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ARISTOLOLACTAMS OF *ARISTOLOCHIA ARGENTINA*

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Key Word Index—*Aristolochia argentina*; Aristolochaceae; aristololactams; phenanthrene alkaloids; 10-amino,3-hydroxy,4-methoxyphenanthrene-1-carboxylic acid lactam.

Abstract—Four new lactams have been isolated and characterized from the roots of *Aristolochia argentina*.

INTRODUCTION

IN CONTINUATION of our investigation on the constituents of *Aristolochia argentina* Gris,[1,2] we report the isolation and characterization of four new aristololactams from its roots extract.

RESULTS AND DISCUSSION

Structure

Extraction of the roots of *A. argentina* and separation of the neutral constituents have yielded four substances, which were identified as the new aristololactams AII (**1**), AIII (**2**), BII (**3**) and BIII (**4**).

Aristololactam AII, m.p. 271° ($C_{16}H_{11}NO_3$; M^+ 265) showed a UV spectrum characteristic of a phenanthrene chromophore, while the bathochromic shift produced by the addition of alkali, showed that a phenolic hydroxyl group was present. The IR spectrum revealed it to possess NH and CO bands. The PMR spectrum verified the NH (δ 10·77, 1 broad H) and OH (δ 10·22, 1H) functions and further indicated a OMe group (δ 4·03, 3H). The singlet centred at δ 7·08 (1H) and 7·62 (1H) could be ascribed to H-9 and H-2 while H-5 appeared as a multiplet centred at δ 9·13. In addition to the PMR signals already mentioned, there are two signals at δ 7·93 (1H) and δ 7·54 (2H). This accounts for all the hydrogens in aristololactam AII and, on the basis of the above spectral data, the compound is the lactam of a 10-amino-3,4-didisubstituted phenanthrene-1-carboxylic acid.

Further evidence of the positions of the substituents of aristololactam AII was obtained by comparison of its methylated product with a sample of the lactam of 10-amino-3,4-dimethoxyphenanthrene-1-carboxylic acid (**3**) prepared by the total synthesis outlined below. That the OH group was located at C-3 was suggested by the difference in chemical

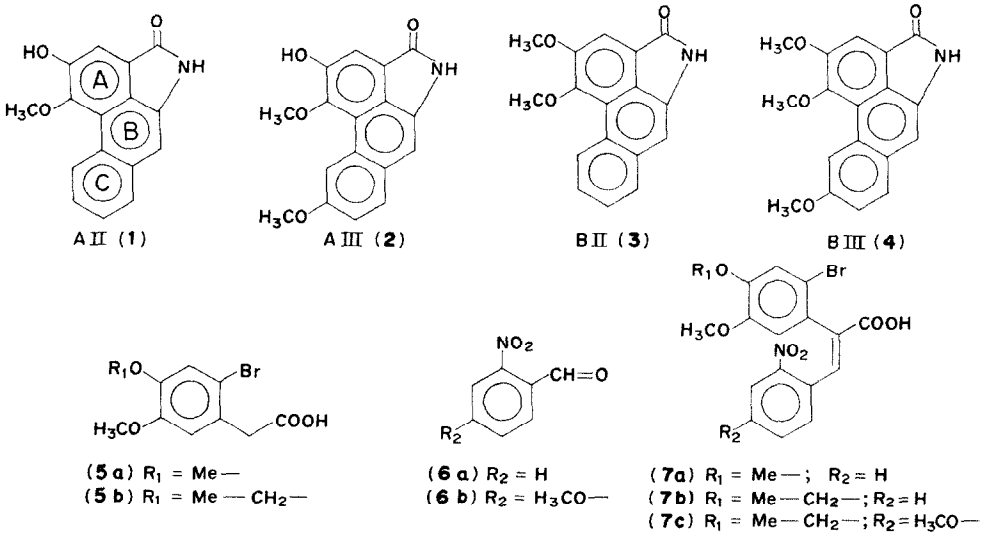
[1] PRIESTAP, H. A., RUVEDA, E. A., MASCARETTI, O. A. and DEULOFEU, V. (1971) *Anal. Asoc. Quim. Argentina* **59**, 245.

