Tetrahedron Vol. 39, No. 12, pp. 1955 to 1962, 1983
Printed in Great Britain

0040-4020/83 $3.00 + .00

DIRECTED ORTHO METALLATION OF TERTIARY AROMATIC AMIDES

A NEW N-HETERORING ANNELATION METHOD AND SYNTHESIS OF PHENANTHRO-QUINOLIZIDINE AND -INDOLIZIDINE ALKALOIDS[1]

M. IWAO, K. K. MAHALANABIS, M. WATANABE, S. O. DE SILVA and V. SNIECKUS*
Guelph-Waterloo Centre for Graduate Work in Chemistry, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1

(*Received in USA* 23 *September* 1982)

Abstract—The synthesis of phenanthro-quinolizidine and -indolizidine alkaloids, cryptopleurine (**8**) and antofine (**9**) via directed ortho metallation of the common phenanthrene (**1**) are described (**Scheme 2**). The utility of this strategy as a new N-heteroring annelation method (**Scheme 1**) is illustrated by the preparation of other aromatic ring-fused quinolizidine (**12,15**) and indolizidine (**18,21**) systems. A Mg for Li transmetallation, crucial for the synthesis of **13** and of potential broader significance in directed metalation chemistry, is reported.

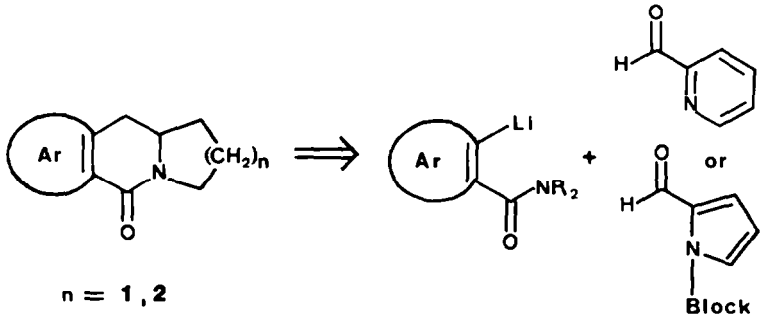
Discovered by Gilman and by Witting and extensively developed by Hauser and his school, heteroatom-directed ortho metallation of aromatic systems provides a useful general alternative to Friedel–Crafts methodology for the synthesis of substituted benzene derivatives.[2] Recently, the tertiary carboxamide moiety has emerged as a useful carbon-based directed metallation group, competitive or better than the secondary carboxamide and oxazolino functions.[3] The use of ortho lithiated tertiary benzamides for efficient solutions to long-standing problems in the construction of polysubstituted aromatics and for applications in the synthesis of diverse natural products (alkaloids, naturally-occurring anthraquinones, isocoumarins, phthalides) has beem amply demonstrated.[3]

The frameworks of the phenanthro-quinolizidine (**8**) and -indolizidine (**9**) alkaloids[4] afforded an opportunity to test the viability of the benzamide directed metallation strategy for more high condensed aromatic substrates[5] and to develop a new method for N-heteroring annelation (Scheme 1). Herein we report on the achievement of these goals by way of the convenient synthesis of cryptopleurine and antofine and the preparation of several simple aromatic ring-fused quinolizidine and indolizidine systems (**12**, **15**, **18**, **21**).

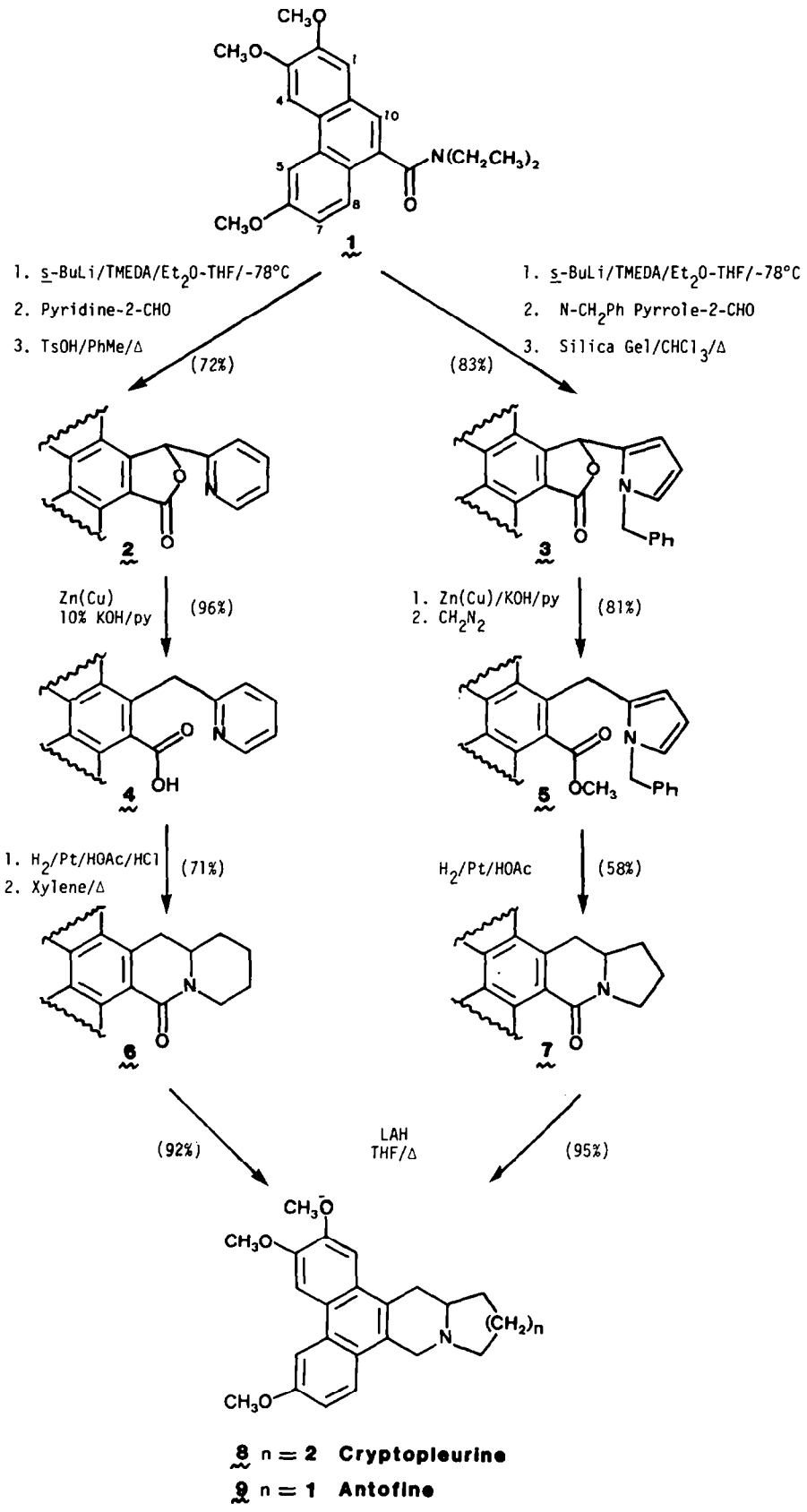
Synthesis of cryptopleurine (**8**) *and antofine* (**9**) (Scheme 2)

