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HETEROATOM DIRECTED PHOTOARYLATION

SYNTHESIS OF FUNCTIONALIZED INDOLINES

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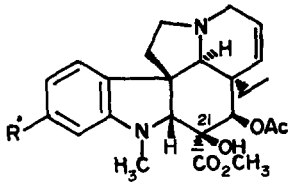
Abstract—The photochemical syntheses of indolines **25–28** are described.

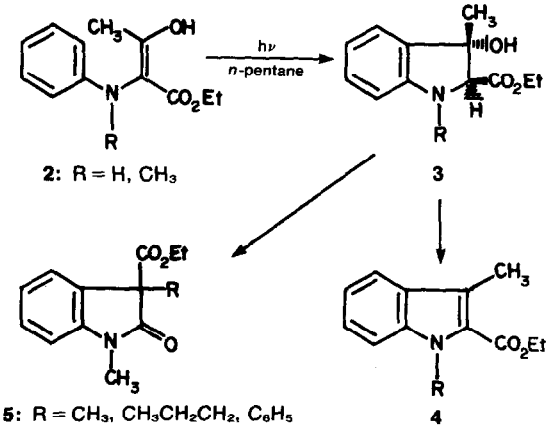
Some years ago Chapman *et al.* reported that N-aryl-N-methyl enamines undergo photocyclization to give indolines.[1] Subsequently, we demonstrated[2] that a variety of aryl vinyl heteroides based on the group VI elements display analogous photochemistry (heteroatom directed photoarylation) to give aryl annelated heterocycles; A→B→C (X=O, S, Se). As part of this general program of study and because of our interest in providing a conceptually new approach to the medicinally important *Aspidosperma* alkaloids vindorosine **1a** and vindoline **1b**, we, too, became interested in N-aryl enamine photochemistry.



1a: R = H
b: R = OCH_3

Early in our photoarylation studies, we discovered that superior chemical and photochemical yields are obtained with aryl vinyl ethers and sulfides which possess a carbonyl attachment to the vinyl group cross conjugated to the heteroatom; e.g. **A**. The CO group in **A** establishes a chromophore with which relatively low energy Pyrex-filtered light may be employed and at the same time presumably provides for stabilization of the intermediate ylide **B** as shown. Further consideration of the stereochemical consequences of photoarylation[1,2] and unique functionalization at C (21) in **1** suggested that a CO group would function as an ideal precursor to C (21) in **1**.

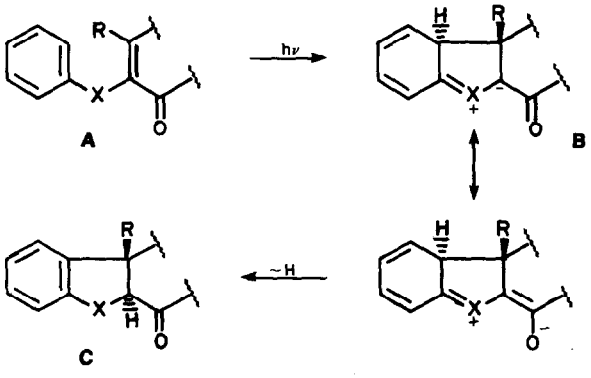
With these considerations in mind, we proceeded to develop a new 3-hydroxyindoline synthesis.[3] Thus, irradiation of the 2-anilinoacetoacetates **2** in the absence of acids leads to the production of 3-hydroxyindolines **3** in near quantitative yield. Here, stereochemical considerations strongly suggest that the photoreaction occurs from the enol tautomer **2** via a photochemically allowed conrotatory photocyclization to give an intermediate ylide (analogous to **B**) which experiences a thermally allowed suprafacial 1,4-hydrogen migration to give the indoline **3**.



