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SYNTHESIS OF 1-[*N*-(ARYL)METHYLCARBAMOYL]-1,10-PHENANTHROLINIUM IODIDES WITH POTENTIAL BIOLOGICAL ACTIVITY

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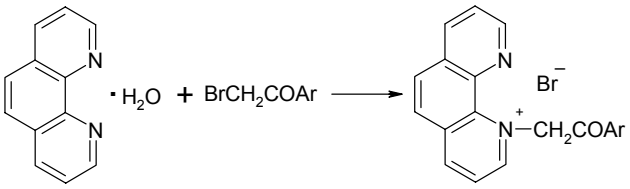
1-[*N*-(aryl)methylcarbamoyl]-1,10-phenanthrolinium iodides **10b-g** were obtained by the reaction between *N*-aryl-2-iodoacetamides **9b-g** and 1,10-phenanthroline. Also, the primary amide **10a** was prepared by quaternization of 1,10-phenanthroline with iodoacetamide. The structure of the quaternary salts **10a-g** was assigned by NMR spectroscopy and non-planarity of the phenanthrolinium cation **10** is discussed.

INTRODUCTION

Along with other 1,10-phenanthroline derivatives, the quaternary salts have long since been shown to possess a variety of uses, especially as biologically active compounds. Among these properties, controlling the selectivity for the intercalating sites in DNA and RNA by changing the substituents in some phenanthrolinium halides is one of the most important.[1] Moreover, quaternary salts of 1,10-phenanthroline have been evaluated as herbicides, carcinostatics and bacteriostatics, as enzyme inhibitors or activators, or as precursors in the field of organic chemistry.[2] A detailed study has been made on a series of substituted *N*-methyl-1,10-phenanthrolinium salts.[3,4] Recently, some new *N*-phenacyl-1,10-phenanthrolinium bromides of type **3** were prepared by quaternization of 1,10-phenanthroline (**1**) with the 2-bromoacetophenone derivatives **2** (Scheme 1).[5,6]



1 **2** **3**

Scheme 1

The phenanthrolinium bromides showed bacteriostatic and fungistatic activity.[5] Also, the salts of type **3** were found to possess helical chirality, a property that was deduced from ^{1}H-NMR spectra in solution and X-ray crystallography in the solid state.[6] The 1,10-phenanthrolines of type **3** were used as starting materials for the synthesis of pyrrolo[1,2-a][1,10]phenanthroline derivatives **4** (Scheme 2), which were also found to possess biological activity.[5-12] Having a helicene-like structure, the pyrrolo[1,2-a][1,10]phenanthroline derivatives **4** exhibit helical chirality, a property that was fully characterized by ^{1}H-NMR spectra and X-ray analysis.[12]

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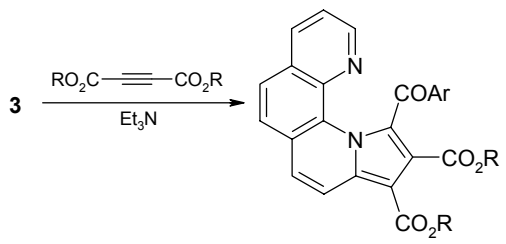
Scheme 2

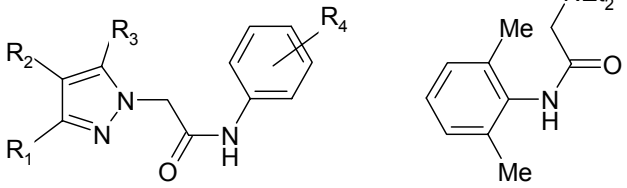


4

Recently, 1-pyrazoleacetic acid derivatives **5** containing an amide group were synthesized and their anesthetic action was evaluated.[13,14]

The present paper reports the synthesis and characterization of *N*-substituted-1-methylcarbamoyl-1,10-phenanthrolinium iodides **10b-g** having lidocaine-like structure **6** (Scheme 3).

