Aza analogues of protoberberine and phthalideisoquinoline alkaloids[1]

JAHANGIR AND DAVID B. MACLEAN[2]
Department of Chemistry, McMaster University, Hamilton, Ont., Canada L8S 4M1

AND

HERBERT L. HOLLAND[2]
Department of Chemistry, Brock University, St. Catharines, Ont., Canada L2S 3A1

Received September 23, 1985

This paper is dedicated to Professor Arthur N. Bourns

JAHANGIR, DAVID B. MACLEAN, and HERBERT L. HOLLAND. Can. J. Chem. **64**, 1031 (1986).

Anions derived from furo[3,4-*c*]pyridin-3(1*H*)-one, by treatment with lithium diisopropylamide, react with substituted, 3,4-dihydroisoquinolines and 2-methyl-3,4-dihydroisoquinolinium salts yielding nitrogen analogues of the protoberberine and phthalideisoquinoline alkaloids, respectively.

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Les anions formés par la réaction de la furo[3,4-*c*]pyridine-(1*H*) one-3 avec le diisopropylamidure de lithium réagissent avec les dihydro-3,4 isoquinoléines substituées et avec les sels de méthyl-2 dihydro-3,4 isoquinolinium pour conduire respectivement aux analogues azotés des alcaloïdes de la protoberbérine et de la phtalideisoquinoléine.

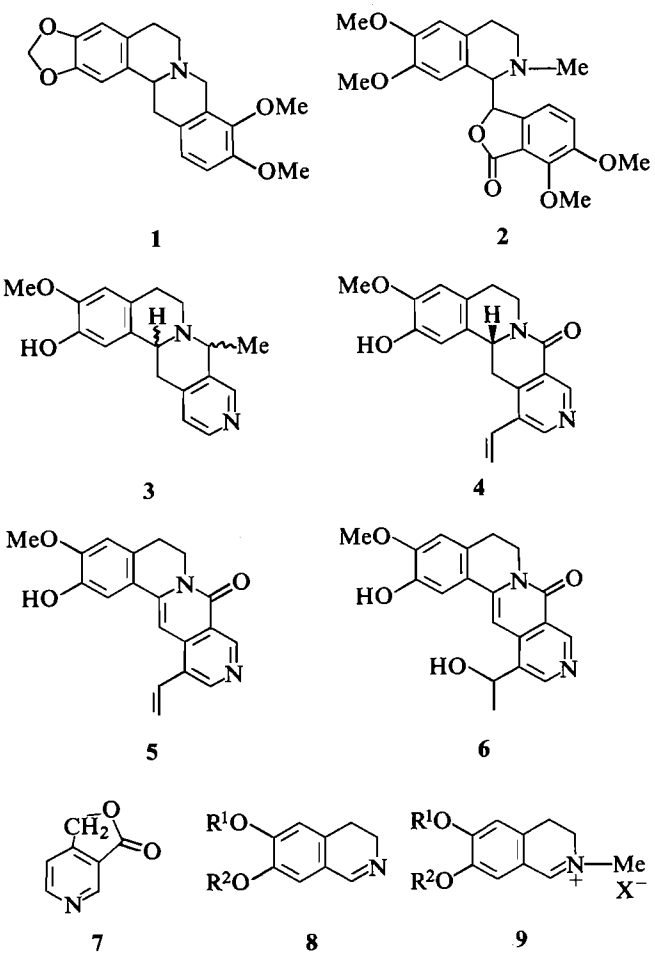
[Traduit par la revue]

In several recent publications from this laboratory we have reported (1–5) the reactions of phthalide anions with imines and iminium salts. These reactions provided convenient routes to protoberberine (e.g., canadine **1**) and phthalideisoquinoline alkaloids (e.g., cordrastine **2**), respectively, and to related compounds in each series. The recent discovery of pyridine analogues of the protoberberines such as **3**, **4**, **5**, and **6** in *Alangium* species (6, 7) prompted us to investigate their synthesis by a route similar to that used for the synthesis of the protoberberine alkaloids from phthalide precursors (1, 2). To this end we prepared the anion derived from furo[3,5-*c*]pyridin-3(1*H*)-one (azaphthalide **7**) and studied its reaction with 3,4-dihydroisoquinolines **8** and also with the corresponding 2-methyl-3,4-dihydroisoquinolinium salts **9**. These reactions, which are reported below, provided, in the case of the reaction with imines, a straightforward route to the ring system of the *Alangium* alkaloids and, in the case of the reaction with iminium salts, a new class of compounds, which are pyridine analogues of the phthalideisoquinolines.

The imines **8***a*–**8***c* were prepared by cyclization of substituted *N*-formylphenylethylamines with $POCl_3$ as condensing agent. This procedure gave better yields than the usual method in which mixtures of acetonitrile and $POCl_3$ were employed. The imines **8***a*–**8***c* were converted to their methiodides **9***a*–**9***c* by standard procedures.

