# A phenanthrolinoquinomethane: synthesis and study of precursors

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Two quinomethane precursors: the *ortho*-hydroxylated methyl ether **6** and the diacetate **8** have been prepared from [1,3]benzodioxino[5,6-*b*][1,7]phenanthroline **2**. The quinomethane intermediate **4** has been trapped by reduction, nucleophilic addition and [4 + 2] addition with ethyl vinyl ether.

*ortho* and *para* Quinomethanes have been extensively studied in the past few years.[1] Such species have been used as key intermediates in the total synthesis of natural products[2] and are involved in various biological and toxicological processes.[3] Quinomethane intermediates have also been postulated as being formed during the biotransformation of several drugs and xenobiotics.[4] Recently Li *et al.* have used quinomethane precursors supported on oligonucleotides for selective modification of DNA.[5] These highly reactive species are most frequently generated *in situ* by thermal degradation of *ortho* phenolic Mannich Bases[6] and *o*-hydroxybenzyl alcohols[7] or by oxidation of alkylphenols.[8] New methods for generating quinomethanes have also been published more recently,[9] starting from benzotriazolylalkylphenol,[9a] alkylsulfanylalkylphenol[9c] or trimethylsilyl derivatives.[9d]

In the course of a programme devoted to the search for new anticancer drugs, we have developed a series of benzo[*b*]-[1,7]phenanthrolines substituted at position 10.[10] As part of this work the 10-hydroxybenzo[*b*][1,7]phenanthroline **1** has been prepared,[11] its reactivity has been studied and a number of derivatives have been obtained. In particular, the position α to the OH group (C-11) appeared to possess a high reactivity with electrophilic species.

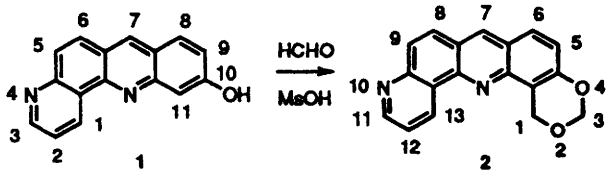
In the search for drugs possessing both affinity for DNA and alkylating properties, we have devised molecules that incorporate a quinomethane precursor moiety into the benzophenanthroline polycyclic system, which exhibits good affinity for DNA. As far as we know, little has been published on the reactivity of heterocyclic *o*-quinomethanes.[12] The 1,3-dioxine **2** appeared to be a good candidate for an entrance into the series as the cleavage of the acetal ring could generate bifunctional molecules such as **6** and **8** as possible quinomethane precursors.

We report here the synthesis of 1*H*-[1,3]benzodioxino-[5,6-*b*][1,7]phenanthroline **2**, the preparation of the stable quinomethane precursors **6** and **8** and the study of their chemical reactivity.

## Results and discussion

### Synthesis of the 1,3-benzodioxine 2

A common method to prepare 1,3-benzodioxines is a two-step procedure consisting of the hydroxymethylation of a phenol derivative with formaldehyde in a basic medium followed by cyclization.[13] Treatment of phenol derivatives with formaldehyde in acidic media has also been used but usually yields are low and many by-products are formed resulting from dimerisations or polycondensations.[14] Treating **1** with formaldehyde in basic conditions (1 mol $dm^{-3}$ NaOH) yielded insoluble products. In contrast, reaction of a large excess of formaldehyde with the hydroxy derivative **1**, performed in methanesulfonic acid gave the dioxine **2** in 70% yield (Scheme 1). The structure of **2** was determined by $^1H$ NMR and mass

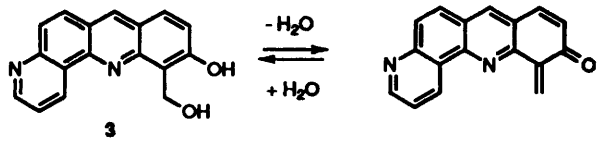



Scheme 1

spectrometry. In the NMR spectrum, the OH signal, present in **1**, had disappeared and two singlets at $\delta$ 5.42 and 5.48, each integrating for two protons, indicated the existence of the 1,3-dioxane structure. The reaction was totally regioselective, no product resulting from reaction at position 9 could be detected by HPLC analysis of the reaction mixture.†