Scheme 3



5 **6**

RESULTS AND DISCUSSION

Initially, the intention was to quaternize 1,10-phenanthroline with *N*-aryl-2-chloroacetamides **8**. The latter were prepared by acylation of substituted anilines **7** with chloroacetyl chloride in the presence of anhydrous sodium acetate added to neutralize the resulting hydrochloric acid.

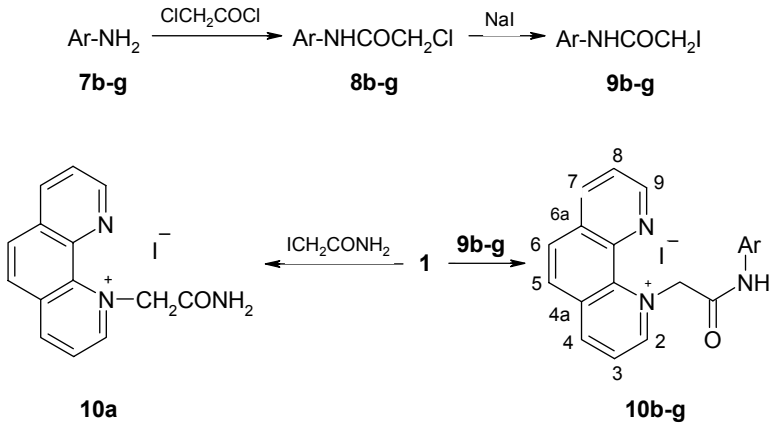
The alkylation of 1,10-phenanthroline with *N*-aryl-2-chloroacetamide **8** was performed in acetone under reflux by the procedure described for bromides **3**. Due to the low reactivity of chloroacetanilides **8**, as well as the low basicity of 1,10-phenanthroline, the yields and purities of the cycloimmonium chlorides were found to be very low. In order to enhance the formation of 1,10-phenanthrolinium salts, in the alkylation reaction of **1**, chloroacetanilides **8** have been replaced by the more reactive *N*-aryl-2-iodoacetanilides **9**. The transformation of the *N*-aryl-2-chloroacetanilides **8** into their iodo derivatives **9** was easily performed with sodium iodide in acetone, under reflux.[15,16]

The quaternization of 1,10-phenanthroline with *N*-aryl-2-iodoacetamides **9b-g**, in acetone, under reflux, led to iodides **10b-g**, as yellow crystals. This method allowed the synthesis of 1,10-phenanthrolinium salts **10b-g** in a highly pure state and with yields of over 60%. Under similar reaction conditions, starting from iodoacetamide and 1,10-phenanthroline, compound **10a** was obtained (Scheme 4).

Amides **10b-g** have an analogous structure to lidocaine **6**. In the iodides **10b-g**, the Et_2N group present in lidocaine is replaced by the less basic 1,10-phenanthroline substituent.

The structure of 1,10-phenanthrolinium iodides **10a-g** was confirmed by elemental analysis and NMR spectroscopy.

In the ^{1}H-NMR spectra of iodides **10**, recorded in DMSO-d_6, the protons of the two terminal rings appear as double doublets. The chemical shifts were established on the basis of the coupling constants values, as well as on HH-COSY experiments. The δ values of the 1,10-phenanthroline moiety are close to those of bromides **3**, except for H-9. In the iodides **10b-g**, the chemical shift for H-9 has a range of 8.48-8.53 ppm, whereas in **3** the signals are in the range 9.13-9.26 ppm. Although the protons H-5 and H-6, in compounds **10b-g**, are not magnetically equivalent, in the ^{1}H-NMR spectra they appear as a singlet (A_2 system), not as two doublets, as in compounds **3** and **10a**. This is due to the very close values of the chemical shifts for protons H-5 and H-6, and a possible overlap of the peaks.



Ar = **b**: 2,5-$Me_2C_6H_3$, **c**: 3,5-$Me_2C_6H_3$, **d**: 4-EtC_6H_4,
e: 3-$CF_3C_6H_4$, **f**: 4-FC_6H_4, **g**: 2-$MeOOCC_6H_4$

Scheme 4

The two protons of the $CONH_2$ group in iodide **10a** appear, in the ^{1}H-NMR spectra, due to the amidic conjugation, as two singlets (7.55 ppm and 8.14 ppm). The signal of the NH protons in the case of amides **10b-g** appears as a singlet, having chemical shift values in the range 10.16-11.30 ppm.