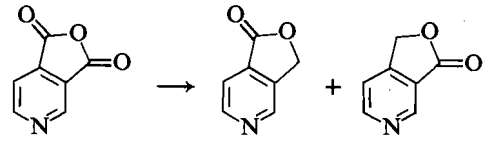
The furo[3,4-*c*]pyridin-3(1*H*)-one used in this study was prepared by reduction of cinchomeronic acid anhydride with sodium borohydride as outlined in Scheme 1. This major isomer was separated by crystallization from the minor regioisomer **10**. This preparation, an adaptation of a method developed by Kayser and Morand (8) for reduction of other acid anhydrides, proved superior to the previously reported reductions of cinchomeronic acid anhydride with LAH (lithium aluminum hydride) (9) and of the half ester of cinchomeronic acid with LAH (10).

Reaction of the lithium salt of the azaphthalide **7** with the 3,4-dihydroisoquinolines **8***a*, **8***b*, and **8***c* is outlined in Scheme 2. The initial products of the reaction were assigned structures **11** on the basis of spectroscopic examination of the compounds and of their *O*-acetates **12** and in analogy with the previously studied products of the reaction of lithium phthalide and 3,4-dihydroisoquinolines (1, 2). The relative configuration at C-13 and C-14 could not be established with certainty by examination



[1]A part of this work was presented at the 14th IUPAC International Symposium on the Chemistry of Natural Products, Poznan, Poland (see ref. 5).

[2]Authors to whom correspondence may be addressed.



10 **7**

SCHEME 1

of the nmr spectra of compounds **11**, but their *O*-acetyl derivatives **12** showed that H-13 and H-14 were *trans* to one another, $J_{13,14}$ = 10.5 Hz (ref. 2, and references therein). The dehydration of **11***a*, **11***b*, and **11***c* was effected by treatment with $POCl_3$, yielding the isocarbostyril system found in compounds **13**. Again, these compounds showed the anticipated spectroscopic behaviour. Thus, the condensation of the azaphthalide with the imines provided a convenient route to the ring system found in the *Alangium* alkaloids.

Alternative routes to this ring system, which are not regiospecific, and which involve photochemical (11, 12) or thermal (12) cyclization of tricyclic enamides, have been described. Both methods have been applied successfully to the synthesis of the *Alangium* alkaloids, alamarine **6** and alangimarine **5** (13).

The mass spectral fragmentation of the compounds **11**(*a*–*c*) prepared in this study is analogous to that of the corresponding protoberberines examined in the previous study (2). The major fragmentation involves a retro-Diels–Alder opening of ring C of the azaberberine system. Ions corresponding to the isoquinoline moiety plus a hydrogen are observed in the three compounds at *m/z* 192, 176, and 268, respectively, and an ion derived from rings C and D is present in all three compounds at *m/z* 135.

We recently described the synthesis of phthalideisoquinoline alkaloids and related compounds by treatment of lithium phthalides with 2-methyl-3,4-dihydroisoquinolinium salts (3). Here we report that the lithium salt of furo[3,4-*c*]pyridin-3(*H*)-one behaves in an exactly analogous fashion to lithium phthalide in its reaction with isoquinolinium salts, as shown in Scheme 3, yielding mixtures of the racemic *threo* **14** and *erythro* **15** diastereomers. The yields reported for the two isomers refer to crystalline product isolated from the reaction system and should not be used as a measure of the *threo*:*erythro* ratio present in the crude reaction product, which is expected to be nearly 1:1.

The assignment of configuration to the *threo* and *erythro* isomers is based on a comparison of the properties of the isomeric compounds prepared in this study with those of phthalideisoquinoline alkaloids where the configurational assignments are secure (14, 15). In the *threo* compounds examined in this work, the proton at C-7′ is always deshielded relative to the corresponding proton in the *erythro* series. This situation is similar to that observed for the phthalideisoquinoline alkaloids themselves (16, 17), indicating that the isoquinoline–azaphthalide system in compounds **14** and **15** adopts the same preferred conformation as the corresponding rings in the alkaloids. In the *erythro* systems, the preferred conformation places the hydrogen at C-7′ in the shielding cone of the aromatic ring of the isoquinoline moiety, whereas in the preferred *threo* conformation this hydrogen is not in a position where it can be similarly affected. There is also consistency with respect to the coupling constants between the hydrogens at C-1 and C-1′. In each series the *threo* isomer has a smaller coupling constant than the *erythro* isomer. Moreover, the *erythro* and *threo* isomers also exhibit a similar chromatographic behaviour in each series. The *threo* isomer is less polar than the *erythro* on silica columns and shows a higher R_f value on tlc plates.

Experimental

Apparatus, materials, and methods

Unless otherwise stated, the ^1H nmr spectra were continuous wave, run at 90 MHz on a Varian EM 390 spectrometer. The samples were dissolved in $CDCl_3$ using tetramethylsilane (TMS) as the internal standard. Chemical shifts, quoted as δ values, were measured in relation to TMS. The symbols s, singlet, d, doublet, t, triplet, q, quartet, and m, multiplet are used in reporting spectra. The Fourier transform spectra were run on either a Bruker WP80 (80 MHz) or WM250 (250 MHz) spectrometer. The ^{13}C nmr spectra were run at 62.9 MHz on a Bruker WM250 FT spectrometer or at 20.115 MHz on a Bruker WP80 FT spectrometer, both at ambient temperature.