### Opening of the dioxine ring

To obtain the 10-hydroxy-11-hydroxymethyl derivative **3**, the direct precursor of the quinomethane **4**, we used the strategy proposed by Kaslow and Raymond (Scheme 2).[14c] These

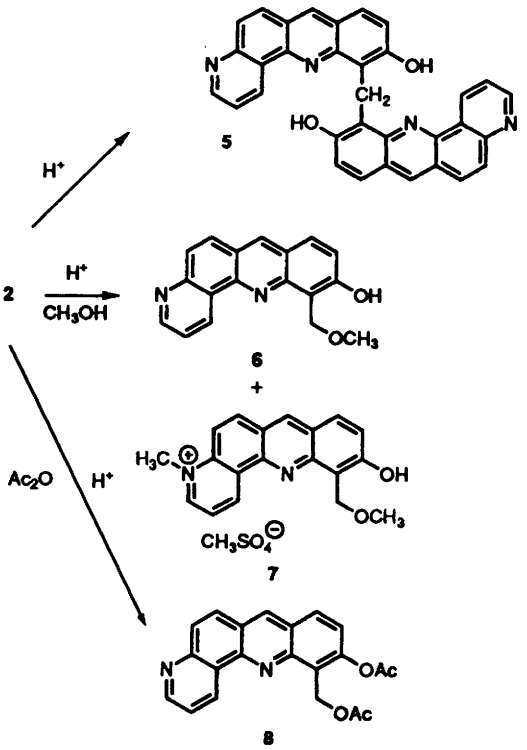



Scheme 2

authors have shown that the dioxino[5,4-*f*]quinoline ring system is resistant to hydrolysis in dilute acid medium, in concentrated hydrochloric acid however the dioxine ring could be opened to give a diquinolylmethane derivative. The authors trapped the hydroxymethyl intermediate by carrying out the reaction in a mixture of acetic anhydride–sulfuric acid and obtained the diacetate derivative which was subsequently deacetylated by sodium ethoxide in ethanol. In a similar way, heating compound **2** in an acidic medium (methanesulfonic acid–water) gave as the major product a compound that was almost totally insoluble in all solvents used. This insolubility prevented any correct NMR analysis. However mass spectrometry indicated a molecular mass of 504. By analogy with data reported in the literature,[15,7a,14c] we propose the 11,11′-methylenebis(hydroxybenzo[*b*]phenanthroline) structure **5** that accounts for the indicated mass. The same type of bridged structure has also been described in the acridine series. It was obtained by heating 3-hydroxyacridine with formalde-

† This regioselectivity of the aromatic electrophilic substitution on compound **2** was confirmed by the result of a proton–deuterium exchange in acidic medium studied by $^1H$ NMR. In a deuteriated trifluoroacetic acid–water (1:1) mixture the only exchange takes place at position 11. The half-life was estimated to be 1 h at 65 °C.

hyde in the presence of sodium acetate.[15a] Dioxine ring opening to generate the diacetate **8**, was accomplished by treating compound **2** with methanesulfonic acid in a mixture of acetic acid and acetic anhydride (Scheme 3). Compound **8** was

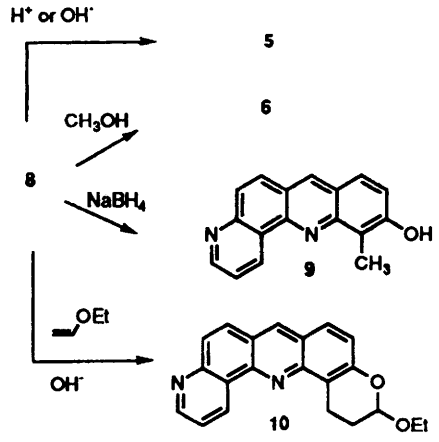



Scheme 3

isolated in 75% yield. The $^1$H NMR spectrum was characterized by two singlets at $\delta$ 1.99 and 2.41 corresponding to the two acetyl groups (benzylic and phenolic, respectively). The diester **8** was easily purified by column chromatography. Carrying out the solvolysis of **2** in methanesulfonic acid in the presence of methanol gave the methyl ether **6** in 80% yield. The corresponding quaternary compound **7** was isolated as the methyl sulfate as a by-product. This compound was identified by comparison with an authentic sample obtained by methylation of the methyl ether **6**.