The phenanthro-quinolizidine and -indolizidine alkaloids have ellicited lively synthetic effort[6] as a result of their interesting biosynthesis and their significant antitumor activity.[4a] Previous syntheses of these alkaloids, which involved phenanthrene starting materials, invariably terminate with the construction of the piperidine ring by Friedel–Crafts type cyclizations into 9- or 10-positions.[4,6]

Qualitative knowledge that the tertiary amide is a much more powerful ortho metallation director than methoxy[7] coupled with the demonstrated efficient condensation of ortho lithiated benzamides with aromatic aldehydes,[8] encouraged our experiments with the readily available[9] carboxamide **1**. Metallation under standard conditions[8] followed by quenching with pyridine-2-aldehyde gave crude material which was shown to be a mixture of the pyridinolactone **2** and the corresponding amide alcohol (TLC analysis). Without further purification, this mixture was treated with TsOH in refluxing toluene to give the crystalline lactone **2** in 72% overall yield. Hydrogenolysis using $CuSO_4$-activated Zn[10] in basic solution furnished the carboxylic acid **4** which upon catalytic hydrogenation and thermolysis in xylene yielded the known lactam **6**.[11] The synthesis was concluded by LAH reduction



Scheme 1.


1. s-BuLi/TMEDA/Et2O-THF/-78°C
2. Pyridine-2-CHO
3. TsOH/PhMe/Δ
(72%)
1. s-BuLi/TMEDA/Et2O-THF/-78°C
2. N-CH2Ph Pyrrole-2-CHO
3. Silica Gel/CHCl3/Δ
(83%)
Zn(Cu)
10% KOH/py
(96%)
1. Zn(Cu)/KOH/py
2. CH2N2
(81%)
1. H2/Pt/HOAc/HCl
2. Xylene/Δ
(71%)
H2/Pt/HOAc
(58%)
(92%)
LAH
THF/Δ
(95%)
8 n = 2 Cryptopleurine
9 n = 1 Antofine

Scheme 2.

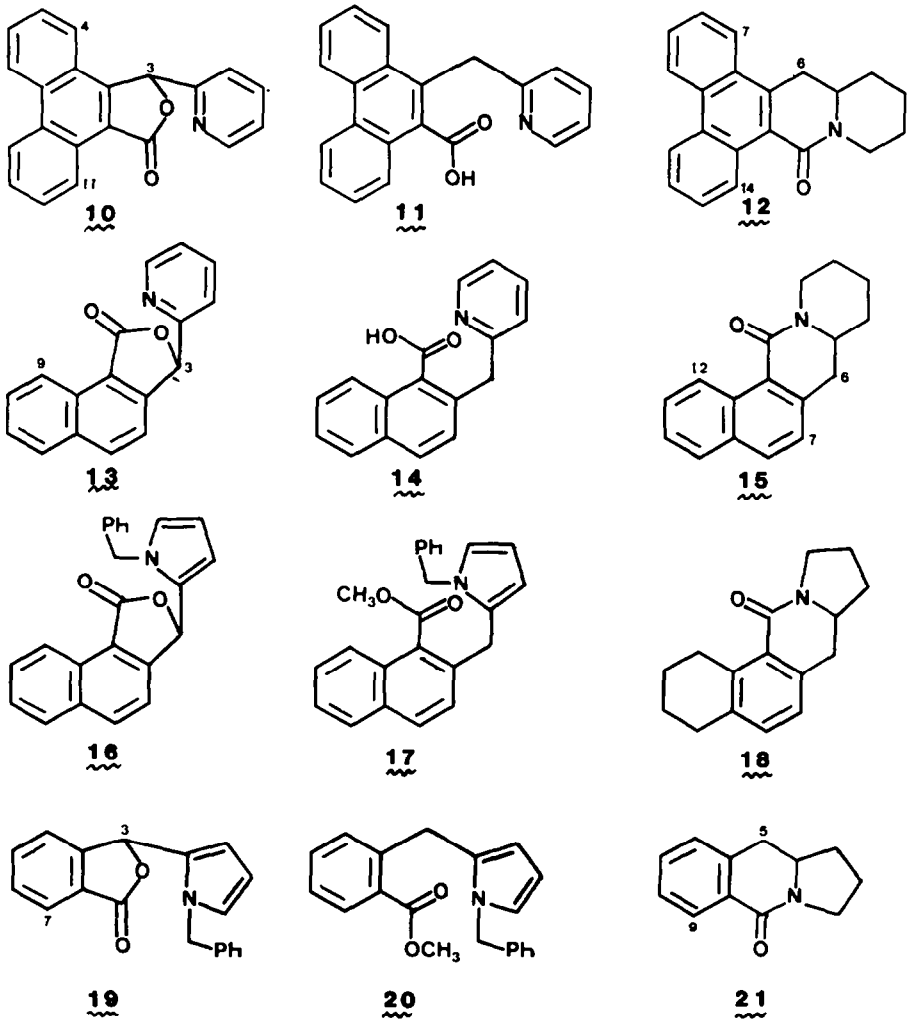
to give (±)-cryptopleurine (**8**) whose identity was established by direct comparison with an authentic sample.

The presence of the identical OMe substitution pattern in cryptopleurine (**8**) and antofine (**9**) allowed the economic use of the phenanthrene carboxamide **1**. Metallation as before followed by treatment with N-benzylpyrrole-2-aldehyde led to an intermediate amide alcohol whose conversion to the pyrrololactone **3** using TsOH was precluded by the notorious instability of pyrroles to acidic conditions.[12] However, this step was smoothly affected using a slurry of silica gel in chloroform to give **3** in 83% overall yield. Sequential zinc–$CuSO_4$ reduction and diazomethane esterification gave **5** whose hydrogenation in acetic acid directly yielded the lactam **7**.[13,14] The N-cyclohexylmethylpyrrolidine derivative corresponding to **5** was obtained as a minor product from this reaction (Experimental). LAH reduction of **7** afforded antofine (**9**) whose physical and spectral properties were shown by direct comparison to be identical with those of an authentic sample.