EI (electron impact) mass spectra were recorded on a V.G. Micromass 7070 F mass spectrometer at 70 eV and CI (chemical ionization) spectra on the same instrument using NH_3 at ca. 1 Torr (1 Torr = 133.3 Pa) as reagent gas. Infrared spectra were recorded on a Perkin–Elmer 283 spectrometer in $CHCl_3$ solution. Melting points were determined using a Gallenkamp apparatus and are uncorrected. The microanalyses were performed by the Guelph Chemical Laboratories Ltd., Guelph, Ontario.

Thin-layer chromatography (tlc) was performed using Polygram Sil G/UV_{254} or Polygram Aloxn/UV_{254} plates. Flash column chromatography (18) was employed using Kieselgel 60 (230–400 mesh).

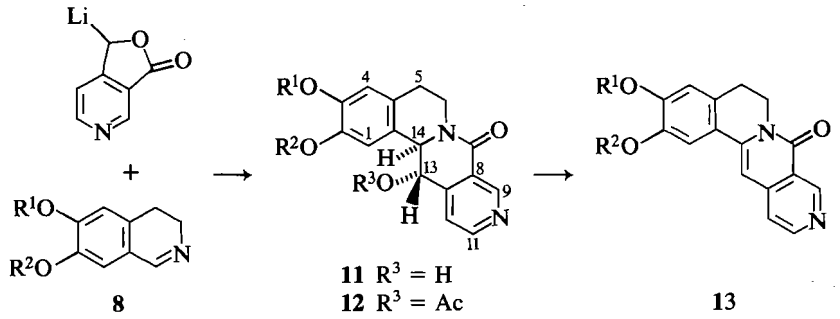
All reactions involving lithiation steps were carried out in flame-dried apparatus under a blanket of argon, using septa and syringes for transfer of reagents. Diisopropylamine was refluxed over calcium hydride and distilled onto molecular sieves (4A). THF (tetrahydrofuran) was dried by distillation from Na/benzophenone under a nitrogen atmosphere just prior to use. The following compounds were obtained commercially or prepared according to literature procedures: cinchomeronic acid, cinchomeronic acid anhydride (19, 20); *N*-formyl-3,4-methylenedioxyphenylethyl amine (2); *N*-formyl-3,4-demethoxyphenylethyl amine (16); 6,7-methylenedioxy-2-methyl-3,4-dihydroisoquinolinium iodide (21); 6,7-dimethoxy-2-methyl-3,4-dihydroisoquinolinium iodide (22).

Preparation of 3,4-dihydroisoquinolines **8**a–**8**c

The appropriate formamides, *N*-formyl-3,4-dimethoxyphenylethyl amine, *N*-formyl-3,4-methylenedioxyphenylethyl amine, and *N*-formyl 3-methoxy-4-benzyloxyphenylethyl amine (25.0 g), were treated slowly and carefully at ice bath temperature with freshly distilled $POCl_3$ (60 mL) in a flask protected with a $CaCl_2$ tube. When the vigorous initial reaction subsided, the mixture was warmed to room temperature over a period of 10–20 min, then heated to 40°C for 5 min, and finally kept at room temperature for 2 h. The excess $POCl_3$ was destroyed by addition of the reaction mixture to crushed ice and the resulting solution made basic with concentrated aqueous NH_3. The mixture was extracted with $CHCl_3$, the $CHCl_3$ extract dried and evaporated, and the residue purified by bulb-to-bulb distillation. Compounds **8***a*–**8***c* were obtained in 80–90% yield; their spectroscopic properties were in accord with those reported in the literature: **8***a* (2), **8***b* (2), and **8***c* (23).

Reduction of cinchomeronic acid anhydride

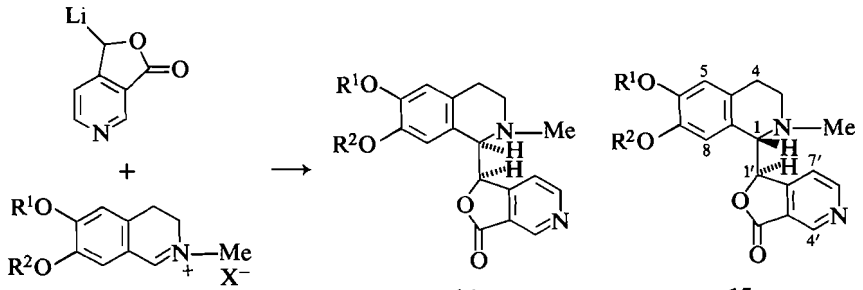
A suspension of $NaBH_4$ (1.9 g, 0.05 mol) in freshly distilled THF (100 mL) and dry DMF (10 mL) was heated under reflux in a 2-necked, flame-dried, round-bottom flask under an argon atmosphere for 20 min. The reaction mixture was then cooled to 0°C in an ice bath and finely powdered cinchomeronic acid anhydride (7.48 g, 0.05 mol) was added in one portion. The mixture, which turned faintly pink, was stirred for 1 h at 0°C, the ice bath was removed, and stirring continued for a further 3 h. Excess $NaBH_4$ was destroyed by careful addition of a few drops of concentrated aqueous HCl at 0°C. The solvent was then evaporated, the residue taken up in 30 mL of 10 *M* HCl (aq) and the mixture heated under reflux for 1 h. The solution was then cooled and carefully neutralized to pH 8–9 with solid K_2CO_3. The neutral solution was extracted with $CHCl_3$, the extract washed with brine, and then dried over Na_2SO_4. The residue obtained on evaporation of the dried $CHCl_3$ extract was a mixture of azaphthalides 7 and **10** in a 4:1 ratio as estimated by ^1H nmr. The crude yields in a number of reactions ranged