**Reactivity of compounds 6 and 8**

The methyl ether **6** appeared to be stable in 1 mol dm$^{-3}$ NaOH. Under acidic conditions (methanesulfonic acid–acetic acid, 1:1, 70 °C, overnight), the methyl ether **6** slowly decomposed to give the bridged compound **5** as the main product as indicated by mass spectrometry. Both under acidic (1 mol dm$^{-3}$ HCl) and basic conditions (1 mol dm$^{-3}$ NaOH), the diacetate **8** rapidly disappeared to give compounds that could not be analysed by HPLC or TLC. Again, we can assume that the methylenebisbenzophenanthroline **5** was predominantly formed in these conditions as it is known from the literature[15b,14c,16] that *o*-hydroxymethylphenols rapidly decompose under basic or acidic conditions to give methylene-bridged structures. Using sodium borohydride, a method described to deprotect selectively a phenol acetate in the presence of a benzyl acetate,[17] we obtained a new compound **9** (Scheme 4). The $^1$H NMR spectrum was characterized by a singlet at $\delta$ 2.68 integrating for three protons indicating that the benzylic acetate has been reduced to a methyl group. In a nucleophilic solvent, *i.e.* in methanol, the diacetate **8** slowly hydrolysed and the final product was identified as the methyl ether derivative **6**. Heating **8** overnight at 50 °C in methanol gave **6** in quantitative yield.

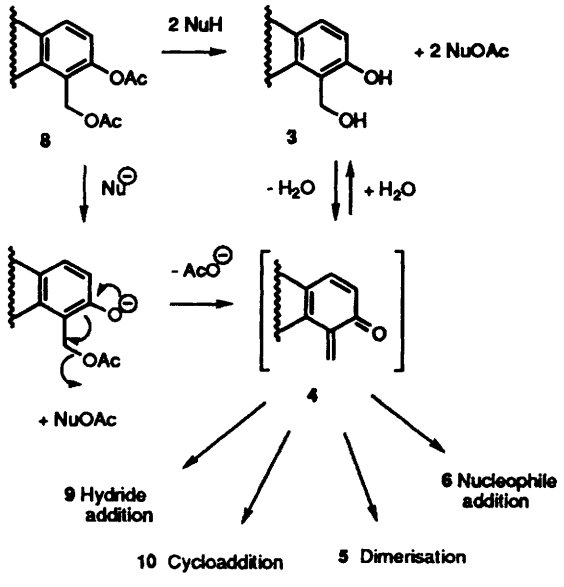



Scheme 4

In an attempt to trap the postulated quinomethane intermediate, the alkaline hydrolysis of diacetate **8** was performed in the presence of ethyl vinyl ether.[18] The reaction proceeded slowly in acetonitrile at room temperature. TLC and HPLC analyses indicated that a new product was formed along with tars. It was isolated in 17% yield and identified as the cyclic compound **10**. In the $^1$H NMR spectrum, all the methylenic protons, resonating between $\delta$ 3.2 and 4.0, appeared as complex multiplets due to the fact that they are diastereotropic. The acetalic proton was identified as a triplet at $\delta$ 5.42 and the methyl protons of the ethoxy group as a triplet at $\delta$ 1.22.

