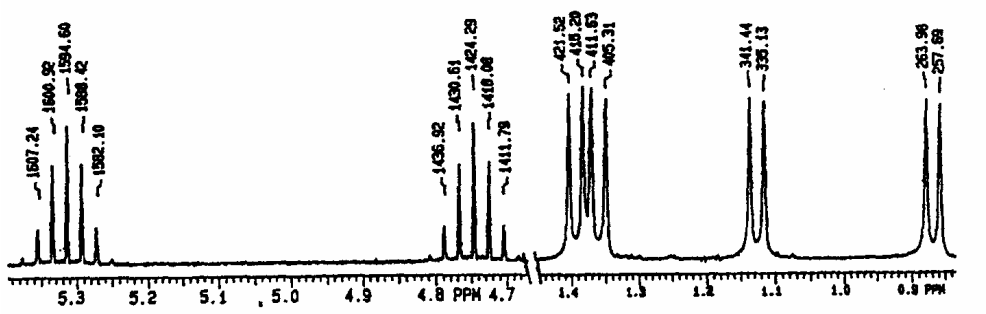


Fig. 1 *^{1}H-NMR of diastereotopic isopropyl groups in* **7c.**

On raising the temperature, coalesce occurred and finally only two doublets were observed. The activation free energy for the terminal rings flipping in **7c** was found to cca. 70 kJ/mol^{-1} (coalescence temperature 60°C; solvent DMSO-d_6). Also, the methyl carbon of each isopropyl radical was found to be non-equivalent in the ^{1}H-NMR spectrum

Conclusion

The pyrrolo[1,2-a][1,10]phenantrolines derivatives **7a-c** were obtained by 1,3-dipolar cycloaddition between 1,10-phenanthrolinium ylide **4** and acetylenic esters.

The c*is* stereochemistry of dihydro-derivatives **6** was assigned by ^{1}H-NMR spectroscopy.

Based on ^{1}H-NMR chemical shift non-equivalence of prochiral groups (ethyl, isopropyl) the pyrrolo[1,2-a][1,10]phenantrolines **7b,c** were found to posses helical chirality. In the case of **7c** the activation free energy was determinated by DNMR experiment.

REFERENCES

1. Surpateanu, G. and Lablanche-Combier, A. (1984) *Heterocycles* **22**, 2079-178.
2. Tsuge, O. and Kanemasa, S. (1989) *Adv. Heterocyclic Chem.* **45**, 231-349.
3. Surpateanu, G., Catteau, J. P., Karafiloglu, P. and Lablanche-Combier, A. (1976) *Tetrahedron* **32**, 2647-63.
4. Ungureanu, M., Mangalagiu, I., Grosu, G. and Petrovanu, M. (1997) *Ann. Pharm. Francaises* **55**(2), 69-73; (1997) Chem Abstr. **126**, 303587.
5. *Houben-Weyl, Organische Stickstoff-Verbindungen mit einer C,N-Doppelbindung,* Thieme: Stuttgart, New-York, (1991) **E-14b**, 143-155.
6. Zugravescu, I. and Petrovanu, M. (1976) **N-Ylid Chemistry**, McGraw-Hill, 95-314.
7. Dumitrascu, F., Mitan, C.I.; Draghici, C., Caproiu, M.T. and Raileanu, D. (2001) *Tetrahedron Lett.* **42**, 8379-82.
8. Calder, J.C. and Sasse, W.H.F.W.D. (1968) *J. Aust. Chem*. **21**, 1023-32.
9. Dumitrascu, F., Mitan, C.I., Draghici, C. and Caproiu, M.T. (2002) *Rev. Roum. Chem.* **47**, 881-4.
10. Kutsuma, T., Sekine, Y., Fujiyama, K. and Kobayashi, Y. (1972), *Chem. Pharm. Bull.* **20**, 2701-6.
11. Kobayashi, Y. Kutsuma, T. and Sekine, Y. (1972) *Tetrahedron Lett.* 3325-8.
12. Petrovanu, M., Mai Van Tri and Barboiu, V. (1976) *Rev. Roum. Chim.* **21**, 717-25.
13. Petrovanu, M., Stefanescu, E. and Druta, I. (1971) *Rev. Roum. Chim.* **17**, 1107-14.
14. Eliel, E.L. and Wilen, S.H. (1994) **Stereochemistry of Organic Compounds**, Wiley, New York, 1163-6.