8 **11** R^3 = H, **12** R^3 = Ac **13**

Note: For compounds 8, 11, 12, and 13 in the (*a*) series, $R^1 = R^2 = CH_3$; in the (*b*) series $R^1 + R^2 = CH_2$, and in the (*c*) series $R^1 = CH_3$, $R^2 = C_6H_5CH_2$

SCHEME 2



14 **15**

a $R^1 = R^2 = CH_3$
b $R^1 + R^2 = CH_2$

SCHEME 3

from 40–65%. The azaphthalides **7** and **10** were purified by fractional sublimation and by fractional crystallization from $CHCl_3$–Et_2O; azaphthalide (**7**), mp 142–143°C (lit. (10) mp 130–135°C; lit. (24) mp 145°C); azaphthalide (**10**), mp 116–118°C (lit. (23) mp 118°C). The spectroscopic properties of **7** and **10** were in agreement with literature values (10, 24).

Reaction of imine (8a) with the lithium salt of azaphthalide (7)

A solution of *n*-BuLi (2.44 mmol) in hexane 1.6 *M* was added dropwise with stirring to a solution of diisopropylamine (2.44 mmol) in THF at −20°C under an argon atmosphere. The LDA solution was stirred for an additional 5 min at the same temperature. After the addition was complete, the temperature of the reaction mixture was then lowered to −60°C and a solution of azaphthalide **7** (300 mg, 2.22 mmol) in THF (2 mL) was added dropwise to the LDA solution. The solution of the red anion so generated was stirred for a further 15 min at −60°C. Imine **8***a* (439 mg, 2.22 mmol) in 3 mL THF was then added dropwise and, when addition was complete, stirring of the solution was continued another 2 h. The temperature was raised to 20°C and the reaction mixture kept at this temperature for ca. 12 h. The mixture was worked up in the usual manner (1, 2) affording the condensation product **11***a* (590 mg, 81%), mp 230–235°C (dec.) ($CHCl_3$, acetone): R_f 0.22 (alumina, EtOAc); ir ($CHCl_3$), ν_{max}: 1645 cm^{-1}; ^1H nmr (90 MHz) δ: 2.8–3.0 (3H, m, C-5 H's and C-6 H_{ax}), 3.87 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.57–4.75 (2H, m, C-13 H and C-14 H), 4.85–5.05 (1H, m, C-6 H_{eq}), 6.75 (1H, s, C-4 H), 7.03 (1H, s, C-1 H), 7.70 (1H, d, J = 5.5 Hz, C-12 H), 8.74 (1H, d, J = 5.5 Hz, C-11 H), 9.13 (1H, s, C-9 H); ^{13}C nmr (62.9 MHz) δ: 30.3 (C-5), 39.3 (C-6); 56.3, 56.5, (2 × OCH_3); 61.4 (C-14), 71.3 (C-13); 112.4, 118.5, 123.3, 123.9, 129.2, 147.9, 149.1, 149.6, 149.7, 153.0 (aromatic carbon atoms);[3] 162.8 (C=O); ms (EI), *m/z* (%): 326 (26.5) $M^{+\cdot}$, 309 (4.5), 192 (100), 135 (10), 134 (6.5), 106 (18). *Anal.* calcd. for $C_{18}H_{18}N_2O_4$: C 66.26, H 5.52, N 8.59; found: C 66.11, H 5.59, N 8.58%. *Exact Mass* (hrms) calcd. for $C_{18}H_{18}N_2O_4$: 326.127; found: 326.127.

Reaction of imine (8b) with the lithium salt of azaphthalide (7)

This reaction was carried out in exactly the same manner as that described above. The condensation product **11***b* was separated as an oil but crystallized from ethyl acetate (420 mg, 61%), mp 230–231°C; R_f 0.46 (alumina, EtOAc); ir ($CHCl_3$), ν_{max}: 1640 cm^{-1}; ^1H nmr (90 MHz), δ: 2.80–3.13 (3H, m, C-5 H's and C-6 H_{ax}), 4.53–4.73 (2H, m, C-13 H and C-14 H), 4.83–5.03 (1H, m, C-6 H_{eq}), 5.97 (2H, s, OCH_2O), 6.73 (1H, s, C-4 H), 6.97 (1H, s, C-1 H), 7.67 (1H, d, J = 5.5 Hz, C-12 H), 8.77 (1H, d, J = 5.5 Hz, C-11 H), 9.20 (1H, s, C-9 H); ^{13}C nmr ($CDCl_3$ + DMSO-d_6) δ: 30.0 (C-5), 38.9 (C-6), 60.7 (C-14), 69.8 (C-13), 100.8 (OCH_2O); 108.1, 109.9, 119.0, 122.8, 125.4, 129.5, 145.4, 146.5, 148.6, 151.2, 152.4 (11 aromatic carbons); 162.0 (C=O); ms (EI), *m/z* (%): 310 (23) $M^{+\cdot}$, 176 (96.5), 135 (20.9), 106 (100). *Anal.* calcd. for $C_{17}H_{14}N_2O_4$: C 65.80, H 4.52, N 9.03; found: C 65.70, H 4.71, N 9.23%. *Exact Mass* for $C_{17}H_{14}N_2O_4$: 310.095; found: 310.094.

