

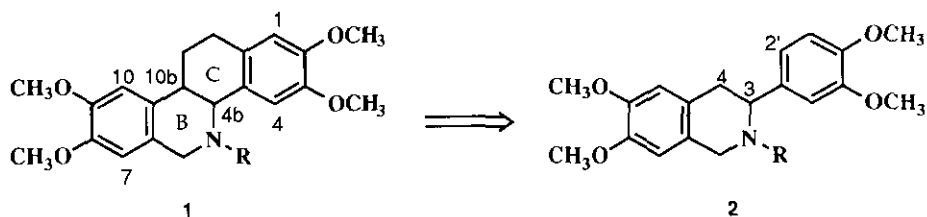
A FACILE ACCESS TO BENZO[*c*]PHENANTHRIDINES VIA 4-FUNCTIONALIZED 3-ARYLISOQUINOLINES

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Abstract-4b,10b-*trans*-*N*-Benzyltetrahydrobenzo[*c*]phenanthridines have been synthesized by a short and efficient route from a 4-functionalized 3-aryltetrahydroisoquinoline. The 3-aryl-4-carboxymethyltetrahydroisoquinoline (**5**) and 4-formylmethyl derivative (**7**) were cyclodehydrated to the corresponding tetracycles.

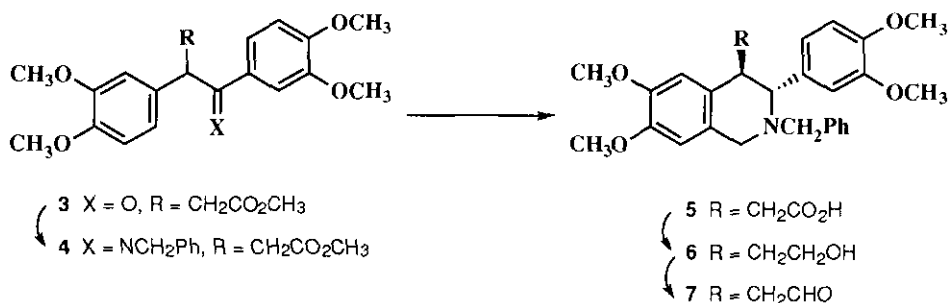
The interest in benzo[*c*]phenanthridines,¹ a group of natural products that are found in the *Fumariaceae*, *Papaveraceae* and *Rutaceae*, has been stimulated by the observations that they exhibit highly promising antitumor² and antileukemic activity.³ In this respect, nitidine and fagaronine are proving particularly interesting as they are shown to inhibit HIV 1 and 2 reverse transcriptase.⁴ More recently nitidine and fagaronine have been reported to act as topoisomerase I inhibitors.⁵ This exciting pharmacological activity coupled with the required diminishing of the undesirable acute toxicity observed in some cases have stimulated numerous synthetic investigations.⁶ Some years ago, we were attracted by the challenge of designing a concise approach to benzo[*c*]phenanthridine skeleton which involved C-2' or C-4 substituted 3-aryltetrahydroisoquinolines. At the outset of our investigations, few examples on the carbocyclization of these nitrogenated intermediates to the targeted tetracycles have been found. Thus, 2'-vinyl,⁷ 2'-dimethoxyethyl,⁸ 2'-methoxycarbonylmethyl-^{6b,9} and 2'-formylmethyl-3-aryltetrahydroisoquinoline derivatives¹⁰ undergo annelation of the C ring to provide the benzo[*c*]phenanthridine skeleton. In this paper we report our results concerning the synthesis of benzo[*c*]phenanthridines from C-4 substituted 3-aryltetrahydroisoquinolines.



