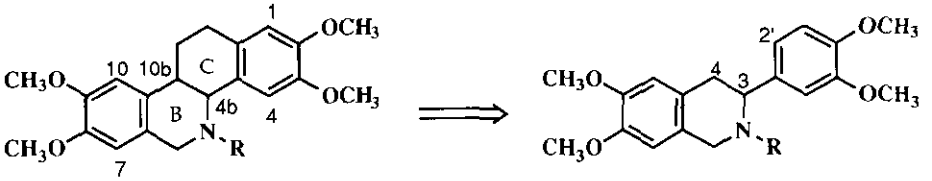
A FACILE ACCESS TO BENZO[*c*]PHENANTHRIDINES *VIA* 4-FUNCTIONALIZED 3-ARYLISOQUINOLINES

Teresa Vicente, Esther Domínguez,* and María Jesús Villa

Departamento de Química Orgánica, Facultad de Ciencias, Universidad del País Vasco P.O. Box 644-48080 Bilbao, Spain

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 antitumor[2] 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-arylisoquinolines. 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-arylisoquinoline derivatives[10] 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.



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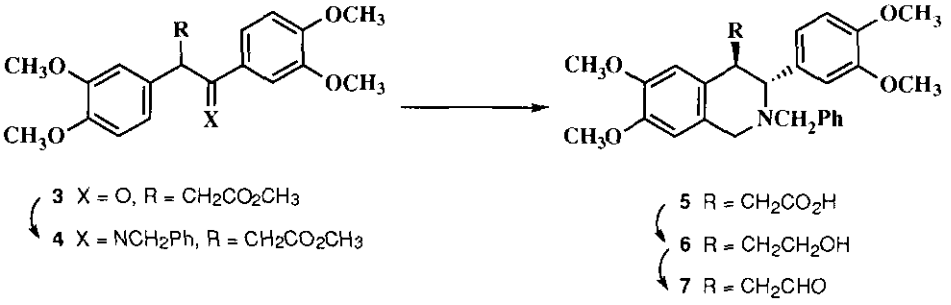
In this sense, Cushman[11] and Shamma[12] have prepared 4-carboxymethyl-2-methyl-1(2*H*)-isoquinolones

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 PPA[11] on a steam bath or a mixture of MSA and P_2O_5 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 $AlCl_3$ in CH_2Cl_2 at low temperature (-10 °C).

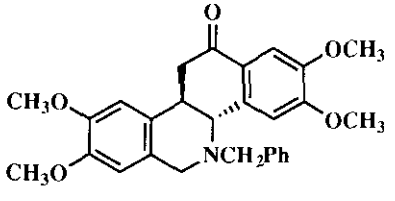
The key intermediate in our synthesis of the benzo[*c*]phenanthridine skeleton is the 3-aryl-*N*-benzyl-4-carboxymethyl-1,2,3,4-tetrahydroisoquinoline (**5**), obtained from the *N*-benzyl-1,2-diarylethylimine (**4**), itself readily prepared from the aryl benzyl ketone (**3**) as previously reported.[14] The 3,4-*trans*-tetrahydroisoquinoline (**5**) was also reduced with $LiAlH_4$ in THF to give the 4-hydroxymethyltetrahydroisoquinoline (**6**) with no loss of stereochemical purity. Oxidation under Swern conditions[15] provided the 4-formylmethyltetrahydroisoquinoline (**7**) with good yield (88%).



3 X = O, R = $CH_2CO_2CH_3$
4 X = NCH_2Ph, R = $CH_2CO_2CH_3$

5 R = CH_2CO_2H
6 R = CH_2CH_2OH
7 R = CH_2CHO

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 CH_2Cl_2. In fact, under these reaction conditions the reaction was monitored by TLC (SiO_2, 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**).



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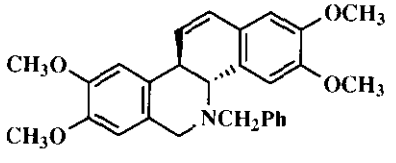

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The H-NMR of the isolated 12(11*H*)-oxobenzo[*c*]phenanthridine (**8**) exhibited four singlets at the aromatic protons resonance field, thus indicating that cyclization had occurred. The complete structure and stereochemistry of **8** was established 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} ($J_{4b\text{-}10b}$= 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_{gem}= 16.5 Hz and $J_{10b\text{-}11}$= 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 H_{11ax}, as well as to confirm the antiperiplanarity of H_{4b} and H_{10b}. Finally, the signal of H_{11eq} (δ 3.47-3.54 ppm) is downfield (δ 0.85-0.92 ppm) of H_{11ax} due to the deshielding effect associated with the anisotropy of the carbonyl group.[17]