[2] PRIESTAP, H. A., RUVEDA, E. A., ALBONICO, S. M. and DEULOFEU, V. (1972) *Anal. Asoc. Quim. Argentina* **60**, 309.

shift of H-2 in the PMR spectra of compounds **1** (δ 7·62) and **3** (δ 7·85), and further confirmed chemically. Treatment of aristololactam AII with diazoethane afforded 3-*O*-ethylaristololactam AII identical to the lactam of 10-amino-3-ethoxy-4-methoxyphenanthrene-1-carboxylic acid (**11**) prepared by total synthesis. This is a final proof that the correct structure of aristololactam AII is **1**.

A similar analysis was applied to aristololactam AIII (**2**), m.p. 275° ($C_{17}H_{13}NO_4$, M^+ 295). It was shown spectrally (UV and IR) to have a phenanthrene chromophore and OH, NH and CO groups. The PMR spectrum verified the above spectral data OH (δ 10·22, 1H) and NH (δ 10·67, 1H) and in addition indicated the presence of two OMe groups (δ 3·95 and 4·08). A study of the aromatic region of the PMR spectrum was particularly useful: the singlets at δ 7·08 (1H) and δ 7·65 (1H), assigned to H-9 and H-2 respectively, showed that the location of substituents on ring A and B was the same as in aristololactam AII (**1**). The characteristic downfield signal of H-5 at δ 8·67 as a doublet and with *meta* coupling (J 3·5 Hz) indicated that the third oxygenated substituent was located at C-6. This was further confirmed by the remaining aromatic signals which could be ascribed to H-8 (δ 7·89) (doublet, J 9 Hz) and H-7 (δ 7·25) (double doublet, J 3·5 and 9 Hz). As in the case of aristololactam AII, the final proof of the correct structure of aristololactam AIII was obtained by comparison of its *O*-ethyl derivative with the lactam of 10-amino-3-ethoxy-4,6-dimethoxyphenanthrene-1-carboxylic acid (**12**) prepared by total synthesis and shown to be identical.

A similar analysis was applied to aristololactam BII and BIII and comparison with reference compounds showed their structures as **3** and **4** respectively.

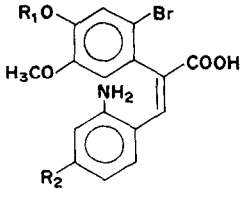


Synthesis of reference compounds

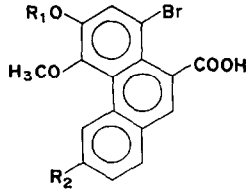
The lactam of 10-amino-3,4-dimethoxy-phenanthrene-1-carboxylic acid (**3**) was prepared following the method of Kupchan and Wormser.[3] By Perkin condensation of 6-bromo-3,4-dimethoxyphenylacetic acid (**5a**) and *o*-nitrobenzaldehyde (**6a**) the 2-bromo-4,5-dimethoxy-2′-nitro-*cis*-stilbene-α-carboxylic acid (**7a**) was obtained. The nitro group of

[3] KUPCHAN, S. M. and WORMSER, H. C. (1965) *J. Org. Chem.* **30**, 3933.

7a was reduced with ferrous sulphate and ammonium hydroxide and the resulting 2-bromo-4,5-dimethoxy-2′-amino-*cis*-stilbene-α-carboxylic acid without purification was submitted to the Pschorr phenanthrene synthesis to yield 1-bromo-3,4-dimethoxyphenanthrene-10-carboxylic acid. The phenanthrylamine **10a** was prepared from **9a** via a Schmidt reaction, which by treatment with *n*-butyl lithium and CO_2 afforded **3**. The lactams of 10-amino-3-ethoxy-4-methoxyphenanthrene-1-carboxylic acid and 10-amino-3-ethoxy-4,6-dimethoxyphenanthrene-1-carboxylic acid were prepared using the same method.