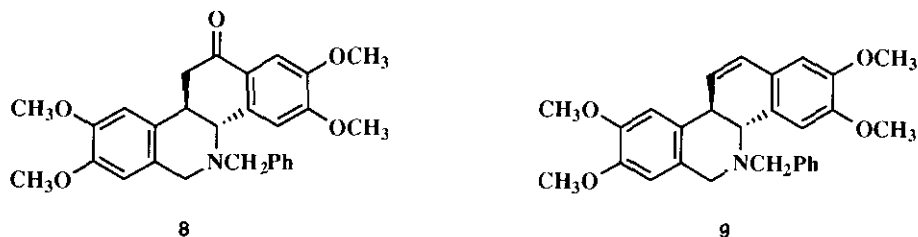
In this sense, Cushman¹¹ and Shamma¹² have prepared 4-carboxymethyl-2-methyl-1(2*H*)-isoquinolones

by condensation of homophthalic anhydrides with imines and subsequent homologation by an Arndt-Eistert sequence. A variety of methods of cyclodehydration of these isoquinolones have been explored, and depending on the substituents, they can be converted into 6,12-dioxobenzo[*c*]phenanthridines using PPA¹¹ on a steam bath or a mixture of MSA and P₂O₅ at room temperature.¹² More recently, diastereomeric 12(11*H*)-oxobenzo[*c*]phenanthridines have been obtained in excellent yields and fully characterized by X-Ray diffraction analysis.^{6c} This route involved the initial preparation of a 3-phenyl-2-(*p*-toluenesulfonyl)-1,2-dihydro-4(3*H*)-isoquinolone, followed by a Reformatsky-type reaction to introduce the methoxycarbonylmethyl group at the C-4 position.¹³ In this case, diastereomeric 4-methoxycarbonylmethyltetrahydroisoquinolines were converted into the corresponding acyl chlorides and then submitted to cyclization with AlCl₃ in CH₂Cl₂ at low temperature (-10 °C).

The key intermediate in our synthesis of the benzo[*c*]phenanthridine skeleton is the 3-aryl-*N*-benzyl-4-carboxymethyl-1,2,3,4-tetrahydroisoquinoline (**5**), obtained from the *N*-benzyl-1,2-diarylethylimine (**4**), itself readily prepared from the aryl benzyl ketone (**3**) as previously reported.¹⁴ The 3,4-*trans*-tetrahydroisoquinoline (**5**) was also reduced with LiAlH₄ in THF to give the 4-hydroxymethyltetrahydroisoquinoline (**6**) with no loss of stereochemical purity. Oxidation under Swern conditions¹⁵ provided the 4-formylmethyltetrahydroisoquinoline (**7**) with good yield (88%).



Treatment of the 3,4-*trans*-tetrahydroisoquinoline (**5**) with PPA at 50 °C for 8 hours afforded the corresponding 4b,10b-*trans*-4b,5,6,10b-tetrahydro-12(11*H*)-oxobenzo[*c*]phenanthridine (**8**) in 78% yield. Attempted cyclization of the isoquinoline (**7**) with aqueous hydrochloric acid with variations in time and temperature reaction conditions (up to 5 days at refluxing 6M HCl) only gave starting material. However, the target tetracycle was obtained by treatment of **7** with TFA in refluxing CH₂Cl₂. In fact, under these reaction conditions the reaction was monitored by TLC (SiO₂, hexane:ethyl acetate 1/1) and the appearance of a product up to the starting material was observed. After work-up, this product was identified as the 4b,10b-*trans*-4b,5,6,10b-tetrahydrobenzo[*c*]phenanthridine (**9**).



The $^1\text{H-NMR}$ of the isolated 12(11*H*)-oxobenzo[*c*]phenanthridine (**8**) exhibited four singlets at the aromatic protons resonance field, thus indicating that cyclization had occurred. The complete structure and stereochemistry of **8** was established on the basis of NOE experiments. Irradiation of methylenic protons H_6 and H_{11} enhances aromatic H_7 (δ 6.85 ppm) and H_{10} (δ 6.53 ppm), respectively. Anisotropic effects of the carbonyl group and the nitrogen atom puts H_1 and H_4 downfield (δ 7.58 and 7.53 ppm, respectively). Furthermore, the coupling constant measured for the methynic protons H_{4b} and H_{10b} ($J_{4b-10b} = 10.9$ Hz) was in agreement with an antiperiplanar disposition of these two protons in a B/C *trans*-fused tetrahydrobenzo[*c*]phenanthridine core.¹⁶ One methylenic H_{11} appeared as a double doublet at δ 2.62 ppm, showing $J_{\text{gem}} = 16.5$ Hz and $J_{10b-11} = 13.9$ Hz, this value corresponding to an axial-axial coupling between H_{10b} and H_{11} . On the other hand, the NOE data collected were also consistent with this proposal. Thus, the observation of NOE between H_{11} and H_{4b} allowed us to assign the mentioned signal at δ 2.62 ppm as $\text{H}_{11\text{ax}}$, as well as to confirm the antiperiplanarity of H_{4b} and H_{10b} . Finally, the signal of $\text{H}_{11\text{eq}}$ (δ 3.47-3.54 ppm) is downfield (δ 0.85-0.92 ppm) of $\text{H}_{11\text{ax}}$ due to the deshielding effect associated with the anisotropy of the carbonyl group.¹⁷