Reaction of imine (8c) with the lithium salt of azaphthalide (7)

The reaction was carried out in the manner described for the reaction between **8***a* and **7** except that 1.85 mmol of **8***c* was used and other quantities adjusted accordingly. The product (**11***c*) was recrystallized from $CHCl_3$–acetone (317 mg, 43%), mp 222–223°C; R_f 0.56 (alumina, EtOAc); ir ($CHCl_3$), ν_{max}: 1650 cm^{-1}; ^1H nmr (90 MHz), δ: 2.67–3.00 (3H, m, C-5 H's and C-6 H_{ax}), 3.97 (3H, s, OCH_3), 4.47–4.67 (2H, m, C-13 H and C-14 H), 4.87–5.03 (1H, m, C-6 H_{eq}), 6.70 (1H, s, C-4 H), 6.95 (1H, s, C-1 H), 7.30–7.53 (5H, m, C_6H_5), 7.60 (1H, d, J = 5.5 Hz, C-12 H), 8.75 (1H, d, J = 5.5 Hz, C-11 H), 9.20 (1H, s, C-9 H); ^{13}C nmr, δ: 29.8 (C-5), 39.0 (C-6), 55.9 (OMe), 60.6 (C-14), 70.2 (C-13 or OCH_2Ar), 71.0 (C-13 or OCH_2Ar); 111.7, 115.7, 119.0, 123.0, 124.4, 127.4, 127.5, 127.8, 128.4, 129.0, 137.0, 146.1, 148.8, 148.9, 151.1, 152.6 (aromatic carbons);[4] 162.5

[3]Ten signals were observed for 11 carbon atoms.

[4]16 signals observed for 17 aromatic carbon atoms.

(C=O); ms (EI), *m/z* (%): 402 (24.1) $M^{+\cdot}$, 268 (12.0), 177 (10.2), 135 (100), 134 (26.2), 106 (75), 91 (68.4). *Anal.* calcd. for $C_{24}H_{22}N_2O_4$: C 71.64, H 5.47, N 6.97; found: 71.98, H 5.76, N 7.14%.

O-*Acetyl derivative of* **11**a

Compound **11***a* (50 mg) was dissolved in pyridine (0.5 mL) and treated with an excess of acetic anhydride (1.5 mL). The mixture was kept in a stoppered flask for ca. 12 h, the excess reagent removed under vacuum, and water (5 mL) added to the residue. The aqueous suspension was extracted with chloroform, and the chloroform extract washed with brine, dried over Na_2SO_4, and evaporated to dryness. The *O*-acetate (**12***a*) crystallized from methanol (47 mg, 83%), mp 249–250°C (dec.) (MeOH); R_f 0.36 (alumina, EtOAc); ir ($CHCl_3$), ν_{max}: 1645, 1745 cm^{-1}; ^1H nmr (250 MHz), δ: 2.23 (3H, s, $OCOCH_3$), 2.78–3.10 (3H, m, C-5 H's and C-6 H_{ax}), 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.92 (1H, d, *J* = 10.7 Hz, C-14 H), 4.90–5.00 (1H, m, C-6 H_{eq}), 6.05 (1H, d, *J* = 10.7 Hz, C-13 H), 6.72 (1H, s, C-4 H), 6.76 (1H, s, C-1 H), 7.15 (1H, d, *J* = 5.20 Hz, C-12 H), 8.76 (1H, d, *J* = 5.2 Hz, C-11 H), 9.27 (1H, s, C-9 H); ^{13}C nmr (62.9 MHz), δ: 21.0 (*CH*$_3$CO), 30.0 (C-5), 39.8 (C-6); 56.0, 56.4 (2 × OCH_3); 59.1 (C-14), 71.3 (C-13); 111.7, 111.8, 118.0, 120.8, 122.3, 125.5, 129.5, 146.2, 150.2, 153.0 (aromatic carbon atoms);[5] 160.57 (lactam C=O), 172.9 (CH_3*CO*); ms (EI), *m/z* (%): 368 (0.8) $M^{+\cdot}$, 325 (22.7), 308 (100), 293 (38.6), 135 (19.3), 134 (65.8). *Exact Mass* (hrms) calcd. for $C_{18}H_{17}N_2O_4$ ($M-C_2H_3O$): 325.119; found: 325.121; calcd. for $C_{18}H_{16}N_2O_3$ ($M-C_2H_4O_2$): 308.116; found: 308.121.