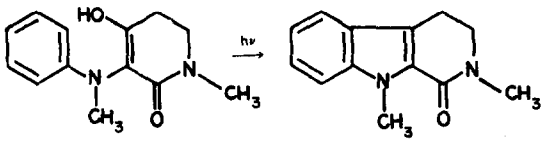
2: R = H, CH_3 **3**

5: R = CH_3, $CH_3CH_2CH_2$, C_6H_5 **4**

A variety of substituents on the benzene ring are compatible with the photocyclization and 3-hydroxyindolines are convertible to indoles **4** on acid-catalyzed dehydration and oxindoles **5** on oxidative rearrangement with lead tetraacetate-pyridine.[4] On the other hand, indoles may be isolated directly by irradiation in protic (acidic)

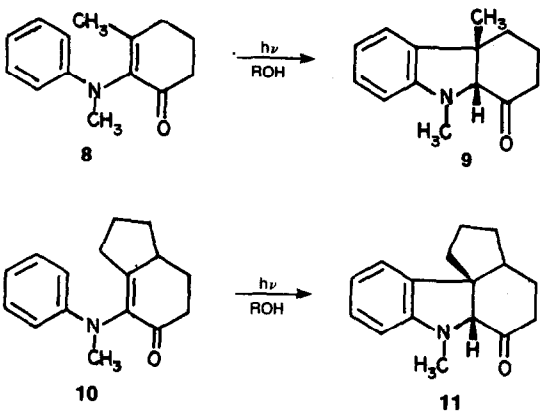


solvent.[3] For example, the tetrahydro-β-carboline **7**[5] is prepared in 71% isolated yield on irradiation of the highly enolic β-ketolactam **6** in degassed benzene–methanol–acetic acid solution (15:15:1).[6]



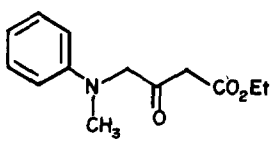
6 **7**

In work closely related to our projected synthesis of the *Aspidosperma* alkaloids, we described[7] the model photoconversions **8**→**9** and **10**→**11**. Both cyclizations occur in good yield and the preparation of **8** and **10** features the common annelation reagent **12**[8] as a key building block.



8 **9**

10 **11**



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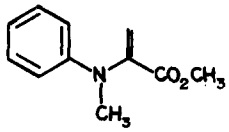
RESULTS AND DISCUSSION

In this report, we examine (1) alternate methods of N-aryl enamine preparation and (2) the effect of the critical second N atom in the vindoline ring system on the photocyclization. Enamines **13–15** have been prepared by the acid catalyzed condensation of α-keto esters with aniline and N-methylaniline. Thus, **13** was prepared from methyl pyruvate and **14** from α-keto ester **16a**.[9]



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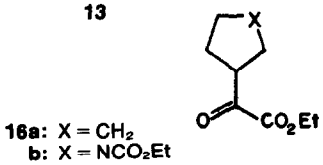
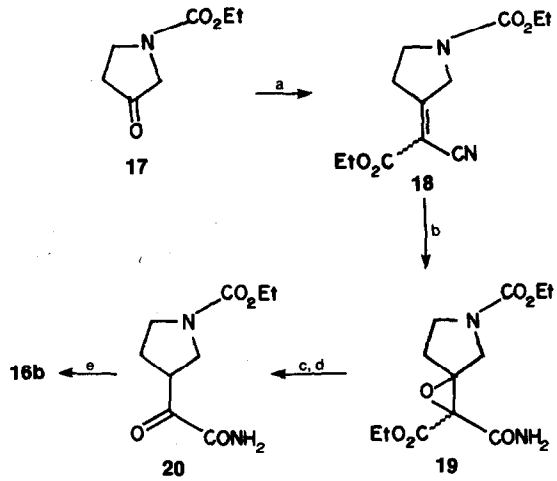


16a: X = CH_2
b: X = NCO_2Et

The preparation of **15** required synthesis of precursor **16b**, and this was accomplished by utilization of a method by Igarashi and Midorikawa (Scheme 1).[9] Knoevenagel condensation of N-ethoxycarbonyl-3-pyrrolidone **17**[10] with ethyl cyanoacetate gives **18** as a mixture of isomers. Without separation of isomers, **18** is reacted with hydrogen peroxide and a catalytic amount sodium tungstate dihydrate to give epoxides **19**, which on reaction with 1N HCl afford α-keto amide **20**; esterification gives **16b**.