The $^1\text{H-NMR}$ of the tetrahydrobenzo[*c*]phenanthridine (**9**) exhibited as more significant signals four singlets at δ between 6.52-7.38 ppm corresponding to the aromatic protons, two double doublets at δ 6.40 ppm ($J_{\text{AB}} = 9.8$ Hz, $J_{\text{AX}} = 1.9$ Hz) and δ 6.53 ppm ($J_{\text{AB}} = 9.8$ Hz, $J_{\text{BX}} = 3.0$ Hz), corresponding to H_{12} and H_{11} respectively. On the other hand, in the $^{13}\text{C-NMR}$ four signals were observed at the aliphatic region (not including the methoxy groups at δ 55.8 and 56.0 ppm) and they were assigned to C_{10b} (δ 32.1 ppm), C_6 and N-CH_2 (δ 49.8 and 52.9 ppm), and C_{4b} (δ 63.6 ppm). In a similar way, a B/C *trans*-fused ring could be proposed on the basis of the coupling constant value $J_{4b-10b} = 17.7$ Hz. However, in this case it was not possible to perform selective irradiation experiments to measure this constant, as signals due to both protons overlapped with the methylenic and methoxylic protons. $^1\text{H-}^{13}\text{C}$ correlation experiments (HMQC) allowed us to establish the correlation between the signals of C_{4b} (δ 63.4 ppm) and C_{10b} (δ 32.1 ppm) with the protons that resonated at δ 4.29 and 3.78 ppm assigned as H_{4b} and H_{10b} respectively. In this case, the signal of H_{4b} at δ 4.29 ppm appeared as a doublet of $J = 17.7$ Hz.

In summary, a new and highly efficient synthetic approach to the benzo[*c*]phenanthridine nucleus from C-4 substituted 3-arylisquinolines, based on newly found cyclodehydration reaction (route from **7** to **9** by the treatment with TFA), is described. Besides, this current development represents to date, one of the most straightforward route to the above mentioned tetracycles.

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus and are uncorrected. IR spectra were obtained by using a Perkin-Elmer 1430 spectrophotometer on KBr pellets (solids) or CHCl_3 solution (oils). NMR spectra were recorded on a Bruker AC-250 spectrometer at 20-25 °C, running at 250 MHz for ^1H and 62.8 MHz for ^{13}C in CDCl_3 as solvent and TMS as internal standard. Chemical shifts (δ) are given in ppm and coupling constants (J) are reported in herz (Hz). $^1\text{H-}^1\text{H}$ NOE experiments were carried out in the difference mode by irradiation of all the lines of a multiplet. Assignment of individual ^{13}C resonances are supported by DEPT experiments. Elemental analyses were performed on a Perkin-Elmer 2400 CHN apparatus. Mass

spectrometry was performed at a 70 eV ionization potential to obtain impact spectra. TLC was carried out with 0.2 mm thick silica gel plates (Merck Kieselgel GF₂₅₄) and visualized by UV light or by spraying with Dragendorff's reagent. Flash column chromatography on silica gel was performed with Merck Kieselgel 60 (230-400 mesh). All solvents used in reactions were anhydrous and purified according to standard procedures. Transfers of solvents and solutions were performed by syringe or *via* canula.