Deuteration of the amidic protons occurs easily in the presence of D_2O, in the NMR vial. Spectra carried out at different time intervals clearly show the absence of the signal corresponding to the amidic protons in the case of the deuterated product.

It is interesting to note that the signal for the methylenic protons, in the ^{1}H-NMR spectra of compounds **10b-g**, appeared as a sharp singlet, whereas in bromides **3** the same protons appear as a broad singlet (7.26-7.36 ppm).[8,9,11] The broad singlet in **3** resembles the AB system near coalescence. The magnetic non-equivalence of the methylenic protons was explained on the basis of the non-coplanarity of the pyridine and pyridinium rings. This hypothesis was verified by X-ray analysis of 1-(4-chlorophenacyl)-1,10-phenanthrolinium bromide, the results of the analysis clearly indicating a dihedral angle between the least-squares planes of the two terminal rings of 6.8(2)°.[6]

The sharp singlet observed for the methylenic protons in the ^{1}H-NMR spectra of the iodides **10** indicates that the two protons are either over the coalescence temperature or that the phenanthrolinium cation is planar. Most probably, due to amidic conjugation, the intermolecular hydrogen bonding of type C-H···N involving the methylene group and the uncharged nitrogen of the pyridine moiety are too weak as compared to **3**, to cause ring distortion. Also, the influence on the distortion, due to the aryl substituent at the amidic group might be diminished by the different sequence of atoms since it contains an additional atom.

^{13}C-NMR spectra show all the expected signals. The values of the chemical shifts for the carbon atoms of the phenanthroline moiety in compounds **10a-g** were established by HETCOR experiments and match the corresponding values in compounds **3**. The carbon atoms in the α and γ positions with respect to the nitrogen atoms of the pyridine and pyridinium rings are strongly deshielded when compared to the carbon atoms in the β positions. The chemical shifts of the carbonyl groups are in the range 164.2-167.7 ppm.

It is well known that the deprotonation of the cycloimmonium salts, in the presence of base, give *N*-ylides which undergo 1,3-dipolar cycloaddition with olefinic and acetylenic activated dipolarophiles, resulting in the formation of fused five membered heterocycles,[17,18] as we recently reported.[19] Therefore, the 1,10-phenanthrolinium iodides **10** could be used as starting materials for the synthesis of new pyrrolo [1,2-a][1,10]phenanthroline derivatives bearing amide groups in their structure. The biological activity of the new iodides will be also investigated.

EXPERIMENTAL

Melting points were determined on Boëtius hot plate and are uncorrected. The NMR spectra were recorded on a Varian Gemini 300 BB instrument, operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Supplementary evidence was given by HETCOR and COSY experiments.

*Methylcarbamoyl 1,10-phenanthrolinium iodides (**10a-g**). General procedure*

2 g (10 mmol) of 1,10-phenanthroline monohydrate **1** and 11 mmol of iodoacetamide **9a** or of *N*-aryl-2-iodoacetamides **9b-g** were dissolved in 100 mL of acetone and refluxed for 48 hrs. After cooling of the reaction mixture, the precipitate was filtered by suction and washed with acetone; the resulting 1,10-phenanthrolinium iodides **10a-g** were subsequently purified by recrystallization.