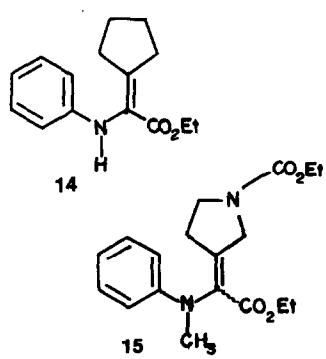
17 **18** **19** **20** **16b**

(a) Ethyl cyanoacetate/HOAc, NH_4OAc
(b) 30% $H_2O_2/Na_2WO_4 \cdot 2H_2O$
(c) KOH/EtOH
(d) 1 N HCl
(e) $EtOH/H_2SO_4$

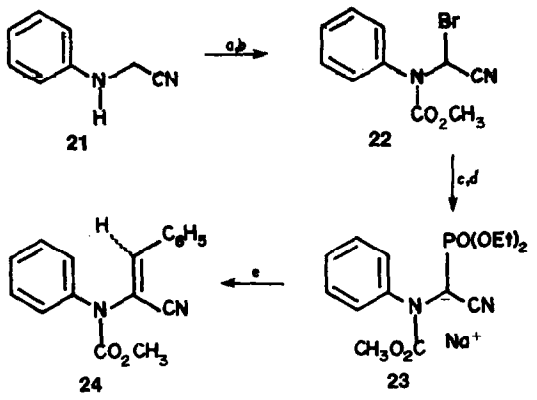
Scheme 1.

We also have examined enamine preparation via nitrile-stabilized phosphonate ylide **23** (Scheme 2).[11] Condensation of **23** with benzaldehyde gives N-aryl enamine **24** in reasonable yield (64% isolated); however, cyclopentanone and cyclohexanone both fail to react with **23**, indicating that this approach will have limited applicability.

N-aryl enamines **13–15** and **24** all undergo high yield photocyclization to indolines **25–28** on Pyrex-filtered irradiation in degassed benzene solution (Table I). The method is especially attractive for preparation of spiro-fused indolines such as **26** and **27**, which would be difficult to assemble using other procedures.[12] It is noteworthy that the photocyclization of **15** occurred in excellent yield to give **27** as a mixture of diastereoisomers. Prior to this experiment, we were



14 **15**

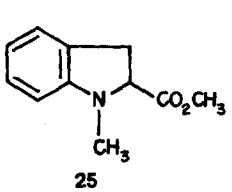


(a) $ClCO_2CH_3/NaHCO_3$, CH_2Cl_2
(b) NBS/C_6H_6, $H\nu$
(c) $P(OEt)_3$
(d) NaH/THF
(e) C_6H_5CHO/THF, reflux

Scheme 2.

concerned about the possibility of photoinduced cleavage of the allylic carbon–nitrogen bond in **15**.

The photoconversion **24**→**28** is of special significance, because placement of electron withdrawing substituents on the amine N atom might have been expected to reduce the capacity for electrocyclization; *cf.* structure **B**. However, incorporation of the urethane functionality as in **24** seems to have little overall effect on the photoreaction. Indolines which lack N-substitution also are readily available by photoarylation (e.g. **26**).



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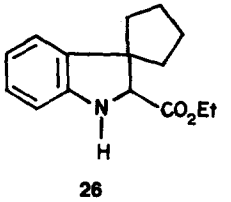

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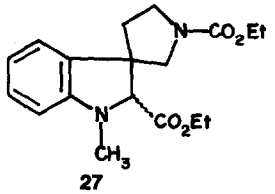

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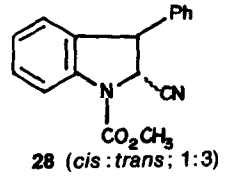

28 (*cis*:*trans*; 1:3)

We wish to emphasize that photoarylation should be the method of choice for preparation of indolines for which more established procedures would be at best marginally effective.[13] For example, 2-indolinecarboxylic esters have been prepared by the tin-hydrogen chloride reduction of indoles; however, this method would be ineffective for the preparation of acid-sensitive indolines.[14] Furthermore, the direct utilization of α-keto esters and aniline derivatives in the photoarylation method stands in marked contrast to the traditional Fischer synthesis of 2-indolecarboxylic esters,[15] which relies on the Japp–Klingemann reaction for the preparation of the appropriate hydrazone. The Japp–Klingemann reaction involves coupling of an arenediazonium salt with a β-carbonyl carboxylic acid derivative and subsequent decarboxylation.[16]

EXPERIMENTAL

General. ^1H NMR spectra were obtained on a Varian A-60A, T-60A or EM-390 NMR spectrometer (TMS standard, $CDCl_3$ solvent). IR spectra were recorded on a Perkin–Elmer 137B infrared spectrometer. UV spectra were obtained on a Perkin–Elmer 552 spectrophotometer. Mps were measured on a calibrated Thomas–Hoover capillary m.p. apparatus. The light source for irradiation was a 450 W Ace-Hanovia medium pressure, mercury vapor lamp. Mass spectra were obtained on a Finnigan 3300 gas chromatograph-mass spectrometer or a Hitachi–Perkin–Elmer RMU-6E mass spectrometer. Preparative thin layer plates were made of E. Merck AG Darmstadt silica gel PF-254 or GF-254.