In conclusion, we have prepared different precursors of the 10-hydroxy-11-hydroxymethyl derivative **3**: the methyl ether derivative **6** and the diacetate **8**. All the reactivity data can be interpreted as involving the intermediacy of a quinomethane intermediate **4**. In acidic or basic conditions both compounds **6** and **8** decompose to give the bridged molecule **5**. The postulated quinomethane intermediate **4** has been trapped by a 4 + 2 cycloaddition with ethyl vinyl ether. The strong electrophilic character of this intermediate also accounts for the nucleophilic addition of methanol or hydride on the benzylic carbon, to give respectively derivatives **6** and **9**.[19] From a mechanistic point of view, it seems reasonable to consider that in an acidic medium, solvolysis of the methyl ether **6** gives the protonated quinomethane **4**·HCl, which immediately decomposes in the absence of nucleophiles to give **5**. Hydrolysis in basic conditions of a diacetate derivative (6-acetoxy-5-acetoxymethylquinoline) has been previously used in the literature to prepare a 6-hydroxy-5-hydroxymethylquinoline;[14c] this compound was isolated in good yield. In the present case however we have not been able to isolate the corresponding dihydroxy derivative **3** by hydrolysis of the diacetate **8**, even when working under very mild conditions. Two hypotheses can be proposed for this: either a very high reactivity of compound **3** that transforms instantaneously into the quinomethane intermediate **4**, or direct formation of the quinomethane from compound **8** as shown in Scheme 5. In any case, the quoted derivatives in the present series appear to be much more reactive than most of the analogous compounds already described in the literature.[13,14c] This high reactivity added to the affinity of the phenanthroline skeleton for DNA could confer to this series interesting properties as DNA modifying agents.‡

‡ The affinity constant was measured on calf thymus DNA by the displacement of ethidium bromide technique. A 6 × 10$^3$ dm$^3$ mol$^{-1}$ affinity binding constant has been found.




Scheme 5

## Experimental

### General methods

$^{13}C$ NMR spectra were recorded on a Bruker AM 300 spectrometer using [$^2H_6$]dimethyl sulfoxide ([$^2H_6$]DMSO) ($\delta_C$ 43.5 ppm) or $CDCl_3$ ($\delta_C$ 77.0 ppm) as internal reference. $^1H$ NMR spectra were recorded on Bruker AM 300, AM 200 or AM 400 spectrometers using [$^2H_6$]DMSO ($\delta_H$ 2.49 ppm) or $CDCl_3$ ($\delta_H$ 7.24 ppm) as internal reference. All $J$ values are given in Hz. Mass spectra were obtained on Varian MAT311 and AET MS30 spectrometers. IR spectra were obtained on 298 and 1320 Perkin-Elmer spectrometers as KBr pellets. Column chromatography was carried out using Kieselgel 60 (Merck) silica gel. Melting points were recorded on a Totoli melting point apparatus and are uncorrected. Elemental analyses were performed by the 'service central de microanalyse du CNRS'. UV spectra were recorded on a Perkin-Elmer Lambda UV–VIS instrument.

### 1*H*-[1,3]Benzodioxino[5,6-*b*][1,7]phenanthroline 2

A solution of compound **1** (0.15 g, 0.6 mmol), paraformaldehyde (0.06 g, 2 mmol) and methanesulfonic acid (4 $cm^3$) was stirred at room temperature for 30 min. The mixture was then added dropwise to a mixture of dichloromethane–aqueous ammonia–ice (1:0.05:0.15). The organic layer was separated, dried, concentrated and directly purified by silica gel column chromatography (gradient elution: dichloromethane–ethyl acetate) to yield compound **2** as a pale yellow solid (0.129 g, 75%), mp 219 °C (Found: C, 74.8; H, 4.05; N, 9.9. Calc. for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.2; N, 9.72%); $\lambda_{max}$(EtOH)/nm 255 ($\varepsilon$/$dm^3$ $mol^{-1}$ $cm^{-1}$ 44 600), 296 (29 800) and 309 (34 100); $\nu_{max}$(KBr)/$cm^{-1}$ 3420, 3010, 2900, 1640, 1620, 1590, 1480, 1440, 1400, 1290, 1250, 1200, 1150, 1100, 1020, 980 and 830; $\delta_H$(300 MHz; [$^2H_6$]DMSO) 5.2 (2 H, s, $OCH_2O$), 5.48 (2 H, s, Ar$CH_2$O), 7.25 (1 H, d, $J$ 9.1, 5-H), 7.68 (1 H, dd, $J$ 8.2 and 4.4, 12-H), 7.79 (1 H, d, $J$ 9.2, 9-H), 7.98 (1 H, d, $J$ 9.01, 6-H), 8.06 (1 H, d, $J$ 9.2, 8-H), 8.89 (1 H, s, 7-H), 8.97 (1 H, dd, $J$ 4.4 and 1.7, 11-H) and 9.44 (1 H, dd, $J$ 8.2 and 1.7, 13-H); $m/z$ (EI) 288 (50%, $M^+$), 258 (100, M − $CH_2O$) 230 (56) and 203 (35).