*1-Methylcarbamoyl-1,10-phenanthrolinium iodide (**10a**)*

The product was recrystallized from dimethylformamide and yellow crystals with m.p. 237-9°C were obtained. Yield 69%. *Anal.* Calcd. $C_{14}H_{12}IN_3O$: N 11.77. Found: N 11.51. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 6.50 (2H, s, CH_2); 7.55, 8.14 (2H, 2bs, NH_2); 8.03 (1H, dd, *J* = 8.2, 4.3 Hz, H-8); 8.41, 8.45 (2H, 2d, *J* = 8.8 Hz, H-5, H-6); 8.51 (1H, dd, *J* = 8.2, 5.9 Hz, H-3); 8.79 (1H, dd, *J* = 8.2, 1.8 Hz, H-7); 9.21 (1H, dd, *J* = 4.3, 1.8 Hz, H-9); 9.49 (1H, dd, *J* = 8.2, 1.5 Hz, H-4); 9.54 (1H, dd, *J* = 5.9, 1.5 Hz, H-2). ^{13}C-NMR (75 MHz, DMSO-d_6) δ 65.9 (CH_2); 124.3 (C-3); 125.4 (C-8); 126.8, 130.4 (C-5, C-6); 131.4, 131.9 (C-4a, C-6a); 137.2, 139.7 (C-10a, C-10b); 137.7 (C-7); 147.7 (C-4); 149.5 (C-9); 152.2 (C-2); 167.7 ($CONH_2$).

*1-[N-(2,5-dimethylphenyl)methylcarbamoyl]-1,10-phenanthrolinium iodide (**10b**)*

The product was recrystallized from dimethylformamide and yellow crystals with m.p. 220-2°C were obtained. Yield 71%. *Anal.* Calcd. $C_{22}H_{20}IN_3O$: N 9.21. Found: N 8.95. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.17, 2.26 (6H, 2s, 2 Me); 6.75 (2H, s, CH_2); 6.88 (1H, dd, *J* = 7.8, 1.5 Hz, H-4'); 7.09 (1H, d, *J* = 7.8 Hz, H-3'); 7.15 (1H, d, *J* = 1.5 Hz, H-6'); 8.06 (1H, dd, *J* = 8.2, 4.3 Hz, H-8); 8.43 (2H, s, H-5, H-6); 8.56 (1H, dd, *J* = 8.2, 5.9 Hz, H-3); 8.80 (1H, dd, *J* = 8.2, 1.8 Hz, H-7); 9.26 (1H, dd, *J* = 4.3, 1.8 Hz, H-9); 9.52 (1H, dd, *J* = 8.2, 1.5 Hz, H-4); 9.65 (1H, dd, *J* = 5.9, 1.5 Hz, H-2); 10.16 (1H, s, NH). ^{13}C-NMR (75 MHz, DMSO-d_6) δ 17.5 (2-Me); 21.5 (5-Me); 66.3 (CH_2); 124.3 (C-3); 125.1, 126.0, 130.2 (C-3', C-4', C-6'); 125.4 (C-8); 126.8, 130.4 (C-5, C-6); 128.4, 134.9, 135.4 (C-1', C-2', C-5'); 131.4, 131.9 (C-4a, C-6a); 137.2, 139.7 (C-10a, C-10b); 137.7 (C-7); 147.8 (C-4); 149.4 (C-9); 152.2 (C-2); 164.6 (CONH).

*1-[N-(3,5-dimethylphenyl)methylcarbamoyl]-1,10-phenanthrolinium iodide (**10c**)*

The product was recrystallized from dimethylformamide + ethanol and yellow crystals with m.p. 225-7°C were obtained. Yield 63%. *Anal.* Calcd. $C_{22}H_{20}IN_3O$: N 9.27. Found: N 8.95. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.20 (6H, s, 2 Me); 6.67 (2H, s, CH_2); 6.70 (1H, s, H-4'); 7.20 (2H, s, H-2', H-6'); 8.03 (1H, dd, *J* = 8.2, 4.3 Hz, H-8); 8.45 (2H, s, H-5, H-6); 8.57 (1H, dd, *J* = 8.2, 5.9 Hz, H-3); 8.81 (1H, dd, *J* = 8.2, 1.8 Hz, H-7); 9.15 (1H, dd, *J* = 4.3, 1.8 Hz, H-9); 9.55 (1H, dd, *J* = 8.2, 1.5 Hz, H-4); 9.62 (1H, dd, *J* = 5.9, 1.5 Hz, H-2); 10.72 (1H, s, NH). ^{13}C-NMR (75 MHz, DMSO-d_6) δ 21.0 (2 Me); 66.5 (CH_2); 116.9 (C-2', C-6'); 124.3 (C-3); 125.1 (C-4'); 125.4 (C-8); 126.8, 130.4 (C-5, C-6); 131.4, 131.8 (C-4a, C-6a); 137.0, 139.4 (C-10a, C-10b); 137.7 (C-7); 137.8 (C-3', C-5'); 138.5 (C-1'); 147.8 (C-4); 149.3 (C-9); 152.3 (C-2); 164.4 (CONH).