Preparation of ethyl cyano (1-ethoxycarbonylpyrrolidin-3-ylidene) acetate (**18**). To a soln of **17**, (1.57 g, 10.0 mmol) in benzene (5 mL) was added a soln of ethyl cyanoacetate (1.13 g, 10.0 mmol) in benzene (5 mL), followed by addition of ammonium acetate (0.15 g) and glacial AcOH (0.46 mL). The mixture was heated to reflux in a Dean–Stark apparatus for 9 hr. The resulting soln was diluted with benzene (10 mL); washed with water (2 × 10 mL) and brine (10 mL); and dried with $MgSO_4$. Concentration and distillation (Kugelrohr oven 135–150°C/0.15 mm) gave **18** (1.5 g, 60%) as a mixture of two isomers. ^1H NMR δ 1.26 and 1.36 (two t, J = 7.5 Hz, 6 H), 3.12 and 3.35 (two t, J = 7.5 Hz, 2 H), 3.70 and 3.75 (two t, J = 7.5 Hz, 2 H), 4.19 and 4.31 (two q, J = 7.5 Hz, 4 H), 4.50 (broad s, 0.6 H), 4.68 (broad s, 1.4 H). IR (neat) 4.47, 5.85 μ.

Preparation of ethyl 2-carbamoyl-5-ethoxycarbonyl-1-oxa-5-azaspiro[2,4] heptane-2-carboxylate (**19**). To a soln of **18**, (1.3 g, 5.1 mmol EtOH (5 mL) was added sodium tungstate dihydrate (150 mg) and H_2O_2 (30%, 60 mL). The mixture was heated at 70°C with stirring for 3 hr. EtOH was distilled and the aqueous soln was extracted with $CHCl_3$ (3 × 10 mL). The combined $CHCl_3$ extracts were dried with $MgSO_4$. Concentration and crystallization (hexane: Et_2O; 1:9) gave **19**, (6.15 g, 42%), m.p. 105–107°. ^1H NMR δ = 1.15–1.45) (apparent q, 6 H), 1.70–2.55 (m, 2 H), 3.40–3.90 (m, 4 H), 4.02–4.46 (m, 4 H) 5.96 (broad s, 1 H), 6.66 (broad s, 1 H). IR (neat), 3.00, 5.75, 5.95 μ.

Preparation of ethyl 1-ethoxycarbonylpyrrolidin-3-yl-α-oxoacetate (**16b**). To a soln of **19** (629 mg, 2.19 mmol) in EtOH (3 mL) was added a soln of KOH (280 mg, 4.99 mmol) in EtOH (2 mL). After standing at room temp for 6 hr, EtOH was removed. The white solid residue was dissolved in a minimum amount of water (3 mL). The aqueous soln was acidified with 1 N HCl and stirred for 18 hr. After heating at 90° for 20 min, the soln was concentrated to yield a white solid residue. To the residue

Table 1. Photocyclization of *N*-Aryl enamines

N-Aryl enamines Irradiated	Product Isolated	Isolated Yield (%)
13	25	87
14	26	70
15	27	87
24	28	64

was added a soln of conc H_2SO_4 (3 mL) in EtOH (50 mL), and the mixture was heated to reflux for 18 hr. EtOH was distilled and the aqueous soln was extracted with $CHCl_3$ (3 × 30 mL). The combined $CHCl_3$ extracts were washed with sat $NaHCO_3$aq and dried over $MgSO_4$. Concentration and preparative tlc (silica gel, Et_2O) gave **16b** (119 mg, 23% from **19**). ^1H NMR δ 1.15–1.45 (m, 6 H), 2.00–2.30 (m, 1 H), 3.36–4.49 (m, 10 H). IR (neat) 5.75, 5.90 μ. MS (*m/e*) 243 (M^+).