(**8a**) R_1 = Me—; R_2 = H
(**8b**) R_1 = Me—CH_2—; R_2 = H
(**8c**) R_1 = Me—CH_2—; R_2 = H_3CO—



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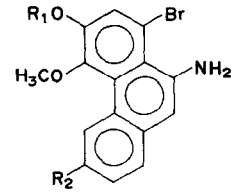

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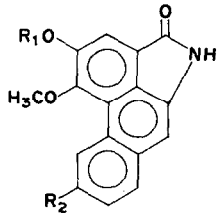
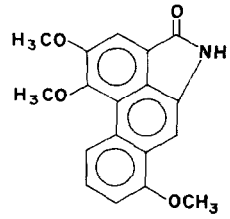


(**3**) R_1 = Me; R_2 = H
(**11**) R_1 = Me—CH_2—; R_2 = H
(**12**) R_1 = Me—CH_2—; R_2 = H_3CO—



(**13**)

Some aristololactams have been reported in the literature[4–6] and most of them have the substitution pattern of the known aristolochic acids. The aristololactams now reported, as well as taliscanine (**13**) differ in that they lack methylenedioxy substituents.

EXPERIMENTAL

All m.ps were determined on a Kofler block or in open capillaries and are uncorrected. UV spectra were determined, unless otherwise specified, in 95% EtOH. IR spectra were determined, unless otherwise specified, in KBr discs. PMR were determined with Varian Associates A-60 and T-60 spectrometers. The following chromatographic systems were employed on silicic acid: (1) $CHCl_3$:MeOH (93:7); (2) C_6H_6:butanone (3:2); (3) C_6H_6:butanone (7:3).

Extraction of Aristolochia argentina. Finely ground roots (10 kg) of *A. argentina* were extracted twice with petrol. The remaining powder was then extracted three times with boiling EtOH. The ethanolic extracts evaporated *in vacuo* afforded a dark brown oil that was suspended in a mixture of H_2O and Et_2O, and NH_3 was added to pH 9·7. The ethereal phase was separated and the remaining aqueous phase extracted with Et_2O until the extracts gave a negative alkaloidal reaction. To the remaining water solution, conc HCl was added to pH 3 and extracted with Et_2O when the aristolochic acids passed into the organic phase. The remaining H_2O soln gave a strong alkaloidal reaction due to the quaternary base magnoflorine. The ethereal extracts containing the alkaloids and the one containing the aristolochic acids were throughly extracted with H_2O buffered to pH 1·5 and with aqueous 5% $NaHCO_3$ respectively. The remaining ethereal solns were combined and evaporated to dryness

[4] TOMITA, M. and SASAGAWA, S. (1959) *J. Pharm. Soc. Japan* **79**, 973. *Chem. Abstr.* **53**, 21841 (1959).
[5] TOMITA, M. and SASAGAWA, S. (1959) *J. Pharm. Soc. Japan* **79**, 1470. *Chem. Abstr.* **54**, 6688 (1960).
[6] MALDONADO, L. A., HERRAN, J. and ROMO, J. (1966) *Ciencia (Mexico)* **24**, 237.

to yield a dark brown oil (212 g). TLC analysis of which showed several components, one of them with R_f 0·73 (system 1) identical to that of aristololactam I, isolated as described in a previous publication.[1]

Isolation of the aristololactams. The oily mixture containing the aristololactams (212 g) was dissolved in C_6H_6 (200 ml) and chromatographed over 500 g of silicic acid, 500 ml fractions being collected and monitored by TLC in the following order: Fr. 1–2 C_6H_6, fr. 3–4 C_6H_6–$CHCl_3$ (1:1), fr. 5–7 $CHCl_3$, fr. 8–10 $CHCl_3$–2% MeOH, fr. 11–13 $CHCl_3$–4% MeOH, fr. 14–16 $CHCl_3$–6% MeOH. Fractions 8–12 revealed by TLC the presence of aristololactam I and other non-phenolic aristololactams, which were isolated as described below. Fractions 13–14 revealed by TLC a component (R_f 0·33) with the properties of a phenolic aristololactam. By two successive silicic acid and acidic alumina columns a crystalline product was obtained (93 mg); m.p. 268–270°, from AcOH. This product was shown to be a mixture of two components (TLC, system 2) which were resolved by preparative TLC. After developing the plates showed two yellow bands of R_f 0·58 (blue fluorescence) and 0·52 (yellow fluorescence). Each band was scraped off the plates and eluted.