O-*Acetyl derivative of* **11**b

This compound was prepared from 50 mg of **11***b* under the conditions used to prepare **12***a*. The product **12***b* crystallized from methanol (55 mg, 97%), mp 232–233°C (MeOH); R_f 0.63 (Al_2O_3, EtOAc); ir ($CHCl_3$), ν_{max}: 1650, 1750 cm^{-1}; ^1H nmr (250 MHz), δ: 2.23 (3H, s, *CH*$_3$CO), 2.76–3.05 (3H, m, C-5 H's and C-6 H_{ax}), 4.87 (1H, d, *J* = 10.7 Hz, C-14 H), 4.90–4.96 (1H, m, C-6 H_{eq}), 5.96 (2H, s, OCH_2O), 5.97 (1H, d, *J* = 10.7 Hz, C-13 H), 6.69 (1H, s, C-4 or C-1 H), 6.71 (1H, s, C-1 or C-4 H), 7.16 (1H, d, *J* = 5.2 Hz, C-12 H), 8.76 (1H, d, *J* = 5.2 Hz, C-11 H), 9.26 (1H, s, C-9 H); ms (EI), *m/z* (%): 352 (<1.0%) $M^{+\cdot}$, 2.09 (7.6), 292 (57.2), 277 (29.7), 176 (14.3), 135 (11.3), 134 (33). *Anal.* calcd. for $C_{19}H_{16}N_2O_5$: C 64.77, H 4.55, N 7.95; found: C 64.42, H 4.62, N 7.86. *Exact Mass* (hrms) calcd. for $C_{19}H_{13}N_2O_4$ ($M-C_2H_3O$): 309.088; found: 309.082.

O-*Acetyl derivative of* **11**c

This compound was prepared from 25 mg of **11***c* under the conditions used to prepare **12***a*. The product **12***c* crystallized from chloroform–ether (23 mg, 83%), mp 182–185°C; R_f 0.80 (alumina, EtOAc), 0.52 (silica, EtOAc); ir ($CHCl_3$), ν_{max}: 1760, 1655 cm^{-1}; ^1H nmr (250 MHz), δ: 2.08 (3H, s, CH_3CO), 2.80–3.10 (3H, m, C-6 H's and C-5 H_{ax}), 3.88 (3H, s, —OCH_3), 4.80–5.00 (2H, m, C-14 H, C-5 H_{eq}), 5.08 (2H, s, CH_2Ar), 5.95 (1H, d, *J*=10.3 Hz, C-13 H), 6.72 (1H, s, C-1 or C-4 H), 6.80 (1H, s, C-1 or C-4 H), 7.09 (1H, d, *J* = 5.0 Hz, C-12 H), 7.30–7.50 (5H, m, C_6H_5), 8.72 (1H, d, *J* = 5.0 Hz, C-11 H), 9.24 (1H, s, C-9 H); ms (EI), *m/z* (%): 444 (3.1) $M^{+\cdot}$, 384 (44), 293 (20), 134 (20), 91 (100). *Exact Mass* (hrms) calcd. for $C_{24}H_{20}N_2O_3$ $(M-C_2H_4O_2)^{+\cdot}$: 384.147; found: 384.147.

Dehydration of alcohol **11**a

To a solution of alcohol **11***a* (100 mg) in dry pyridine (5 mL) was added freshly distilled $POCl_3$ (1 mL) and the reaction mixture was left at ~20°C for 3 h. The excess of the reagent was evaporated *in vacuo* and the residue dissolved in water (10 mL), made basic with concentrated aqueous NH_3, and thoroughly extracted into chloroform. The combined chloroform extracts were washed with brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The last traces of pyridine were removed by codistillation using benzene. The crude material on crystallization from MeOH gave product **13***a* (62 mg, 65.6%), mp 185–186°C (MeOH) (lit. (11) mp 169–172°C; R_f 0.37 (alumina, EtOAc); ir ($CHCl_3$), ν_{max}: 1650 cm^{-1}; ^1H nmr (250 MHz), δ: 2.97 (3H, t, *J* = 6.1 Hz, C-5 H's), 3.96 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 4.33 (2H, t, *J* = 6.1 Hz, C-6 H's), 6.77 (1H, s, C-1 or C-4 H), 7.27 (1H, s, C-13 H), 7.37 (1H, d, *J* = 5.5 Hz, C-12 H), 8.67 (1H, d, *J* = 5.5 Hz, C-11 H), 9.58 (1H, s, C-9 H); ^{13}C nmr, δ: 27.7 (C-5), 39.4 (C-6), 56.0, 56.3 (2 × OMe); 99.1, 108.5, 110.6, 118.9, 120.2, 129.5, 141.7, 142.9, 148.6, 150.4, 151.1, 151.2 (vinylic and aromatic carbons);[6] 161.6 (C=O); ms (EI), *m/z* (%): 308 (100) $M^{+\cdot}$, 307 (17), 294 (13.3), 293 (67.9), 291 (5.0), 277 (3.6), 265 (4.8). *Exact Mass* (hrms) calcd. for $C_{18}H_{16}N_2O_4$: 308.117, found: 308.116.

Dehydration of alcohol **11**b

This reaction was carried out under the same conditions used for the preparation of **13***a*. The product **13***b* was obtained in 77% yield, mp 288–290° (dec.); R_f 0.58 (alumina, EtOAc); ir ($CHCl_3$), ν_{max}: 1650 cm^{-1}; ^1H nmr (250 MHz), δ: 2.94 (2H, t, *J* = 6.2 Hz, C-5 H's, 4.33 (2H, t, *J* = 6.2 Hz, C-6 H's), 6.05 (2H, s, OCH_2O), 6.75 (2H, s, C-1 and C-4 H's), 7.26 (1H, s, C-13 H), 7.34 (1H, d, *J* = 5.3 Hz, C-12 H), 8.67 (1H, d, *J* = 5.3 Hz, C-11 H), 9.58 (1H, s, C-9 H); ms (EI), *m/z* (%): 292 (97) $M^{+\cdot}$, 291 (34.3), 277 (100), 233 (26.3), 205 (23.6). *Exact Mass* (hrms) calcd. for $C_{17}H_{12}N_2O_3$: 292.085; found: 292.082.