N-Heteroring annelation

In inverse of normal practice, we undertook model studies of the directed metallation coupling with heterocyclic aldehydes subsequent to the natural product synthesis. These studies were aimed at generalizing this reaction for N-heteroring annelation (Scheme 1). Thus lithiated N,N-diethylphenanthrene-9-carboxamide was condensed with pyridine-2-aldehyde under standard conditions to give, after acid-catalyzed cyclization, a crystalline compound in high yield whose IR (1750 cm^{-1}) and low field NMR (δ 9.22, m, 1H, H-11) spectra were consistent with structure **10**. Hydrogenolysis using the Zn–Cu couple procedure provided the carboxylic acid **11**. Hydrogenation-cum-cyclization afforded lactam **12** whose IR and NMR spectra showed significant similarities to those observed for the known trimethoxy analogue **6**.

In spite of previous results demonstrating that the 2-lithiated species of N,N-diethylnaphthamide may be generated and smoothly condensed with aromatic aldehydes and ketones,[5a,c] the analogous reaction with pyridine-2-aldehyde resulted in several dramatic color changes and, eventually, black solutions from which the expected product (**13**) could not be isolated after acid-catalyzed cyclization. This result is puzzling in light of the unproblematical condensations of pyridine-2-aldehyde with the lithiated phenanthrene amides and its well-established reactivity with aryllithium and Grignard reagents.[15] It may be a consequence of appropriate redox potentials in the two



reagents which promote dissipative electron transfer reactions. On the basis of this assumption, the ortho lithiated species was allowed to react at −78° with $MgBr_2 \cdot Et_2O$[16] in order to effect *in situ* conversion into the more covalent Grignard intermediate. Reaction with pyridine-2-aldehyde now ensued normally to provide, after *p*-toluenesulfonic acid treatment, the naphthalene lactone **13** in high yield.[17] Zn–Cu hydrogenolysis gave **14** which upon hydrogenation and thermolysis produced the naphthoquinolizidine lactam **15**.

In order to demonstrate the N-heteroring annelation method for the preparation of aromatic-ring-fused indolizidines, the condensation of 2-lithio-1-naphthamide and ortho lithiated benzamide with N-benzylpyrrole-2-aldehyde was investigated. In the first case, the condensation-lactonization to give **16** and the subsequent Zn–Cu hydrogenolysis-esterification to afford **17** proceeded uneventfully and in high yield. However, catalytic hydrogenation of **17** under the conditions used for the successful conversion of **5** into **7** resulted in over-reduction to give **18** as the major product (55%) together with the N-cyclohexylmethylpyrrolidine derivative corresponding to **17** in 25% yield (Experimental). Variation in time and catalyst (Pd/C) failed to change this result significantly and did not lead to detection of the naphthalene indolizidine lactam corresponding to **18**. This suggests that the hydrogenation of the naphthalene ring occurs rapidly in competition with pyrrole reduction and debenzylation.

As a final N-heteroring annelation example, the sequence of reactions initiated by coupling of ortho lithiated benzamide with N-benzylpyrrole-2-aldehyde led, as anticipated, *via* intermediates **19** and **20**, to the benzoindolizidine lactam **21**.

CONCLUSIONS

The directed metallation reaction of tertiary benzamides[3] have been extended to the corresponding 9-phenanthrene amide and 1-naphthamide in condensation reactions with pyridine-2-aldehyde and N-benzylpyrrole-2-aldehyde. The products of these reactions afford, after several simple transformations, aromatic ring-fused quinolizidines and indolizidines. This synthetic strategy provides cryptopleurine (**8**) and antofine (**9**) by short and efficient routes and appears adaptable for the preparation of other phenanthro-quinolizidine and -indolizidine alkaloids and their analogues.[4] Furthermore, the directed metallation approach constitutes a new entry into several types of heterocycles (**12**,**15**,**18**,**21**). The finding that transmetallation, Li→MgBr, dramatically modifies reactivity (synthesis of **13**) may have synthetic applications with tertiary amide[3,17] as well as other ortho metallation directing groups.[2]

Overall, this new N-heteroring annelation method presents an attractive alternative to classical Friedel–Crafts chemistry previously used for the construction of fully unsaturated (quinolizinium) derivatives of **12** and **15**.[18] Obvious functional group modification of intermediates **11** and **14** should, in fact, allow access to these quinolizinium systems.[19] Other heteroring annelations may be envisaged within the broad scope of the aromatic directed metallation reaction.[2]

EXPERIMENTAL

General methods. Microanalyses were performed by Canadian Microanalytical Services, Ltd. Vancouver, B.C. M.pts were measured on a Fisher–Johns or a Buchi SMP-20 apparatus and are uncorrected. IR spectra were determined on a Beckman Acculab 10 spectrometer and NMR spectra were obtained on a Bruker WP-80 spectrometer using TMS as internal standard. Mass spectra were determined on a high resolution CH-7 spectrometer. Silica gel 60 (0.04–0.063 mm and 0.063–0.20 mm) and silica gel GF-254 obtained from Brinkmann (Canada) were used for column and TLC, respectively. sec-BuLi as a soln in hexane and tetramethylenediamine (TMEDA) (distilled from CaH and stored over 4A molecular sieves) were purchased from Aldrich Chem. Co. THF and Et_2O were freshly distilled from sodium–benzophenone ketyl before use. Metallations were carried out in an air conditioned laboratory using syringe-septum cap techniques. The phrase standard work up refers to treatment of the reaction mixture with sat NH_4Cl aq, extraction with either CH_2Cl_2 or $CHCl_3$, drying (Na_2SO_4) of the organic extract and evaporation to dryness under reduced pressure. Unless otherwise indicated, chromatography was carried out using silica gel and $CHCl_3$–Me_2CO mixtures (4:1 to 9:1) as eluents.