3,4-*trans*-N-Benzyl-6,7-dimethoxy-3-(3,4-dimethoxyphenyl)-4-(2-hydroxyethyl)-

1,2,3,4-tetrahydroisoquinoline (6). A slurry of LiAlH₄ (0.11 g; 3.0 mmol) in ether (15 mL) was stirred while a solution of the tetrahydroisoquinoline (5)¹⁴ (0.75 g; 1.5 mmol) in ether (30 mL) was added dropwise at 0 °C and under argon atmosphere. The reaction mixture was left to attain rt and then stirred an additional 5 h. After cooling on an ice-bath, water (10 mL) was carefully added and the mixture was extracted with CH₂Cl₂ (3 x 75 mL). The combined organic extracts were washed with saturated NaCl solution (2 x 20 mL), dried (Na₂SO₄) and concentrated on a rotatory evaporator. The residue was crystallized from methanol to give the 4-(2-hydroxyethyl)tetrahydroisoquinoline (6) (0.63 g, 91%). mp 158-159 °C (MeOH). R_f (hexane: ethyl acetate 1:1): 0.12. IR (KBr) (cm⁻¹): 3350-3550 (br, OH). ¹H-NMR (δ, ppm): 2.15-2.20 (m, 2H, CH₂CH₂OH), 3.15-3.25 (m, 3H, H_{1A} and CH₂Ph), 3.33 (m, 1H, H₄), 3.46-3.51 (m, 2H, CH₂CH₂OH), 3.58-3.65 (m, 1H, H_{1B}),[#] 3.63 (s, 3H, OCH₃),[#] 3.80 (s, 3H, OCH₃), 3.84 (s, 3H, OCH₃), 3.85 (s, 3H, OCH₃), 4.05 (s, 1H, H₃), 6.45 (s, 1H, H₈), 6.57-6.62 (m, 3H, H₅, H₂ and H₆), 6.77 (d, 1H, J_o = 8.1, H₅), 7.30-7.35 (m, 5H, Ph). ([#] Overlapped signals). ¹³C-NMR (δ, ppm): 40.8 (CH₂CH₂OH), 42.8 (C₄), 48.2 (CH₂Ph), 55.5, 55.7, 55.9 (OCH₃), 58.3 (C₁), 60.2 (CH₂CH₂OH), 67.0 (C₃), 108.7, 110.7, 112.0, 121.1 (C_{arom}-H), 126.4, 127.0, 127.1 (C_{arom}-C), 127.5, 128.6, 130.3 (C_{arom}-H), 130.4, 136.9 (C_{arom}-C), 147.5, 148.4 (C_{arom}-O). Anal. Calcd for C₂₈H₃₃NO₅: C, 78.55; H, 7.17; N, 3.02. Found: C, 77.48; H, 7.15; N, 3.19.

3,4-*trans*-N-Benzyl-6,7-dimethoxy-3-(3,4-dimethoxyphenyl)-4-formylmethyl-1,2,3,4-

tetrahydroisoquinoline (7). To a stirred solution of oxalyl chloride (90 mL; 1.1 mmol) in dry CH₂Cl₂ (9 mL) at -60 °C under argon, a solution of DMSO (0.15 mL, 2.1 mmol) in dry CH₂Cl₂ (3 mL) was added. After the mixture was stirred for a further 10 min, a solution of the 4-hydroxymethyltetrahydroisoquinoline (6) (0.45 g; 1.0 mmol) in dry CH₂Cl₂ (15 mL) was added dropwise at -60 °C to the reaction mixture (*ca.* 1 h) and then quenched with water (15 mL). The aqueous layer was extracted with additional CH₂Cl₂ and the combined organic extracts were washed with 1M HCl (3 x 50 mL), water (3 x 50 mL), 5% NaHCO₃ (3 x 20 mL) and water (3 x 50 mL), dried over MgSO₄ and evaporated to dryness. Flash column chromatography on silica gel, eluting with hexane:ethyl acetate 7:3 afforded the 4-formylmethyltetrahydroisoquinoline (7) (0.39 g, 88%). mp 121-123 °C (ethyl acetate). R_f (hexane: ethyl acetate 1:1): 0.32. IR (KBr) (cm⁻¹): 1710 (C=O), 1610. ¹H-NMR (δ, ppm): 2.77 (ddd, 1H, J_{AB} = 16.9, J_{AX} = 4.0, J_{AY} = 3.1, CH_AH_BCHO), 3.09 (ddd, 1H, J_{BA} = 16.9, J_{BX} = 6.0, J_{BY} = 1.2, CH_AH_BCHO), 3.35 (d, 1H, J = 15.5, NCH_AH_BPh),[#] 3.46 (d, 1H, J = 13.1, H_{1A}),[#] 3.50-3.61 (m, 2H, H₄ and H_{1B}),[#] 3.59 (d, 1H, J = 15.4, NCH_AH_BPh),[#] 3.68 (s, 3H, OCH₃), 3.73 (d, 1H, J = 3.0, H₃), 3.81 (s, 3H, OCH₃), 3.85 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 6.47 (s, 1H, H₈), 6.59-6.63 (m, 3H, H₂ and H₆), 6.69 (s, 1H, H₅), 6.77 (d, 1H, J_o = 8.6, H₅), 7.30-7.34 (m, 5H, Ph), 9.70 (m, 1H, CHO).