The ^{1}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_{AB}= 9.8 Hz, J_{AX}= 1.9 Hz) and δ 6.53 ppm (J_{AB}= 9.8 Hz, J_{BX}= 3.0 Hz), corresponding to H_{12} and H_{11} respectively. On the other hand, in the ^{13}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 $J_{4b\text{-}10b}$= 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}H-^{13}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-arylisoquinolines, 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 ^{1}H 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}H-^{1}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 GF_{254}) 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 $LiAlH_4$ (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 CH_2Cl_2 (3 x 75 mL). The combined organic extracts were washed with saturated NaCl solution (2 x 20 mL), dried (Na_2SO_4) 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). Rf (hexane: ethyl acetate 1:1): 0.12. **IR** (KBr) (cm^{-1}): 3350-3550 (br, OH). **^{1}H-NMR** (δ, ppm): 2.15-2.20 (m, 2H, $C\underline{H}_2CH_2OH$), 3.15-3.25 (m, 3H, H_{1A} and CH_2Ph), 3.33 (m, 1H, H_4), 3.46-3.51 (m, 2H, $CH_2C\underline{H}_2OH$), 3.58-3.65 (m, 1H, H_{1B}),# 3.63 (s, 3H, OCH_3),# 3.80 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.85, (s, 3H, OCH_3), 4.05 (s, 1H, H_3), 6.45 (s, 1H, H_8), 6.57-6.62 (m, 3H, H_5, $H_{2'}$ and $H_{6'}$), 6.77 (d, 1H, J_o= 8.1, $H_{5'}$), 7.30-7.35 (m, 5H, Ph). (# Overlapped signals). **^{13}C-NMR** (δ, ppm): 40.8 ($\underline{C}H_2CH_2OH$), 42.8 (C_4), 48.2 ($\underline{C}H_2Ph$), 55.5, 55.7, 55.9 (OCH_3), 58.3 (C_1), 60.2 ($CH_2\underline{C}H_2OH$), 67.0 (C_3), 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 $C_{28}H_{33}NO_5$: 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 CH_2Cl_2 (9 mL) at -60 °C under argon, a solution of DMSO (0.15 mL, 2.1 mmol) in dry CH_2Cl_2 (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 CH_2Cl_2 (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 CH_2Cl_2 and the combined organic extracts were washed with 1M HCl (3 x 50 mL), water (3 x 50 mL), 5% $NaHCO_3$ (3 x 20 mL) and water (3 x 50 mL), dried over $MgSO_4$ 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). Rf (hexane: ethyl acetate 1:1): 0.32. **IR** (KBr) (cm^{-1}): 1710 (C=O), 1610. **^{1}H-NMR** (δ, ppm): 2.77 (ddd, 1H, J_{AB}= 16.9, J_{AX}= 4.0, J_{AY}= 3.1, $C\underline{H}_AH_BCHO$), 3.09 (ddd, 1H, J_{BA}= 16.9, J_{BX}= 6.0, J_{BY}= 1.2, $CH_A\underline{H}_BCHO$), 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, H_4 and H_{1B}),# 3.59 (d, 1H, J= 15.4, NCH_AH_BPh),# 3.68 (s, 3H, OCH_3), 3.73 (d, 1H, J= 3.0, H_3), 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.86, (s, 3H, OCH_3), 6.47 (s, 1H, H_8), 6.59-6.63 (m, 3H, $H_{2'}$ and $H_{6'}$), 6.69 (s, 1H, H_5), 6.77 (d, 1H, J_o= 8.6, $H_{5'}$), 7.30-7.34 (m, 5H, Ph), 9.70 (m, 1H, CHO).

(# exchangeables signals). **^{13}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 (C_{arom}-H), 126.9, (C_{arom}-C), 127.1 (C_{arom}-H), 128.2 (C_{arom}-C), 128.3, 128.9 (C_{arom}-H), 130.2, 138.7 (C_{arom}-C), 147.6, 148.0 148.3, 148.5 (C_{arom}-O), 201.7 (CHO). Anal. Calcd for $C_{28}H_{31}NO_5$: 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(11*H*)-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(11*H*)-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}H-NMR** (δ, ppm): 2.59-2.65 (dd, 1H, J_{AB}= 16.5, J_{AX}= 1.9, H_{11ax}), 3.47-3.54 (m, 3H, 2 x H_6 and H_{11ec}), 3.74-3.94 (m, 2H, H_{10b} and NCH_AH_BPh),# 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, H_{4b} and NCH_AH_BPh), 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}C-NMR** (δ, ppm): 33.6 (C_{10b}), 43.5 (C_{11}), 49.5, 52.7 (NCH_2Ph and C_6), 55.9, 56.0, 56.1 (OCH_3), 63.1 (C_{4b}), 107.8, 108.4, 108.8, 110.2 (C_{arom}-H), 126.0, (C_{arom}-C), 126.9, 127.6 (C_{arom}-H), 127.8 (C_{arom}-C), 128.5 (C_{arom}-H), 139.4, 139.6 (C_{arom}-C), 148.0, 148.1, 148.5, 154.3 (C_{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 $C_{28}H_{29}NO_5$: 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}H-NMR** (δ, ppm): 3.48 (d, 1H, J= 14.6, NCH_AH_BPh),# 3.73-3.80 (m, 2H, H_{10b} and H_{6A}#), 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, H_{6B} and NCH_AH_BPh), 4.30 (d, 1H, J= 17.7, H_{4b}), 6.40 (dd, 1H, J_{AB}= 9.8, J_{AX}= 1.9, H_{12}), 6.52 (s, 1H, H_7), 6.53 (dd, 1H, J_{BA}= 9.8, J_{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}C-NMR** (δ, ppm): 32.1 (C_{10b}), 49.8, 52.9 (NCH_2Ph and C_6), 55.8, 56.0 (OCH_3), 63.6 (C_{4b}), 108.0, 108.9, 110.1, 110.2 (C_7, C_1, C_{10} and C_4), 126.8, 127.4, 127.8 (C_{arom}-H), 127.6 (C_{arom}-C), 128.5, 129.2 (C_{11} and C_{12}), 129.5, 129.7, 140.0 (C_{arom}-C), 147.6, 147.8, 148.5 (C_{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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