Dehydration of alcohol **11**c

This reaction was carried out in the same manner used for the dehydration of **11***a*. The product **13***c* was obtained in 95% yield, mp 180–182°C (EtOAc–hexane); R_f 0.68 (alumina, EtOac); ir ($CHCl_3$), ν_{max}: 1655 cm^{-1}; ^1H nmr (90 MHz), δ: 3.05 (2H, t, *J* = 6.2 Hz, C-5 H's), 4.05 (3H, s, OCH_3), 4.40 (2H, t, *J* = 6.2 Hz, C-6 H's), 5.34 (2H, s, OCH_2Ar), 6.73 (1H, s, C-1 H or C-4 H), 6.90 (1H, s, C-4 H or C-1 H), 7.30–7.67 (7H, m, C_6H_5, C-12 H and C-13 H), 8.87 (1H, d, *J* = 5.5 Hz, C-11 H), 9.58 (1H, s, C-9 H); ^{13}C nmr, δ: 29.9 (C-5), 41.5 (C-6), 58.1 (OMe), 74.0 (*OCH*$_2$Ar); 101.1, 113.1, 114.1, 120.7, 123.5, 129.6, 130.2, 130.7, 132.4, 138.9, 143.9, 149.8, 152.6, 153.6, 154.4 (vinylic and aromatic carbons);[7] 163.1 (C=O); ms (EI), *m/z* (%): 384 (74.3) $M^{+\cdot}$, 383 (8.8), 293 (29.0), 265 (7.2), 91 (100). *Exact Mass* (hrms) calcd. for $C_{24}H_{20}N_2O_3$: 384.147; found: 384.148.

*Reaction of iminium salt (***9**a*) with the anion of azaphthalide (7)*

n-BuLi (2.56 mmol) in hexane (1.6 *M*) was added to a stirred solution of disopropylamine (2.56 mmol) in dry THF (5 mL) at −78°C under an argon atmosphere. The temperature of the LDA solution was raised to 0°C for 10–15 min and then cooled again to −78°C before proceeding with the dropwise addition of a solution of the azaphthalide **7** (2.2 mmol in THF, 3 mL). Towards the end of the addition the initially formed red solution became turbid but became homogeneous again on raising the temperature to −40°C. The temperature was kept at −40°C during the remainder of the addition and for an additional 20 min. The solution was then transferred through a syringe tube into a flask fitted with a magnetic stirrer containing a suspension of 6,7-dimethoxy-2-methyl-3,4-dihydroisoquinolinium iodide (**9***a*) (740 mg, 2.2 mmol) in dry THF (3 mL). The mixture was stirred at −40°C for 3–4 h and then at ambient temperature overnight. The solvent was evaporated from the reaction mixture and the crude residue passed through a column of neutral alumina (activity I) using EtOAc as eluant. The residue obtained upon evaporation of the EtOAc was taken up in EtOH and from this solution the crystalline *threo* isomer **14***a* was obtained. The mother liquors were taken to dryness and the residue, dissolved in EtOAc, was separated into *threo* (**14***a*) and *erthryo* (**15***a*) components by flash chromatography.

Threo, **14***a* (213 mg, 25.6%); mp 198°C (from EtOH); R_f 0.48 (SiO_2, EtOAc); ir ($CHCl_3$), ν_{max}: 1762 cm^{-1}; ^1H nmr (250 MHz), δ: 2.4–3.2 (4H, m, C-3 H's, and C-4 H's), 2.71 (3H, s, —NCH_3); 3.71 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.19 (1H, d, *J* = 3.7 Hz, C-1 H), 5.75 (1H, d, *J* = 3.7 Hz, C-1′ H), 6.31 (1H, s, C-5 H), 6.66 (1H, s, C-8 H), 7.72 (1H, d, *J* = 5.1 Hz, C-7′ H), 8.63 (1H, d, *J* = 5.1 Hz,

[5] 10 signals observed for 11 aromatic carbon atoms.

[6] 12 signals observed for 13 carbon atoms.

[7] 15 signals observed for the 17 carbon atoms.