(# exchangeables signals). $^{13}\text{C-NMR}$ (δ , ppm): 39.9 (C_4), 50.4, 51.5 (NCH_2Ph and CH_2CHO), 55.5, 55.7, 55.8, 55.9 (OCH_3), 59.5 (C_1), 65.8 (C_3), 108.7, 110.6, 111.6, 121.1 ($\text{C}_{\text{arom-H}}$), 126.9, ($\text{C}_{\text{arom-C}}$), 127.1 ($\text{C}_{\text{arom-H}}$), 128.2 ($\text{C}_{\text{arom-C}}$), 128.3, 128.9 ($\text{C}_{\text{arom-H}}$), 130.2, 138.7 ($\text{C}_{\text{arom-C}}$), 147.6, 148.0, 148.3, 148.5 ($\text{C}_{\text{arom-O}}$), 201.7 (CHO). Anal. Calcd for $\text{C}_{28}\text{H}_{31}\text{NO}_5$: C, 72.86; H, 6.77; N, 3.03. Found: C, 72.79; H, 6.80; N, 3.12.

4b,10b-trans-N-Benzyl-12(11H)-oxo-4b,5,6,10b-tetrahydro-2,3,8,9-tetramethoxybenzo[c]phenanthridine (8). A suspension of the tetrahydroisoquinoline (**5**) (0.16g, 0.3 mmol) in PPA (15 mL) was stirred at 50 °C for 8 h. The mixture was left to attain rt and then treated sequentially with water (50 mL), 40 % NaOH (10 mL) and CH_2Cl_2 (5 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated on a rotatory evaporator to give a crude oil that was chromatographed on column under pressure (SiO_2 , hexane:ethyl acetate 6:4), thus obtaining the 12(11H)-oxobenzo[c]phenanthridine (**8**) (0.12 g, 78%). mp 250-251 °C (MeOH). Rf (hexane: ethyl acetate 1:1): 0.36. IR (KBr) (cm^{-1}): 1660 (C=O). $^1\text{H-NMR}$ (δ , ppm): 2.59-2.65 (dd, 1H, $J_{\text{AB}} = 16.5$, $J_{\text{AX}} = 1.9$, $\text{H}_{11\text{ax}}$), 3.47-3.54 (m, 3H, 2 x H_6 and $\text{H}_{11\text{ec}}$), 3.74-3.94 (m, 2H, $\text{H}_{10\text{b}}$ and $\text{NCH}_A\text{H}_B\text{Ph}$),[#] 3.83 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.94, (s, 3H, OCH_3), 4.29-4.37 (m, 2H, $\text{H}_{4\text{b}}$ and $\text{NCH}_A\text{H}_B\text{Ph}$), 6.53 (s, 1H, H_{10}), 6.85 (s, 1H, H_7), 7.27-7.48 (m, 5H, Ph), 7.53 (s, 1H, H_4), 7.58 (s, 1H, H_1) (#Overlapped signals with those of methoxy groups). $^{13}\text{C-NMR}$ (δ , ppm): 33.6 ($\text{C}_{10\text{b}}$), 43.5 (C_{11}), 49.5, 52.7 (NCH_2Ph and C_6), 55.9, 56.0, 56.1 (OCH_3), 63.1 ($\text{C}_{4\text{b}}$), 107.8, 108.4, 108.8, 110.2 ($\text{C}_{\text{arom-H}}$), 126.0, ($\text{C}_{\text{arom-C}}$), 126.9, 127.6 ($\text{C}_{\text{arom-H}}$), 127.8 ($\text{C}_{\text{arom-C}}$), 128.5 ($\text{C}_{\text{arom-H}}$), 139.4, 139.6 ($\text{C}_{\text{arom-C}}$), 148.0, 148.1, 148.5, 154.3 ($\text{C}_{\text{arom-O}}$), 195.5 (C=O). MS (EI) [m/z (%)]: 459 (M^+ , 5), 458 (6), 368 (14), 177 (6), 146 (6), 91 (100). Anal. Calcd for $\text{C}_{28}\text{H}_{29}\text{NO}_5$: C, 71.60; H, 8.37; N, 2.98. Found: C, 71.45; H, 8.30; N, 3.12.