N,N-Diethyl-(2,3,6-trimethoxyphenanthrene)-9-carboxamide (**1**)

A soln of 2,3,6-trimethoxyphenanthrene-9-carboxylic acid monohydrate[9a] (4.83 g, 14.2 mmol) in THF (100 mL) was treated with oxalyl chloride (5.40 g, 42.5 mmol). After the initial vigorous reaction subsided, the soln was refluxed for 0.5 hr and evaporated to dryness. The residue was dissolved in THF (100 mL) and the soln was treated with diethylamine (5.0 g, 68 mmol). The mixture was stirred overnight and evaporated to dryness. Water was added and the whole was extracted with CH_2Cl_2. Evaporation to dryness *in vacuo* and recrystallization from CH_2Cl_2–Et_2O–hexane gave, in two crops, compound **1** (4.22 g, 81%), as pale yellow prisms: m.p. 151.5–152.5°; IR (Nujol) ν max 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.01 (t, 3H, J = 7 Hz), 1.38 (t, 3H, J = 7 Hz), 3.17 (q, 2H, J = 7 Hz), 3.68 (br q, 2H, J = 7 Hz), 4.02, 4.03, 4.12 (3s, 9H), 7.19 (dd, 1H, J = 2.5, 9.0 Hz, H-7), 7.20 (s, 1H, H-1), 7.44 (s, 1H, H-10), 7.77 (d, 1H, J = 9.0 Hz, H-8), 7.87 (br s, 2H, H-4, H-5). (Found: C, 72.02; H, 6.72; N, 3.83. Calc for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.85; N, 3.81%).

N,N-Diethylphenanthrene-9-carboxamide was prepared in 93% yield according to the above procedure for **1**. Purification by trituration (hexane–Et_2O), chromatography (silica gel, EtOAc–hexane 1:1 eluent), and recrystallization (Et_2O) gave material (m.p. 99°) sufficiently pure for metallation experiments. (Found: C, 81.90; H, 6.75; N, 4.90. Calc for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05%).

General metallation procedure

Preparation of pyridinotrimethoxyphenanthrene lactone **2**. To a stirred soln of **1** (3.47 g, 9.4 mmol) in anhyd THF–Et_2O (265 mL, 1:10)[20] at −78° under N_2 was added sequentially TMEDA (1.41 mL, 9.44 mmol) and sec-BuLi (7.4 mL, 10.4 mmol, 1.4 M soln in hexane) by syringe injection. After 1 hr, the pale yellow heterogeneous mixture was treated with freshly-distilled pyridine-2-aldehyde (1.01 g, 9.4 mmol), stirred at −78° for 2 hr and warmed to room temp over 3 hr. Standard work up gave crude material which was dissolved in toluene (120 ml), *p*-toluenesulfonic acid (550 mg) was added and the mixture was refluxed for 5 hr. The mixture was evaporated to dryness under reduced pressure and the residue was dissolved in CH_2Cl_2. This soln was washed with dil $NaHCO_3$ aq, dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed to give, after recrystallization from toluene, **2** (2.72 g in two crops, 72%): m.p. 239–241°; IR (Nujol) ν max 1760 cm^{-1}; NMR ($CDCl_3$) δ 3.93, 4.04, 4.10 (3s, 9H), 6.79 (s, 1H, H-3), 7.1–7.7 (m, 4H, pyr H, H-10), 7.66 (s, 1H, H-4), 7.85, 7.86 (2s, 2H, H-7,

H-8), 8.67 (m, 1H, α-pyr H), 9.09 (d, 1H, J = 9.0 Hz, H-11). (Found: C, 72.04; H, 4.86; N, 3.50. Calc for $C_{24}H_{19}NO_5$: C, 71.81; H, 4.77; N, 3.49%).

General procedure for Zn–Cu *hydrogenolysis*

Preparation of Zn–Cu *couple.* The following procedure was found to be critical in order to obtain the given yields in all the lactone hydrogenolysis reactions. A suspension of Zn dust was stirred in 10% HCl aq for 5 min, the aqueous layer was decanted, and the Zn was washed first with acetone until the filtrate was neutral to litmus and then with anhyd ether. The silver white Zn powder was air dried (2–3 hr) and used *on the same day.*

Preparation of pyridinotrimethoxyphenanthrene carboxylic acid **4**

A mixture of freshly-prepared Zn–Cu couple [Zn (8.0 g), $CuSO_4$ (330 mg)], lactone **3** (1.34 g, 3.3 mmol), 10% KOH aq (70 mL), and pyridine (7 mL) was refluxed for 13 hr. The excess Zn was removed by filtration and the filtrate was acidified (HOAc) and extracted with $CHCl_3$. The extract was evaporated to dryness and redissolved in dil HCl aq. Water was added and the soln was neutralized with NaOAc. Extraction with $CHCl_3$ followed by evaporation to dryness gave a residue which upon crystallization from EtOH gave **4** (1.29 g in two crops, 96%), as an amorphous solid: m.p. 180–190° (resolidifies), 278–280° (dec); IR (Nujol) ν max 1718, 1620 cm^{-1}; NMR ($CDCl_3$) δ 4.00, 4.03, 4.06 (3s, 9H), 4.60 (s, 2H), 7.1–8.18 (m, 9H, ArH, $\equiv N^+-H$), 8.45 (br d, 1H, α-pyr H). Determination of analytical data was poorly reproduceable.

General procedure for hydrogenation of heterocyclic ring

Preparation of trimethoxyphenanthroquinolizidine lactam **6**. A mixture of **4** (300 mg, 0.74 mmol), PtO_2 (100 mg) in a soln of glacial AcOH (30 mL) and 6N HCl (1 mL) was hydrogenated at 85° for 17 hr, the H_2 gas being supplied from a balloon attached to the top of the condenser. The catalyst was collected by filtration and the filtrate was basified with 5% Na_2CO_3 aq. The mixture was evaporated to dryness, water was aded to the residue, and the resulting soln was extracted with $CHCl_3$. The extract was evaporated to dryness and the residue was dissolved in xylene (30 mL). The soln was refluxed for 0.5 hr, evaporated to dryness and the remaining solid was chromatographed. Recrystallization from EtOH gave **6** (206 mg, 71%): m.p. 197–198.5° (lit.[11] m.p. 194–195°) whose spectral properties (IR, NMR) corresponded to those reported in Ref. 11.

Cryptopleurine (**8**).

Lactam **6** (100 mg, 0.26 mmol) was reduced with LAH (100 mg, 2.64 mmol) in THF (60 mL) at reflux for 5 hr. Standard work up gave a yellow oil which after chromatography and two recrystallizations from acetone gave **8** [89 mg, 92%, m.p. 197–200° (lit.[11] m.p. 199–200°)], which was shown to be identical (IR, NMR, MS, TLC) with an authentic sample provided by Dr. J. Douros.