### Reaction of compound 2 under acidic conditions: formation of 11,11′-methylenebis(benzo[*b*][1,7]phenanthrolin-10-ol) 5

A solution of compound **2** (0.6 g, 2.1 mmol), methanesulfonic acid (60 $cm^3$) and water (60 $cm^3$) was heated at 70 °C for 10 h. The mixture was then cooled to room temperature, basified with aqueous potassium carbonate and washed with dichloromethane. The emulsion thus formed was dissolved in methanol and concentrated. Compound **5** was precipitated as a yellow solid (0.4 g, 80%), mp 320 °C (Found: C, 72.3; H, 4.1; N, 9.9. Calc. for $C_{33}H_{20}N_4O_2$·2.5 $H_2O$: C, 72.12; H, 4.58; N, 10.19%); $\lambda_{max}$(EtOH)/nm 219 ($\varepsilon$/$dm^3$ $mol^{-1}$ $cm^{-1}$ 23 000), 238 (25 000), 258 (42 900), 298 (27 900), 310 (23 300), 335 (9200), 352 (7200), 380 (6600) and 396 (3000); $\nu_{max}$(KBr)/$cm^{-1}$ 3000, 1600, 1570, 1475, 1420, 1380, 1270, 1240, 1085, 975, 915 and 790; $m/z$ (DCI/$NH_3$/$Bu^i$) 505 (100%, $M^+$ + 1) and 259 (94, M − $C_{16}H_9N_2$).

### Reaction of compound 2 in acidic methanol: formation of 10-hydroxy-11-methoxymethylbenzo[*b*][1,7]phenanthroline 6 and 10-hydroxy-11-methoxymethyl-4-methylbenzo[*b*][1,7]-phenanthrolin-4-ium methyl sulfate 7

A solution of compound **2** (0.108 g, 0.38 mmol) in methanesulfonic acid–methanol (2 $cm^3$, 1:1, v:v) was heated at 70 °C for 10 h. The mixture was then cooled to room temperature, treated with saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane. Compounds **6** and **7** were precipitated by the addition of diethyl ether–hexane. The crude solid was stirred in ethyl acetate and the insoluble compound **7** was filtered off (10%). The filtrate was concentrated and upon dilution with diethyl ether compound **6** was precipitated as a yellow solid (0.080 g, 80%).

Compound **6**: mp 145 °C (Found: C, 74.3; H, 4.75; N, 9.6. Calc. for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65%); $\lambda_{max}$(EtOH)/nm 258 ($\varepsilon$/$dm^3$ $mol^{-1}$ $cm^{-1}$ 51 800), 298 (32 300), 310 (39 900), 337 (8500), 350 (5800), 380 (5100) and 399 (4700); $\nu_{max}$(KBr)/$cm^{-1}$ 3020, 2920, 2640, 1630, 1610, 1570, 1540, 1470, 1430, 1400, 1360, 1280, 1240, 1220, 1150, 1110, 1080, 1050, 1000, 900, 820, 790 and 720; $\delta_H$(300 MHz; $CDCl_3$) 3.62 (3 H, s, $OCH_3$), 5.61 (2 H, s, Ar$CH_2$O), 7.18 (1 H, d, $J$ 9, 9-H), 7.53 (1 H, dd, $J$ 8.2 and 4.5, 2-H), 7.73 (1 H, d, $J$ 9, 8-H), 7.80 (2 H, m, 5-H and 6-H), 8.39 (1 H, s, 7-H), 8.94 (1 H, dd, $J$ 4.5 and 1.6, 3-H), 9.35 (1 H, s, OH) and 9.46 (1 H, dd, $J$ 8.2 and 1.6, 1-H); $m/z$ (EI) 290 (31%, $M^+$), 275 (100, M − $CH_3$) and 258 (35, M − $CH_3OH$).