4b,10b-trans-N-Benzyl-4b,5,6,10b-tetrahydro-2,3,8,9-tetramethoxybenzo[c]phenanthridine (9). TFA (8 mL) was added dropwise to a solution of the 4-formylmethyltetrahydroisoquinoline (**7**) (0.23 g; 0.5 mmol) in dry CH_2Cl_2 (10 mL) under argon atmosphere at 0 °C. The mixture was refluxed for 7 h and after cooling at rt, it was poured into ice-water (50 mL), basified with 40% KOH and then extracted with CH_2Cl_2 (5 x 50 mL). The organic extracts were dried (Na_2SO_4) and evaporated to dryness and the so-obtained yellow oil was flash column chromatographed (SiO_2 , hexane:ethyl acetate 7.5:2.5) to afford the benzo[c]phenanthridine (**9**) (0.14 g, 65%). mp 152-153 °C (MeOH). Rf (hexane: ethyl acetate 1:1): 0.42. IR (KBr) (cm^{-1}): 1605, 1510. $^1\text{H-NMR}$ (δ , ppm): 3.48 (d, 1H, $J = 14.6$, $\text{NCH}_A\text{H}_B\text{Ph}$),[#] 3.73-3.80 (m, 2H, $\text{H}_{10\text{b}}$ and $\text{H}_{6\text{A}}$), 3.79 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.12-4.21 (m, 2H, $\text{H}_{6\text{B}}$ and $\text{NCH}_A\text{H}_B\text{Ph}$), 4.30 (d, 1H, $J = 17.7$, $\text{H}_{4\text{b}}$), 6.40 (dd, 1H, $J_{\text{AB}} = 9.8$, $J_{\text{AX}} = 1.9$, H_{12}), 6.52 (s, 1H, H_7), 6.53 (dd, 1H, $J_{\text{BA}} = 9.8$, $J_{\text{BX}} = 3.0$, H_{11}), 6.74 (s, 1H, H_1), 6.99 (s, 1H, H_{10}), 7.20-7.28 (m, 5H, Ph), 7.31 (s, 1H, H_4) (#Exchangeables signals). $^{13}\text{C-NMR}$ (δ , ppm): 32.1 ($\text{C}_{10\text{b}}$), 49.8, 52.9 (NCH_2Ph and C_6), 55.8, 56.0 (OCH_3), 63.6 ($\text{C}_{4\text{b}}$), 108.0, 108.9, 110.1, 110.2 (C_7 , C_1 , C_{10} and C_4), 126.8, 127.4, 127.8 ($\text{C}_{\text{arom-H}}$), 127.6 ($\text{C}_{\text{arom-C}}$), 128.5, 129.2 (C_{11} and C_{12}), 129.5, 129.7, 140.0 ($\text{C}_{\text{arom-C}}$), 147.6, 147.8, 148.5 ($\text{C}_{\text{arom-O}}$). MS (EI) [m/z (%)]: 443 (M^+ , 7), 352 (18), 350 (7), 338 (10), 335 (10), 106

(56), 91 (100). Anal. Calcd for $C_{28}H_{29}NO_4$: C, 75.82; H, 6.59; N, 3.16. Found: C, 75.75; H, 6.55; N, 3.28.

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16. This value is in agreement with the coupling constants measured in 12(11*H*)-benzo[c]phenanthridines ($J = 11.1$ Hz, ref. 6c) and 6,12-dioxobenzo[c]phenanthridine ($J = 11$ Hz, ref. 11; and $J = 11.5$ Hz, ref. 12). 17. G.R. Lenz, *J. Org. Chem.*, 1974, **39**, 2846; G.E. Hankes, P.D. Palasz, J.H.P. Utley, and J.D. Hardstone, *J. Chem. Res. (S)*, 1983, 208.
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