Preparation of methyl 2-(N-*methylanilino*) *propenoate* (**13**). To a soln of methyl pyruvate (1.02 g, 10.0 mmol) and N-methylaniline (2.14 g, 20.0 mmol) in benzene (15 mL) was added *p*-toluenesulfonic acid (2 mg). The mixture was heated to reflux in a Dean–Stark apparatus for 7 hr. After cooling, the soln was washed with $NaHCO_3$aq and dried with $MgSO_4$. Concentration and distillation (Kugelrohr oven, 100°)/0.15 mm gave **13** (766 mg, 40%). ^1H NMR: δ 3.12 (s, 3 H), 3.57 (s, 3 H), 5.00 (s, 1 H), 5.51 (s, 1 H), 6.40–7.40 (m, 5 H). IR (neat) 5.80, 6.25 μ.

Preparation of ethyl cyclopentylideneanilinoacetate (**14**). Enamine **14** was prepared by the same procedure as that for **13**. Aniline (242 mg, 2.6 mmol) and **16a** (219 mg, 1.3 mmol) gave **14** (185 mg, 58%) after distillation (Kugelrohr oven, 147°/0.15 mm). ^1H NMR δ 1.20 (t, J = 7.5 Hz, 3 H), 1.44–1.95 (m, 4 H), 2.35 (t, J = 6.0 Hz, 2 H), 2.85 (t, J = 6.0 Hz, 2 H), 4.15 (q, J = 7.5 Hz, 2 H), 5.10 (broad s, 1 H), 6.47–7.30 (m, 5 H). IR 2.99, 5.80, 6.25 μ.

Preparation of ethyl 2-(N-*methylanilino*)-2-(1-*ethoxycarbonylpyrrolidin*-3-*ylidene*)-*acetate* (**15**). To a soln of **16b** (486 mg, 2.00 mmol) in benzene (8 mL) was added N-methylaniline (430 mg, 4.01 mmol), *p*-toluenesulfonic acid (2 mg), and anhyd $MgSO_4$ (20 mg). The mixture was heated in a Dean–Stark apparatus for 18 hr. Filtration and concentration gave a brown oil (830 mg). Preparative tlc (silica gel, ether) gave **15** (201 mg, 30%). ^1H NMR δ 1.00–1.42 (m, 6 H), 2.55–3.80 (m, 4 H), 3.03 (s, 3 H), 3.95–4.60 (m, 6 H), 6.55–7.40 (m, 5 H). IR (neat 5.72, 5.85, 6.25 μ. UV (methanol) λ 242 nm (ε = 14300), MS (*m/e*) 332 (M^+).

Preparation of N-*methoxycarbonylanilinobromoacetonitrile* (**22**). To a soln of anilinoacetonitrile (40 g, 0.30 mole) in CH_2Cl_2 (200 mL) was added a soln of methyl chloroformate (46 mL, 0.60 mole) in CH_2Cl_2 (100 mL) followed by $NaHCO_3$ (1 N, 600 mL). The mixture was stirred at room temp for 15 hr. The CH_2Cl_2 layer was separated and washed with 10% HCl (2 × 50 mL), sat $NaHCO_3$aq (2 × 50 mL), and brine (100 mL), and dried over $MgSO_4$. Evaporation of solvent and distillation (123–4°/0.25 mm) afforded N-methoxycarbonylanilinoacetonitrile (42.5 g, 75%). ^1H NMR δ 3.70 (s, 3 H), 4.47 (s, 2 H), 7.15–7.50 (m, 5 H), IR (neat) 5.84, 6.23 μ.

To a soln of N-methoxycarbonylanilinoacetonitrile (9.5 g, 50 mmol) in benzene (200 mL) was added N-bromosuccinimide (10.6 g, 59.6 mmol). The mixture was irradiated with a sun lamp and heated to reflux for 10 hr. After cooling, the soln was washed with 1 N $Na_2S_2O_3$ (2 × 50 mL), water (2 × 50 mL) and brine (1 × 50 mL) and dried over $MgSO_4$. Evaporation of solvent gave **22** (12.5 g, 93%). ^1H NMR δ 3.83 (s, 3 H), 7.19 (s, 1 H), 7.45 (broad s, 5 H). IR (neat) 5.80, 6.25 μ.