*1-[N-(4-ethylphenyl)methylcarbamoyl]-1,10-phenanthrolinium iodide (**10d**)*

The product was recrystallized from nitromethane and yellow crystals with m.p. 220-2°C were obtained. Yield 67%. *Anal.* Calcd. $C_{22}H_{20}IN_3O$: N 9.15. Found: N 8.95. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.13 (3H, t, *J* = 7.6 Hz, $CH_2C\mathbf{H}_3$); 2.54 (2H, q, *J* = 7.6 Hz, $C\mathbf{H}_2CH_3$); 6.67 (2H, s, CH_2); 7.15 (2H, d, *J* = 8.4 Hz, H-3', H-5'); 7.47 (2H, d, *J* = 8.4 Hz, H-2', H-6'); 7.99 (1H, dd, *J* = 8.2, 4.3 Hz, H-8); 8.45 (2H, s, H-5, H-6); 8.57 (1H, dd, *J* = 8.2, 5.9 Hz, H-3); 8.77 (1H, dd, *J* = 8.2, 1.8 Hz, H-7); 9.13 (1H, dd, *J* = 4.3, 1.8 Hz, H-9); 9.54 (1H, dd, *J* = 8.2, 1.5 Hz, H-4); 9.63 (1H, dd, *J* = 5.9, 1.5 Hz, H-2); 10.83 (1H, s, NH). ^{13}C-NMR (75 MHz, DMSO-d_6) δ 15.5 ($CH_2\mathbf{C}H_3$); 27.5 ($\mathbf{C}H_2CH_3$); 66.5 (CH_2); 119.4 (C-2', C-6'); 124.3 (C-3); 125.4 (C-8); 126.8, 130.4 (C-5, C-6);128.0 (C-3', C-5'); 131.4, 131.8 (C-4a, C-6a); 137.0, 139.4 (C-10a, C-10b); 136.3, 139.0 (C-1', C-4'); 137.7 (C-7); 147.9 (C-4); 149.3 (C-9); 152.3 (C-2); 164.3 (CONH).

*1-[N-(3-trifluoromethylphenyl)methylcarbamoyl]-1,10-phenanthrolinium iodide (**10e**)*

The product was recrystallized from nitromethane + ethanol and yellow crystals with m.p. 236-8°C were obtained. Yield 68%. *Anal.* Calcd. $C_{21}H_{15}F_3N_3O$: N 8.47. Found: N 8.25. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 6.74 (2H, s, CH_2); 7.45-7.48 (1H, m, H-6'); 7.61-7.66 (1H, m, H-5'); 7.83-7.86 (1H, m, H-4'); 8.03 (1H, dd, *J* = 8.2, 4.3 Hz, H-8); 8.04-8.06 (1H, m, H-2'); 8.49 (2H, s, H-5, H-6); 8.62 (1H, dd, *J* = 8.2, 5.9 Hz, H-3); 8.82 (1H, dd, *J* = 8.2, 1.8 Hz, H-7); 9.16 (1H, dd, *J* = 4.3, 1.8 Hz, H-9); 9.60 (1H, dd, *J* = 8.2, 1.5 Hz, H-4); 9.67 (1H, dd, *J* = 5.9, 1.5 Hz, H-2); 11.30 (1H, s, NH). ^{13}C-NMR (75 MHz, DMSO-d_6) δ 66.5 (CH_2); 115.1 (q, *J* = 3.7 Hz, C-2'); 120.0 (q, *J* = 4.2 Hz, C-4'); 122.7 (C-6'); 124.5 (C-3); 124.8 (q, J = 272.0 Hz, CF_3); 125.4 (C-8); 126.8, 130.5 (C-5, C-6); 129.5 (q, *J* = 32.0 Hz, C-3'); 130.2 (C-5'); 139.3 (C-1'); 131.4, 131.8 (C-4a, C-6a); 136.9, 139.4 (C-10a, C-10b); 137.7 (C-7); 148.1 (C-4); 149.3 (C-9); 152.3 (C-2); 164.2 (CONH).