C-6′ H), 8.89 (1H, s, C-4′ H); ^{13}C nmr (62.9 MHz), δ: 29.5 (C-4), 45.1 (NCH_3), 50.8 (C-3); 55.8, 56.1 (2 × OCH_3); 65.5 (C-1), 81.4 (C-1′); 110.1, 111.2, 118.8, 152.4, 156.7, (5 × ArCH); 123.0, 123.5, 128.1, 147.3, 147.5, 148.0, (6 × ArC); 169.1 (C=O); ms (CI), *m/z* (%): 341 (16) $(M+1)^+$, 207 (13.5), 206 (100), 136 (44). *Anal.* calcd. for $C_{19}H_{20}N_2O_4$: C 67.06, H 5.88, N 8.24%; found: C 66.92, H 5.62, N 8.32%. *Erythro*, **15***b* (65.8 mg, 9%); mp 108–110°C (from EtOH); R_f 0.22 (SiO_2, EtOAc); ir ($CHCl_3$), ν_{max}: 1768 cm^{-1}; ^{1}H nmr (250 MHz), δ: 2.17–2.9 (4H, m, C-3 H's, C-4 H's); 2.57 (3H, s, NCH_3), 3.80 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 4.16 (1H, d, J = 4.5 Hz, C-1 H), 5.66 (1H, d, J = 4.5 Hz, C-1′ H), 6.50 (1H, s, C-5 H), 6.64 (1H, s, C-8 H), 6.65 (1H, d, J = 5.1 Hz, C-7′ H), 8.66 (1H, d, J = 5.1 Hz, C-6′ H), 9.12 (1H, s, C-4′ H); ^{13}C nmr (62.9 MHz), δ: 27.0 (C-4), 45.6 (NCH_3); 50.0 (C-3), 56.3 (2 × OCH_3); 65.30 (C-1), 84.7 (C-1′); 111.1, 111.8, 118.5, 147.7, 152.6 (5 × ArCH); 123.5, 124.1, 129.5, 147.9, 148.9, 156.3 (6 × ArC); 168.5 (C=O); ms (CI), *m/z* (%): 341 (23) $(M+1)^+$, 206 (100). *Anal.* calcd. for $C_{19}H_{20}N_2O_4$: C 67.06, H 5.88, N 8.24; found: C 66.83, H 6.20, N 7.90%.

*Reaction of iminium salts (***9***b) with the anion of azaphthalide (***7***)*

This reaction was carried out in the same manner as that described in the previous section except that 6,7-methylenedioxy-2-methyl-3,4-dihydroisoquinolinium iodide (**9***b*) was used. The reaction mixture was worked up similarly and the mixture of isomeric products separated by flash chromatography using 1% MeOH in EtOAc as eluant.

Threo, **14***b* (212 mg, 30%), mp 151–153°C (dec.) (from EtOH, Et_2O); R_f 0.66 (SiO_2, EtOAc); ir ($CHCl_3$), ν_{max}; 1765 cm^{-1}; ^{1}H nmr (250 MHz), δ: 2.43–3.17 (4H, m, C-3 and C-4 H's), 2.62 (3H, s, —NCH_3), 4.14 (1H, d, J = 3.5 Hz, C-1 H), 5.70 (1H, d, J = 3.5 Hz, C-1′ H), 5.82 (2H, d, J = 4.9 Hz, OCH_2O), 6.34 (1H, s, C-5 H), 6.63 (1H, s, C-8 H), 7.69 (1H, d, J = 5.1 Hz, C-7′ H), 8.67 (1H, d, J = 5.1 Hz, C-6′ H), 8.96 (1H, s, C-4′ H); ^{13}C nmr (62.9 MHz), δ: 29.6 (C-4), 45.2 (NCH_3), 51.5 (C-3); 66.0 (C-1), 82.0 (C-1′), 101.1 (OCH_2O); 107.4, 108.5, 118.7, 147.6, 152.5 (5 × ArCH); 123.7, 124.3, 129.8, 146.3, 146.9, 156.6 (6 × ArC); 168.7 (C=O); ms (CI), *m/z* (%): 325 (5.0), $(M+1)^+$, 191 (28.2), 190 (100). *Anal.* calcd. for $C_{18}H_{16}N_2O_4$: C 66.66, H 4.94, N 8.64; found: C 66.32, H 5.31, N 8.28%. *Erythro*, **15***b* (180 mg, 25%); mp 144–146°C (dec.) (from EtOH, Et_2O); R_f 0.38 (SiO_2, EtOAc); ir ($CHCl_3$), ν_{max}: 1760 cm^{-1}; ^{1}H nmr (250 MHz), δ: 2.1–2.9 (4H, m, C-3 and C-4 H's), 2.54 (3H, s, —NCH_3), 4.11 (1H, d, J = 4.8 Hz, C-1 H), 5.57 (1H, d, J = 4.8 Hz, C-1′ H), 5.98 (2H, s, —OCH_2O), 6.62 (1H, s, C-5 or C-8 H), 6.65 (1H, d, J = 5.1 Hz, C-7′ H), 6.66 (1H, s, C-8 or C-5 H), 8.66 (1H, d, J = 5.1 Hz, C-6′ H), 9.13 (1H, s, C-4′ H); ^{13}C nmr (62.9 MHz), δ: 27.6 (C-4), 45.8 (NCH_3), 50.1 (C-3), 65.6 (C-1), 84.8 (C-1′), 101.3 (OCH_2O); 108.0, 108.8, 118.6, 147.8, 152.7 (5 × ArCH); 124.1, 124.7, 130.8, 146.6, 147.4, 156.1 (6 × ArC); 168.6 (C=O); ms (CI), *m/z* (%): 325 (34.5) $(M+1)^+$, 191 (38), 190 (100). *Anal.* calcd. for $C_{18}H_{16}N_2O_4$: C 66.66, H 4.94, N 8.64; found: C 66.26, H 5.15, N 8.33%.

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada for financial support of this work through grants to H.L.H. and D.B.M. We also thank B. Sayer for recording the 250-MHz spectra and F. Ramelan for the mass spectra.

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