Preparation of α-(N-*methoxycarbonylanilino*)*cinnamonitrile* (**24**). To crude bromide **22** (11.5 g, 42.0 mmol) was added triethyl phosphite (7.7 g, 46 mmol). The mixture was heated to reflux for 3 hr. After cooling, the mixture was distilled at 150°–2°/0.003 mm to give diethyl cyano(N-methoxycarbonylanilino)methylphosphonate (7.1 g, 52%). ^1H NMR δ 1.10–1.40 (apparent q, 6 H), 3.69 (s, 3 H), 3.83–4.31 (m, 4 H), 5.80 (d, J = 25.0 Hz, 1 H), 7.29–7.55 (broad s, 5 H). IR (neat) 5.83, 6.21 μ.

To a suspension of sodium hydride (144 mg, 6.00 mmol) in THF (5 mL) was added a soln of diethyl cyano(N-methoxycarbonylanilino)methylphosphonate (1.63 g, 5.00 mmol) in THF (5 mL). After being stirred for 15 min, the mixture was heated to reflux for 15 min and cooled to room temp. A soln of benzaldehyde (1.06 g, 10 mmol) in THF (2 mL) was added dropwise and the mixture was heated to reflux for 3 hr. After cooling, water (40 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The CH_2Cl_2 soln was washed with water (2 × 30 mL) and brine (1 × 30 mL) and dried over $MgSO_4$. Evaporation of solvent gave a brown oil (1.3 g), which was chromatographed on a silica gel column (hexane:ether; 2:3) to give **24** (0.89 g, 64%). ^1H NMR δ 3.79 (s, 3 H), 7.07 (s, 1 H), 7.15–7.45 (m, 8 H), 7.65–7.77 (m, 2 H). IR (neat) 4.49, 5.80, 6.25 μ.

Photolysis of enamines

Preparation of methyl 1-*methylindoline*-2-*carboxylate* (**25**). A soln of **13** (392 mg, 2.05 mmol) in benzene (4 mL) was degassed with argon for 20 min and irradiated with Pyrex-filtered light for 7.5 hr. Concentration and distillation (Kugelrohr oven, 110°/0.15 mm) gave **25** (340 mg, 87%). ^1H NMR δ 2.80 (s, 3 H), 3.01–3.38 (m, 2 H), 3.77 (s, 3 H), 4.03 (dd, J = 9.5 Hz, 8.5 Hz, 1 H), 6.30–7.25 (m, 4 H). IR (neat) 5.75, 6.23 μ. MS (*m/e*) 191 (M^+). (Found: C, 68.91; H, 6.97. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85%).

Preparation of ethyl spiro[*cyclopentane* - 1, 3' - *indoline*] - 2' - *carboxylate* (**26**). A soln of **14** (43 mg, 0.18 mmol) in benzene (2 mL) was degassed with argon for 20 min and irradiated with Pyrex-filtered light for 1.5 hr. Evaporation of solvent and preparative tlc on silica gel (hexane: EtOAc; 2:1) gave **26** (30 mg, 70%). ^1H NMR δ 1.30 (t, J = 7.5 Hz, 3 H), 1.60–2.18 (m, 8 H), 4.19 (s, 1 H), 4.21 (q, J = 7.5 Hz, 2 H), 6.50–7.38 (m, 5 H). IR (neat) 2.90, 5.75, 6.20 μ. MS (*m/e*) 245 (M^+). (Found: C, 73.32; H, 7.70; N, 5.81. Calcd. for $C_{15}H_{19}NO_2$: C, 73.43; H, 7.82; N, 5.71%).

Preparation of ethyl 1-*methyl*-1'-*ethoxycarbonylspiro*[*indoline*-3, 3' - *pyrrolidine*] - 2 - *carboxylate* (**27**). A soln of **15** (33 mg, 0.99 mmol) in benzene (2 mL) was degassed with argon for 20 min and irradiated with Pyrex-filtered light for 20 min. Evaporation of solvent and preparative tlc on alumina (hexane: EtOAc; 2:1) gave **27** (29 mg, 87%). ^1H NMR δ 1.10–1.42 (*m*, 6 *H*), 1.85–2.69 (m, 2 H), 3.30–3.80 (m, 4 H), 3.89–3.91 (d, 1 H) 4.00–4.40 (m, 4 H), 6.44–7.38 (m, 4 H). IR (neat) 5.73, 5.87, 6.23 μ. MS (*m/e*) 332 (M^+).