N-*Benzylpyrrole-2-aldehyde*

To a stirred suspension of NaH (1.66 g, 34.7 mmol, 50% dispersion in mineral oil, previously washed with dry Et_2O) in anhyd DMF (25 mL) at 0° under N_2 was added a soln of pyrrole-2-aldehyde (3.00 g, 31.5 mmol) in DMF (5 mL). After stirring for 0.5 hr, benzyl chloride (3.99 g, 31.5 mmol) was added and the mixture stirred for 1 hr at 0° and then at room temp for 16 hr. Standard work up with ether extraction gave an oil which was distilled to furnish 3.74 g (64%) of N-benzylpyrrole-2-aldehyde: b.p. 91–99°/0.05 mm (lit.[21] b.p. 168–170°/15 mm).

Pyrrolotrimethoxyphenanthrene lactone **3**

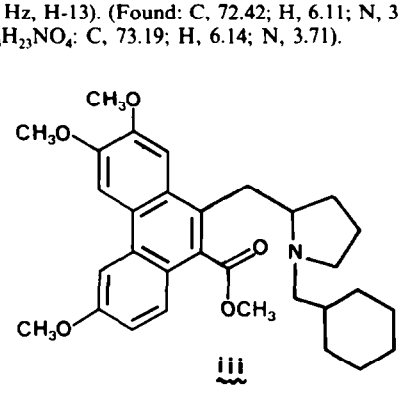
Using exactly the general procedure described for the synthesis of **2**, **1** (1.47 g, 4.0 mmol) was lithiated and condensed with N-benzylpyrrole-2-aldehyde (741 mg, 4.0 mmol) to give, after standard work up, crude material which was refluxed with a slurry of silica gel (20 g) in $CHCl_3$ (100 mL) for 2 hr. Recrystallization from CH_2Cl_2–Et_2O gave colorless prisms of **3**: m.p. 248–250°; IR (Nujol) ν max 1740 cm^{-1}; NMR ($CDCl_3$) δ 3.71, 4.03, 4.11 (3s, 9H), 5.22 (q, 2H, J = 16 Hz), 5.88 (dd, 1H, J = 3.7 Hz, pyrrole H-3), 6.09 (t, 1H, J = 1.7, 3.7 Hz, pyrrole H-4), 6.48 (s, 1H), 6.84 (masked dd, 1H, J = 1.7, 2.5 Hz, pyrrole H-5), 6.77 (s, 1H, H-4), 6.9–7.3 (m, 5H), 7.33 (dd, 1H, J = 9.0, 2.4 Hz, H-10), 7.84, 7.85 (2 s, 2H, H-7, H-8), 9.03 (d, 1H, J = 9.0 Hz, H-11). (Found: C, 74.92; H, 5.39; N, 3.00. Calc for $C_{30}H_{25}NO_5$: C, 75.14; H, 5.25; N, 2.92%).

Pyrrolotrimethoxyphenanthrene carboxylic acid methyl ester **5**

The procedure for the preparation of **4** was adopted except that large excess of KOH and pyridine was used. Thus from **3** (200 mg, 0.46 mmol, finely powdered before use), Zn–Cu couple [prepared from Zn (2.4 g) and $CuSO_4$ (40 mg)], 10% KOH soln (100 mL) and pyridine (10 mL) there was obtained, after filtration, acidification to pH 5–6 (conc HCl), and extraction ($CHCl_3$), crystalline material which upon standard esterification with diazomethane followed by crystallization from CH_2Cl_2–Et_2O afforded **5** (150 mg, 81%): m.p. 171–172°; IR (Nujol) ν max 1720 cm^{-1}; NMR ($CDCl_3$) δ 3.66, 3.83, 4.01, 4.08 (4s, 12H), 4.22 (s, 2H), 5.13 (s, 2H), 5.61 (dd, 1H, pyrrole H-3), 6.02 (t, 1H, pyrrole H-4), 6.68 (dd, 1H, pyrrole H-5), 6.9–7.3 (m, 7H, ArH, H-1, H-7), 7.63 (d, 1H, J = 9.2 Hz, H-8), 7.82 (s, 1H, H-4), 7.86 (d, 1H, H-5). (Found: C, 74.86; H, 5.76; N, 2.88. Calc for $C_{31}H_{29}NO_5$: C, 75.13; H, 5.90; N, 2.83%).

General procedure for hydrogenation-debenzylation of pyrrole ring

Trimethoxyphenanthroindolizidine lactam (**7**). Ester **5** (200 mg, 0.40 mmol) was hydrogenated over PtO_2 (100 mg) in glacial AcOH (50 mL) at room temp for 16 hr. Standard work up followed by chromatography gave fraction 1: lactam **7**: 88 mg (58%), m.p. 254–256° (CH_2Cl_2–Et_2O); IR (Nujol) 1635, 1615 cm^{-1}; NMR ($CDCl_3$) δ 1.7–3.1 (m, 3H), 3.25–4.2 (m, 5H), 4.01, 4.04, 4.11 (3s, 9H), 4.6 (br d, 1H), 7.25 (dd, 1H, J = 2.4, 9.3 Hz, H-12), 7.29 (s, 1H, H-6), 7.84 (d, 1H, J = 2.4 Hz, H-10), 7.88 (s, 1H, H-9), 9.31 (d, 1H, J = 9.3 Hz, H-13). (Found: C, 72.42; H, 6.11; N, 3.75. Calc for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71).



iii

Fraction 2: Compound **iii**, 52 mg (26%), m.p. 160° (CH_2Cl_2–Et_2O), NMR ($CDCl_3$) δ ~ 1.0–2.4 (br m, 16H), 2.6–3.7 (br m, 6H), 4.0, 4.06, 4.13 (3s, 12H), 7.2 (dd, 1H, H-7) 7.57 (s, 1H, H-1), 7.6 (d, 1H, H-8), 7.9 (m, 2H, H-5, H-4). (Found: C, 73.50; H, 7.98; N, 2.85. Calc for $C_{31}H_{39}NO_5$: 73.64; N, 7.77; N, 2.77%).

Antofine (**9**)

Reduction of **7** (24 mg) with LAH, as described for the preparation of **8**, gave 22 mg (95%) of product, which upon recrystallization from acetone provided antofine: m.p. 212–213° (lit[22] m.p. 213–215°) whose IR, NMR, and TLC

(SiO_2, $CHCl_3$–MeOH, 9:1) were shown to be identical by direct comparison with spectra and authentic sample provided by Dr. E. Gellert and Dr. R. B. Herbert.

Heteroring annelations

Unless otherwise indicated, the general procedures defined above were used for the respective conversions described below. Condensations between metallated amides and heterocyclic aldehydes were carried out on 2–20 mmol scale with little variation in yields.