Compound **7**: mp >230 °C; $\nu_{max}$(KBr)/$cm^{-1}$ 3430, 3080, 1610, 1470, 1420, 1310, 1190, 1060, 790 and 780; $\delta_H$(200 MHz; $CDCl_3$) 2.29 (3 H, s, $CH_3SO_3^-$), 3.42 (3 H, s, $OCH_3$), 4.70 (3 H, s, $N^+CH_3$), 5.27 (2 H, s, Ar$CH_2$O), 7.56 (1 H, d, $J$ 9, 9-H), 8.2–8.4 (3 H, m), 8.74 (1 H, d, $J$ 9.6, 6-H), 9.24 (1 H, s, 7-H), 9.50 (1 H, d, $J$ 5.9, 3-H), 10.35 (1 H, d, $J$ 8.2, 1-H) and 10.91 (1 H, s, OH); $m/z$ (DCI/$NH_3$/$Bu^i$) 291 (100%, M + $H^+$ − $CH_3$), 275 (10) and 259 (3).

### 10-Acetoxy-11-acetoxymethylbenzo[*b*][1,7]phenanthroline 8

A mixture of compound **2** (0.45 g, 1.56 mmol), methanesufonic acid (12 $cm^3$), acetic acid (12 $cm^3$) and acetic anhydride (6 $cm^3$) was heated at 70 °C for 9 h. The mixture was then cooled to room temperature, treated with saturated aqueous sodium carbonate and extracted with dichloromethane. Compound **8** was precipitated by the addition of diethyl ether–hexane and isolated as a pale brown solid (0.42 g, 75%), mp 215 °C (Found: C, 69.7; H, 4.5; N, 7.6. Calc. for $C_{21}H_{16}N_2O_4$: C, 69.99; H, 4.47; N, 7.77%); $\lambda_{max}$(EtOH)/nm 218 ($\varepsilon$/$dm^3$ $mol^{-1}$ $cm^{-1}$ 33 100), 251 (48 750), 291 (34 100), 301 (44 600), 342 (6900), 358 (5250) and 377 (3300); $\nu_{max}$(KBr)/$cm^{-1}$ 1750, 1730, 1610, 1570, 1465, 1385, 1360, 1270, 1260, 1200, 1080, 1030, 965, 920 and 820; $\delta_H$(200 MHz; [$^2H_6$]DMSO) 1.99 (3 H, s, $ArCH_2OCOCH_3$), 2.41 (3 H, s, $ArOCOCH_3$), 6.0 (2 H, s, Ar$CH_2$O), 7.62 (1 H, d, $J$ 9.4, 9-H), 7.83 (1 H, dd, $J$ 8.2 and 6.1, 2-H), 7.97 (1 H, d, $J$ 9, 5-H), 8.26 (1 H, d, $J$ 9.4, 8-H), 8.35 (1 H, d, $J$ 9, 6-H), 9.10 (1 H, dd, $J$ 6.1 and 1.5, 3-H), 9.21 (1 H, s, 7-H)

and 9.60 (1 H, dd, *J* 8.2 and 1.5, 1-H); *m/z* (DCI/$NH_3$/$Bu^i$) 361 (100%, $M^+ + 1$).