Preparation of 1 - *methoxycarbonyl* - 3 - *phenylindoline* - 2 - *carbonitrile* (**28**). A soln of **24** (156 mg, 0.56 mmol) in benzene (2 mL) was degassed with argon for 20 min and irradiated with Pyrex-filtered light for 3 hr. Concentration and preparative tlc on silica gel (5% MeOH in CH_2Cl_2) gave two fractions. From the faster moving band, the *cis*-isomer of **28** (75 mg) was isolated. ^1H NMR δ 3.86 (s, 3 H), 4.78–5.43 (ABq, J = 9.1 Hz, 2 H), 7.05–7.93 (m, 9 H). IR (neat) 5.82, 6.25 μ. MS (*m/e*) 278 (M^+). From the slower moving band the *trans*-isomer of **28** (25 mg) was isolated. ^1H NMR δ 3.86 (s, 3 H), 4.70–4.95 (ABq, J = 5.0 Hz, 2 H), 7.03–7.95 (m, 9 H). IR (neat) 5.82, 6.25 μ. MS (*m/e*) 278 (M^+).

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REFERENCES

[1]O. L. Chapman, G. L. Eian, A. Bloom and J. Clardy, *J. Am. Chem. Soc.* **93**, 2918 (1971).

[2]For example, see A. G. Schultz, R. D. Lucci, W. Y. Fu, M. H. Berger, J. Erhardt and W. K. Hagmann, *Ibid.* **100**, 2150 (1978); A. G. Schultz, W. Y. Fu, R. D. Lucci, B. G. Kurr, K. M. Lo and M. Boxer, *Ibid*, **100**, 2140 (1978).

[3]A. G. Schultz and W. K. Hagmann, *J. Org. Chem.* **43**, 3391 (1978); A. G. Schultz and W. K. Hagmann, *Chem. Commun.* 726 (1976).

[4]A. G. Schultz and W. K. Hagmann, *J. Org. Chem.* **43**, 4231 (1978).

[5]Identical to that reported by B. T. Ho, W. M. McIsaac and K. E. Walker, *J. Pharm. Sci.* **57**, 1364 (1968).

[6]W. K. Hagmann, Ph.D. Dissertation, Cornell University (1978).

[7]A. G. Schultz and I-Ching Chiu, *Chem. Commun.* **29** (1978).

[8]A method which others have employed for the preparation of **12** is recorded in C. B. Troostwijk and R. M. Kellogg, *Ibid.* 932 (1977).

[9]M. Igarashi and M. Midorikawa, *J. Org. Chem.* **28**, 3088 (1963).

[10]M. Viscontini and H. Buhler, *Helv. Chem. Acta* **50**, 1289 (1967).

[11]A modification of the method of S. E. Dinizo, R. W. Freerksen, W. E. Pabst and D. S. Watt, *J. Org. Chem.* **41**, 2846 (1976).

[12]Many workers involved in *Aspidosperma* alkaloid total synthesis have relied on a Fischer-based indolenine ring construction, followed by metal hydride reduction to the indoline ring, often in very low yield. For example, in the total synthesis of (±)-6,7-didehydroaspidospermine, this operation was performed in 9% isolated yield; see S. S. Klioze and F. P. Darmory, *J. Org. Chem.* **40**, 1588 (1975). The occurrence of rear-

rangements in this kind of indoline preparation have been noted; see Y. Ban, Y. Sata, I. Inou, M. Nagai, T. Oshi, M. Terashima, O. Yonemitsu and Y. Kanaoka, *Tetrahedron Letters* 2261 (1965).

[13]*The Chemistry of Hetereocyclic Compounds—Indoles*, (Edited by W. J. Houlihan), Part 1. Wiley-Interscience, New York (1972).

[14]The preparation of ethyl 2-indolinecarboxylate by the tin-hydrogen chloride reduction of ethyl 2-indolecarboxylate has been reported; E. J. Corey, R. J. McCaully and H. S. Sachdev, *J. Am. Chem. Soc.* **92**, 2476 (1970).

[15]Other less general methods for 2-indolecarboxylic ester preparation are available; for a discussion of these methods, see W. E. Noland and F. J. Baude, *Org. Syn.* **43**, 40 (1963); *Coll.* Vol. 5, 567 (1973).

[16]R. B. Phillips, *Org. Reactions* **10**, 143 (1959).