Pyridinophenanthrene lactone **10**

Using extensively purified N,N-diethylphenanthrene-9-carboxamide, **10** was obtained in 89% yield: m.p. 220° (EtOAc); IR ($CHCl_3$) ν max 1750 cm^{-1}; NMR ($CDCl_3$) δ 6.86 (s, 1H), 7.15–7.37 (m, 2H) 7.55–7.85 (m, 6H), 8.02–8.12 (m, 1H), 8.60–8.77 (m, 3H), 9.22 (m, 1H, H-11); MS *m/e* 311 (M^+). (Found: C, 80.79; H, 4.15; N, 4.40. Calc for $C_{21}H_{13}NO_2$: C, 81.01; H, 4.21; N, 4.50%).

Pyridinophenanthrene carboxylic acid **11**

This compound was obtained in 96% yield: m.p. 176–178° (EtOH); IR ($CHCl_3$) ν max 1720 cm^{-1}; NMR ($CDCl_3$) δ 4.69 (s, 2H), 6.7–7.2 (v br, 2H, area decreased to 1H by exch with D_2O), 7.65–7.85 (m, 6H), 8.12–8.45 (m, 3H), 8.62–8.76 (m, 2H); MS *m/e* 313 (M^+). (Found: C, 80.12; H, 4.70; N, 4.36. Calc for $C_{21}H_{15}NO_2$: C, 80.49; H, 4.82; N, 4.47%).

Phenanthrenequinolizidine lactam **12**

This compound was obtained in 70% yield: m.p. 137–138° (EtOH); IR ($CHCl_3$) ν max 1615 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.2 (br, 5H), 2.5–3.25 (br m, 3H), 3.5–3.8 (m, 2H), 4.75 (br d, 1H), 7.55–7.83 (m, 4H), 8.0–8.2 (m, 1H), 8.6–8.8 (m, 2H), 9.53–9.65 (m, 1H, H-8); MS *m/e* 301 (M^+). (Found: C, 83.29; H, 6.30; N, 4.35. Calc for $C_{21}H_{19}NO$: C, 83.69; N, 6.35; N, 4.65%).

Pyridinonaphthalene lactone **13**

To a stirred THF–Et_2O soln of the lithiated N,N-diethylnaphthamide[5a] (b.p. 130°/0.05 mm) (1.13 g, 5.0 mmol), prepared under standard conditions at −78°, there was injected a soln of complex $MgBr_2 \cdot 2Et_2O$ (4.0 mL, 10.5 mmol, 2.62 N soln in Et_2O[16b]) and the mixture was allowed to warm until a homogeneous soln was observed (10–15 min). After cooling to −78°, freshly distilled pyridine-2-aldehyde (0.642 g, 6.0 mmol) was added, and the mixture was allowed to warm to room temp overnight. Standard workup afforded an oil (1.8 g), which was dissolved in toluene (30 mL), *p*-toluene-sulfonic acid (300 mg) was added and the mixture was refluxed (24 hr). Normal workup followed by trituration with EtOAc–Et_2O gave a yellow powder, which upon recrystallization (EtOAc–hexane) furnished 950 mg (80%) of **13**: m.p. 164°; IR ($CHCl_3$) ν max 1755 cm^{-1}; NMR ($CDCl_3$) δ 6.53 (s, 1H), 7.35–8.2 (m, 8H), 8.67 (m, 1H, α-pyr H), 9.04 (br d, 1H, J = 7 Hz, H-9); MS *m/e* 261 (M^+). (Found: C, 77.75; H, 4.09; N, 5.24. Calc for $C_{17}H_{11}NO_2$: C, 78.15; H, 4.24; N, 5.36%).

Pyridinonaphthalene carboxylic acid **14**

This compound was obtained in 89% yield: m.p. 179° (dec) ($CHCl_3$–Et_2O); IR ($CHCl_3$) ν max 1705 cm^{-1}; NMR ($CDCl_3$) δ 4.35 (s, 2H), 7.16–7.90 (m, 8H), 8.26–8.38 (m, 2H, H-8, α-pyr H); MS *m/e* 263 (M^+). (Found: C, 77.10; H, 4.77; N, 5.09. Calc for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32).

Naphthoquinolizidine lactam **15**

This compound was obtained in 72% yield: m.p. 123° (Et_2O); IR ($CHCl_3$) ν max 1635 cm^{-1}; NMR ($CDCl_3$) δ 1.18–1.95 (br, 7H), 2.6–3.0 (m, 2H), 3.1–3.7 (br, 1H), 4.65 (br t, 1H), 6.74–7.85 (m, 5H), 9.66 (d, 1H, J = 8.3 Hz, H-12); MS *m/e* 251 (M^+). (Found: C, 80.95; H, 6.70; N, 5.49 Calc for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57%).

Pyrrolonaphthalene lactone **16**

Coupling of 2-lithio-1-N,N-diethylnaphthamide[5a] with N-benzylpyrrole-2-aldehyde followed by lactonization (silica gel, $CHCl_3$) gave **16** in 89% yield: m.p. 157° (EtOAc–hexane); IR ($CHCl_3$) ν max 1745 cm^{-1}; NMR ($CDCl_3$) δ 5.29 (dd, 1H, J = 16.0 Hz, CH_2Ph), 5.90 (dd, J = 1.7, 3.6 Hz, pyrrole H-3), 6.11 (br t, 1H, pyrrole H-4), 6.40 (s, 1H, H-3), 6.82 (dd, 1H, J = 1.7, 2.6 Hz, pyrrole H-5), 7.03–8.13 (m, 10H, Ar H), 9.06 (m, 1H, H-9); MS *m/e* 339 (M^+). (Found: C, 81.02; H, 4.95; N, 4.01. Calc for $C_{23}H_{17}NO_2$:C, 81.40; H, 5.05; N, 4.13%).