**11-Methylbenzo[*b*][1,7]phenanthrolin-10-ol 9**

A mixture of compound **8** (0.050 g, 0.14 mmol) and sodium borohydride (0.011 g, 0.28 mmol) in methanol (5 $cm^3$) was stirred at room temperature for 10 min. The mixture was then added dropwise to dichloromethane–water (10:2, v/v). The organic layer was separated, dried with magnesium sulfate and concentrated under reduced pressure. Compound **9** was precipitated as a yellow solid (0.033 g, 90%), mp 240 °C (Found: C, 75.8; H, 4.5; N, 10.25. Calc. for $C_{17}H_{12}N_2O{\cdot}0.5\ H_2O$: C, 75.82; H, 4.87; N, 10.40%); $\lambda_{max}$(EtOH)/nm 311 ($\varepsilon$/$dm^3$ $mol^{-1}$ $cm^{-1}$ 27 500), 300 (22 600), 260 (38 400), 235 (20 200) and 218 (18 700); $\nu_{max}$(KBr)/$cm^{-1}$ 3440, 3200, 2640, 1610, 1520, 1410, 1310, 1240, 1085, 1055, 910 and 790; $\delta_H$(200 MHz; [$^2H_6$]DMSO) 2.68 (3 H, s, ArC$H_3$), 7.41 (1 H, d, *J* 8.9, 9-H), 7.83–8.09 (3 H, m, 2-H, 5-H and 8-H), 8.33 (1 H, d, *J* 9, 6-H), 8.93 (1 H, s, 7-H), 9.13 (1 H, d, *J* 5.1, 3-H) and 9.9 (1 H, d, *J* 8.1, 1-H); *m/z* (EI) 260 (100%, $M^+$).

**3-Ethoxy[1]benzooxino[5,6-*b*][1,7]phenanthroline 10**

A mixture of compound **8** (0.100 g, 0.27 mmol), acetonitrile (20 $cm^3$), ethyl vinyl ether (10 $cm^3$) and aqueous sodium hydroxide (1 mol $dm^{-3}$; 2 $cm^3$) was stirred at room temperature for 4 h. The mixture was then concentrated, diluted with water and extracted with chloroform. The organic layer was evaporated to dryness and the crude solid directly purified by column chromatography on silica gel (gradient elution: chloroform–ethyl acetate) to yield compound **10** as a pale yellow solid (0.015 g, 17%), mp 168–169 °C (Found: C, 74.55; H, 5.4; N, 8.1. Calc. for $C_{21}H_{18}N_2O_2{\cdot}0.5\ H_2O$: C, 74.32; H, 5.64; N, 8.25%); $\nu_{max}$(KBr)/$cm^{-1}$ 3450, 2980, 2920, 1610, 1470, 1420, 1390, 1320, 1280, 1220, 1120, 1100, 1060, 950, 920, 870, 840 and 790; $\delta_H$(300 MHz; $CDCl_3$) 1.22 (3 H, t, *J* 7.02, $CH_3$), [2.32–2.26 (1 H, m), 2.20–2.13 (1 H, m), ArC$H_2$C$H_2$CH], [4.0–3.94 (1 H, m), 3.76–3.66 (2 H, m), 3.52–3.42 (1 H, m), C$H_2$Ar and OC$H_2$$CH_3$)], 5.42 (1 H, t, *J* 2.8, CH), 7.22 (1 H, d, *J* 9, 9-H), 7.62 (1 H, dd, *J* 8.1 and 4.8, 2-H), 7.82 (1 H, d, *J* 9, 8-H), 7.9 (1 H, d, *J* 9.1, 5-H), 7.98 (1 H, d, *J* 9.1, 6-H), 8.58 (1 H, s, 7-H), 9.0 (1 H, dd, *J* 4, 8 and 1.7, 3-H) and 9.74 (1 H, dd, *J* 8.1 and 1.7, 1-H); $\delta_C$($CDCl_3$) 15.19 ($CH_3$), 16.66 (ArC$H_2$C$H_2$CH), 26.35 (ArC$H_2$), 64.11 (OC$H_2$$CH_3$), 97.88 (CH), 116.71, 120.87, 121.73, 122.83, 123.09, 126.93, 127.44, 127.53, 129.72, 133.18, 135.32, 145.96, 147.29, 150.53, 151.09 and 153.27; *m/z* (FAB+, NBA) 331 (73, $M^+ + 1$), 301 (34, $M^+ - C_2H_5$), 285 (23, $M^+ - OC_2H_5$) and 273.

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