*1-[N-(4-fluorophenyl)methylcarbamoyl]-1,10-phenanthrolinium iodide (**10f**)*

The product was recrystallized from nitromethane and yellow crystals with m.p. 223-4°C were obtained. Yield 64%. *Anal.* Calcd. $C_{20}H_{15}FIN_3O$: N 9.44. Found: N 9.15. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 6.67 (2H, s, CH_2); 7.17 (t, 2H, 9.0, H-3', H-5'); 7.59 (dd, 2H, 5.0, 9.0, H-2', H-6'); 8.00 (1H, dd, *J* = 8.2, 4.3 Hz, H-8); 8.45 (2H, s, H-5, H-6); 8.57 (1H, dd, *J* = 8.2, 5.9 Hz, H-3); 8.78 (1H, dd, *J* = 8.2, 1.8 Hz, H-7); 9.14 (1H, dd, *J* = 4.3, 1.8 Hz, H-9); 9.55 (1H, dd, *J* = 8.2, 1.5 Hz, H-4); 9.63 (1H, dd, *J* = 5.9, 1.5 Hz, H-2); 10.94 (1H, s, NH). ^{13}C-NMR (75 MHz, DMSO-d_6) δ 66.4 (CH_2); 115.5 (d, *J* = 22.4 Hz, C-3', C-5'); 121.1 (d, *J* = 7.9 Hz, C-2', C-6'); 125.4 (C-8); 124.3 (C-3); 126.8, 130.4 (C-5, C-6); 131.4, 131.8 (C-4a, C-6a); 137.0, 139.4 (C-10a, C-10b); 134.9 (d, *J* = 3.0 Hz, C-1'); 137.7 (C-7); 147.9 (C-4); 149.3 (C-9); 152.3 (C-2); 159.7 (d, *J* = 240.3 Hz, C-4'); 164.5 (CONH).

*1-[N-(2-carbomethoxyphenyl)methylcarbamoyl]-1,10-phenanthrolinium iodide (**10g**)*

The product was recrystallized from nitromethane + DMSO and yellow crystals with m.p. 219-221°C were obtained. Yield 72%. *Anal.* Calcd. $C_{22}H_{18}IN_3O_3$: N 8.70. Found: N 8.42. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 3.89 (3H, s, OMe); 6.73 (2H, s, CH_2); 7.21-7.27 (1H, m, H-5'); 7.54-7.60 (1H, m, H-4'); 7.90-8.00 (2H, m, H-3', H-6'); 8.02 (1H, dd, *J* = 8.2, 4.3 Hz, H-8); 8.45 (2H, s, H-5, H-6); 8.58 (1H, dd, *J* = 8.2, 5.9 Hz, H-3); 8.79 (1H, dd, *J* = 8.2, 1.8 Hz, H-7); 9.16 (1H, dd, *J* = 4.3, 1.8 Hz, H-9); 9.56 (1H, dd, *J* = 8.2, 1.5 Hz, H-4); 9.67 (1H, dd, *J* = 5.9, 1.5 Hz, H-2); 11.12 (1H, s, NH). ^{13}C-NMR (75 MHz, DMSO-d_6) δ 52.4 (OMe); 66.8 (CH_2); 119.6, 138.3 (C-1', C-2'); 122.1, 124.0, 130.5, 133.6 (C-3', C-4', C-5', C-6'); 124.4 (C-3); 125.4 (C-8); 126.8, 130.5 (C-5, C-6); 131.5, 131.9 (C-4a, C-6a); 136.9, 139.3 (C-10a, C-10b); 137.7 (C-7); 148.1 (C-4); 149.3 (C-9); 152.3 (C-2); 164.9 (CONH); 167.2 (COO).

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