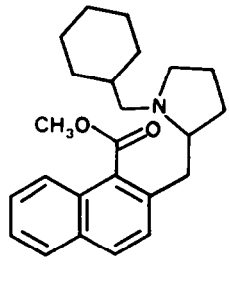
Methyl pyrrolonaphthoate **17**

The pyrrolonaphthoic acid was obtained in 87% yield: m.p. 124° (Et_2O-hexane); IR ($CHCl_3$) ν max 3000 (br), 1695 cm^{-1}; NMR ($CDCl_3$) δ 4.18 (s, 2H, CH_2), 4.95 (s, 2H, CH_2Ph), 6.01 (m, 1H, pyrrole H-3), 6.17 (t, 1H, pyrrole H-4), 6.69 (t, 1H, pyrrole H-5), 6.86–7.89 (m, 10H, Ar H), 8.08 (m, 1H, H-8), 8.6 (br, 1H, OH, exch D_2O); MS *m/e* 341 (M^+). It was converted (100%) by treatment with ethereal diazomethane into **17**: m.p. 77° (Et_2O–hexane); IR ($CHCl_3$) ν max 1720 cm^{-1}; NMR ($CDCl_3$) δ 3.80 (s, 3H), 4.01 (s, 2H, CH_2), 4.90 (s, 2H, CH_2Ph), 5.99 (br, 1H, pyrrole H-3), 6.15 (t, 1H, pyrrole H-4), 6.65 (dd, 1H, J = 1.8, 2.6 Hz, pyrrole H-5), 6.82–7.84 (m, 11H, Ar H); MS *m/e* 355 (M^+). (Found: C, 80.73; H, 5.82; N, 3.81. Calc for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94%).

Tetralenoindolizidine lactam **18**

Ester **17** was hydrogenated under the general conditions described for the preparation of 7 for 3 hr. Standard workup and chromatography furnished (55%) **18**: m.p. 100° (hexane); IR ($CHCl_3$) ν max 1625 cm^{-1}; NMR ($CDCl_3$) δ 1.4–2.4 (br m, 8H), 2.65–3.0 (m, 6H), 3.05–3.95 (m, 3H), 6.90 (d, 1H, J = 7.6 Hz), 7.08 (d, 1H, J = 7.6 Hz), MS *m/e* 241 (M^+). (Found: C, 79.30; H, 7.87; N, 5.71. Calc for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80%).

The second fraction afforded after preparative thick-layer chromatography (silica gel, $CHCl_3$–acetone, 8:2 eluent) iv, 25% yield, oil, IR ($CHCl_3$) ν max 1715 cm^{-1}; NMR ($CDCl_3$) δ 0.85–2.15 (m, 12H), 2.4–3.3 (br, m, 8H), 3.8 (s, 3H), 3.95–4.15 (m, 2H), 7.15–7.5 (m, 5H), 7.65–7,85 (m, 1H), MS *m/e* 365 (M^+). (Found: C, 78.50; H, 8.51; N, 3.71. Calc for $C_{24}H_{31}NO_2$: C, 78.87; H, 8.55; N, 3.83%).



iv

Pyrrolophthalide **19**

Condensation of N,N-diethylbenzamide[7] with N-benzylpyrrole-2-aldehyde followed by lactonization (silica gel, $CHCl_3$) afforded (90%) **19**: m.p. 91° (Et_2O–hexane); IR ($CHCl_3$) ν max 1750 cm^{-1}; NMR ($CDCl_3$) δ 5.24 (dd, 2H, J = 16.1 Hz), 5.87 (m, 1H, pyrrole H-3), 6.08 (dd, 1H, J = 3.8, 2.6 Hz, pyrrole H-4), 6.35 (s, 1H, H-3), 6.79 (dd, 1H, J = 1.8, 2.6 Hz, pyrrole H-5), 7.10–7.66 (m, 8H, Ar H), 7.91 (m, 1H, H-7); MS *m/e* 289 (M^+). (Found: C, 78.55; H, 5.30: N, 4.75. Calc for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84%).

Methyl pyrrolobenzoate **20**

The pyrrolobenzoic acid was obtained in 86% yield: m.p. 136° (hexane–EtOAc); IR ($CHCl_3$) ν max 3300–2500,

1680 cm^{-1}; NMR ($CDCl_3$) δ 4.33 (s, 2H, CH_2Ph), 4.95 (s, 2H), 5.87 (m, 1H, pyrrole H-3), 6.15 (t, 1H, J = 3.2 Hz, pyrrole H-4), 6.73 (m, 1H, pyrrole H-5), 6.95–7.45 (m, 9H, Ar H), 8.05 (m, 1H, H-6); MS *m/e* 291 (M^+). It was directly converted (100%) by treatment with ethereal diazomethane into **20**: b.p. 150–155°/0.05 mm; IR ($CHCl_3$) ν max 1710 cm^{-1}; NMR ($CDCl_3$) δ 3.76 (s, 3H) 4.22 (s, 2H, CH_2Ph), 4.92 (s, 2H), 5.81 (br m, 1H, pyrrole H-3), 6.11 (t, 1H, J = 3 Hz, pyrrole H-4), 6.64 (dd, 1H, J = 1.8, 2.9 Hz, pyrrole H-5), 6.95–7.37 (m, 8H, Ar H), 7.86 (dd, 1H J = 2, 5.6 Hz); MS *m/e* 305 (M^-). (Found: C, 78.39; H, 6.20; N, 4.44. Calc for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59%).

Benzoindolizidine lactam **21**

This compound was obtained in 47% yield: m.p. 98° (Et_2O–hexane); IR ($CHCl_3$) ν max 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.7–2.4 (br m, 5H), 2.75–3.1 (m, 1H), 3.30–4.0 (m, 3H); MS *m/e* 187 (M^+). (Found: C, 76.55; H, 6.91; N, 7.32. Calc for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48%).

Acknowledgements—We gratefully acknowledge the continuing financial support of the Natural Sciences and Engineering Research Council of Canada. M.I. and M.W. are grateful to Nagasaki University, Nagasaki, Japan and K.K.M. is grateful to Jadavpur University, Calcutta, India for leaves of absence. We thank Dr. M. Sibi and R. Billedeau for some important experimental contributions and the late R. Powell for a preliminary study. We are indebted for provision of samples and spectral data to Dr. J. Duros, NIH (cryptopleurine) and Dr. E. Gellert, Wollongong University College, N.S.W., Australia and Dr. R. B. Herbert, Leeds University, England (antofine).

REFERENCES AND FOOTNOTES

[1]Part of this work has appeared in preliminary form: M. Iwao, M. Watanabe, S. O. de Silva and V. Snieckus, *Tetrahedron Letters* 2349 (1981).

[2]Comprehensive review: H. W. Gschwend and H. R. Rodriguez, *Org. Reactions* **26**, 1 (1979).

[3]P. Beak and V. Snieckus, *Accts. Chem. Res.* **15**, 306 (1982); V. Snieckus, *Heterocycles* **14**, 1649 (1980).

[4]Reviews: [a]I. R. C. Bick and W. Sinchai, *The Alkaloids* **19**, 193 (1981); [b]E. Gellert, *J. Nat. Products* **45**, 50 (1982).

[5]For metalation of tertiary naphthamides, see [a]R. A. Harvey, C. Cortez and S. A. Jacobs, *J. Org. Chem.* **47**, 2120 (1982); [b]A. I. Meyers, and W. B. Avila, *Ibid.* **46**, 3881 (1981); [c]M. Watanabe and V. Snieckus, *J. Am. Chem. Soc.* **102**, 1457 (1980).

[6]Recent examples: phenanthroquinolizidines: J. E. Cragg and R. B. Herbert, *J.C.S. Perkin Trans I* 2487 (1982); H. Ida and C. Kibayashi, *Tetrahedron Letters* 1913 (1981); G. G. Trigo, E. Galvez and M. M. Sollhuber, *J. Heterocycl. Chem.* **17**, 69 (1980); phenanthroindolizidines: V. K. Manglia and D. S. Bhakuni, *Tetrahedron* **36**, 2489 (1980); G. Dannhardt and W. Wiegrebe, *Arch. Pharm.* **310**, 802 (1977).

[7]P. Beak and R. A. Brown, *J. Org. Chem.* **47**, 34 (1982).

[8]S. O. de Silva, M. Watanabe and V. Snieckus, *Ibid.* **44**, 4802 (1979); S. O. de Silva, J. N. Reed and V. Snieckus, *Tetrahedron Letters* 5099 (1978).

[9]The carboxylic acid corresponding to **1** [a]was prepared by the Pschorr reaction: C. K. Bradsher and H. Berger, *J. Am. Chem. Soc.* **80**, 930 (1958) and [b] was also available by photolysis of methyl 3,4-dimethoxy-α-(4-methoxyphenyl)-cinnamate according to a method reported for an analogous system [R. B. Herbert and C. J. Moody, *Chem. Commun.* 121 (1970); for mechanistic work, see P. H. G. op het Veld and W. H. Laarhoven, *J. Am. Chem. Soc.* **99**,7221 (1977)] followed by alkaline hydrolysis. While small-scale (100 mg) irradiations (Hanovia 500 A lamp/PhH/64 h) gave acceptable yields (51%), the preparation of gram quantities of the phenanthrene ester were impractical by this method (M. Watanabe and V. Snieckus, unpublished results). An efficient method to effect this type of conversion using vanadium trifluoride oxide has been recently reported: A. J. Liepa and R. E. Summers, *J. Chem. Soc.* Chem. Commun. 826 (1977).

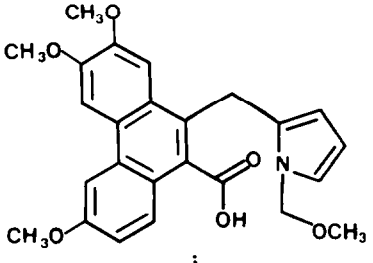
[10]M. S. Newman, V. Sankaran and D. R. Olson, *J. Am. Chem. Soc.* **98**, 3237 (1976).

[11]E. Kotani, M. Kitazawa and S. Tobinga, *Tetrahedron* **30**, 3027 (1974).

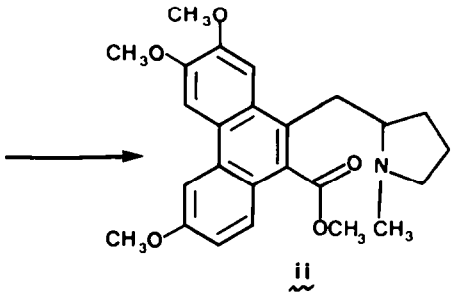
[12]R. A. Jones and G. P. Bean, *The Chemistry of Pyrroles*, p. 115. Academic Press, New York (1977).

[13]For a failure to catalytically debenzylate methyl N-benzylpyrrole carboxylate using Raney nickel, see H. J. Anderson and S. J. Griffiths, *Can. J. Chem.* **45**, 227 (1967).

[14]Pyrrole N-protection with the methoxymethyl group was also attempted in spite of the reported acid stability of an analogue, N-methoxymethylindole (R. J. Sundberg and H. F. Russel, *J. Org. Chem.* **38**, 3324 (1973)). Methoxymethylpyrrole 2-aldehyde, prepared in 70% from pyrrole-2-aldehyde and chloromethylmethyl ether under phase transfer conditions (tetra-N-butylammonium hydroxide, 50% NaOH aq CH_2Cl_2), was converted into the phenanthrene carboxylic ester **i** (71% overall yield) using the same metalation-lactonization hydrogenolysis sequence. Hydrogenation (PtO_2, HOAc) gave, after esterification, the N-methylpyrrolidine **ii** thus terminating further work using this approach (M. Iwao and V. Snieckus, unpublished results). The benzyloxymethyl group, shown to have utility for pyrrole N-protection (J. K. Groves, N. E. Cundasawmy and H. J. Anderson, *Can. J. Chem.* **51**, 1089 (1973)) was not tested.



i



ii

[15]E. V. Brown, In *Pyridine and Its Derivatives* (Edited by E. Klingsberg), Pt. 4, p. 28ff. Wiley-Interscience, New York (1964).

[16][a]B. M. Trost and W. H. Pearson, *J. Am. Chem. Soc.* **103**, 2483 (1981); [b]M. Pohmakotr, K.-H. Geiss and D. Seebach, *Chem. Ber.* **112**, 1420 (1979).

[17]This transmetalation procedure was first used to obtain 3-(2-pyridyl)phthalide whose preparation via direct coupling of the ortho lithiated N,N-diethylbenzamide with pyridine-2-aldehyde also could not be achieved. For reasons unknown, this compound was stable to Zn–Cu hydrogenolysis (reflux, 48 hr) thus precluding the synthesis of the benzo[*b*]quinolizidine lactam. The transmetalation tactic has been successful for other electrophiles (allyl bromide, aliphatic aldehydes) which fail to react with ortho lithiated

benzamides and its scope and limitations are being investigated (M. Sibi and J. Miah, unpublished results).

[18]C. K. Bradsher, *Accts. Chem. Res.* **2**, 181 (1969).

[19]For a recent approach to benzo[b]quinolizinium via coupling of ortho lithiated benzyl chloride with 2-acylpyridines, see C. K. Bradsher and D. A. Hunt, *J. Org. Chem.* **45**, 4248 (1980).

[20]In general, THF was used only if necessitated by the insolubility of the particular carboxamides in Et_2O.

[21]C. Ducrocq, E. Bisagni, J.-M. Lhoste and J. Mispelter, *Tetrahedron* **32**, 773 (1976).

[22]B. Chauncy and E. Gellert, *Austral. J. Chem.* **23**, 2503 (1970).