Aristololactam AII (**1**). The solid residue obtained from the R_f 0·58 band was crystallized from AcOH (8 mg); m.p. 271°. Parent mass 265; calc. for $C_{16}H_{11}NO_3$, 265. IR cm^{-1} 3356 (HO), 3268 (NH), 1709 (CO), 1295; UV max. 209 nm (log ε 4·39); 235 (4·57); 264 (4·40); 277 (4·47); 287 (4·47); 317 (3·87); 394 (3·81); inf. 384 (3·81); UV (EtOH–NaOH) max 252 nm (log ε 4·58); 289 (4·49); 421 (3·90); inf. 301 (4·35); 330 (4·06). PMR (d_6-DMSO): δ 4·03 (3H) *s* (OMe); 7·08 (1H) *s* (H-9); 7·54 (2H) *m* (H-6 and H-7); 7·62 (1H) *s* (H-2); 7·93 (1H) *m* (H-8); 9·13 (1H) *m* (H-5); 10·22 (1H) *s* (HO); 10·77 (1H) *s* (NH).

Aristololactam AIII (**2**). From the R_f 0·52 band a solid residue was obtained which crystallized from AcOH (9 mg); m.p. 275°. Parent mass 295; calc. for $C_{17}H_{13}NO_4$, 295. IR cm^{-1} 3378 (HO), 3226 (NH), 1684 (CO), 1164; UV max. 216 nm (log ε 4·34); 238 (4·58); 253 (4·42); 280 (4·36); 292 (4·36); 322 (3·96); 401 (3·84); UV EtOH–NaOH max 253 nm (log ε 4·57); 297 (4·48); 342 (4); 430 (3·88); inf. 287 (4·41). PMR (d_6-DMSO): δ 3·95 (3H) *s* (OMe-C-6); 4·08 (3H) *s* (OMe-C-4); 7·08 (1H) *s* (H-9); 7·25 (1H) *dd* (9 Hz, 3·5 Hz) (H-7); 7·65 (1H) *s* (H-2); 7·89 (1H) *d* (9 Hz) (H-8); 8·67 (1H) *d* (3·5 Hz) (H-5); 10·22 (1H) *s* (HO); 10·67 (1H) *s* (NH).

O-methylaristololactam AII and O-methylaristololactam AIII. The mixture of aristololactam AII and AIII (100 mg) isolated as described above, was treated in MeOH (10 ml) with ethereal diazomethane in the usual way. The solvent was evaporated *in vacuo* to give a residue which, on TLC (system 3), revealed two components. These were also isolated by preparative TLC. After developing the plates showed two bands of R_f 0·68 and 0·59.

O-methylaristololactam AII (**3**) (*aristololactam BII*). The solid residue obtained from the R_f 0·68 band was crystallized from *n*-BuOH yielding the lactam **3** (36 mg); m.p. 247–250°. Parent mass 279, calc. for $C_{17}H_{13}NO_3$, 279. IR cm^{-1} 3226 (NH), 1724 (CO), 1383; UV max 232 nm (log ε 4·50); 263 (4·42); 277 (4·46); 288 (4·47); 319 (3·90); 387 (3·84). PMR (d_6-DMSO): δ 4·06 (6H) *s* (OMe × 2); 7·13 (1H) *s* (H-9); 7·55 (2H) *m* (H-6 and H-7); 7·85 (1H) *s* (H-2); 7·93 (1H) *m* (H-8); 9·12 (1H) *m* (H-5); 10·78 (1H) *s* (NH).

O-methylaristololactam AIII (**4**) (*aristololactam BIII*). From the R_f 0·59 band a solid residue was obtained which crystallized from *n*-PrOH–*n*-BuOH yielding **4** (22·4 mg); m.p. 225°. Parent mass 309; calc. for $C_{18}H_{15}NO_4$, 309. IR cm^{-1} 3236 (NH); 1730 (CO); 1381; 1244; UV max 236 nm (log ε 4·53); 255 (4·38); 262 (4·40); 281 (4·30); 293 (4·33); 313 (4·01); 321 (4·01); 399 (3·80). PMR (d_6-DMSO): δ 3·92 (3H) *s* (OMe-C-6); 4·05 (6H) *s* (OMe × 2); 7·07 (1H) *s* (H-9); 7·20 (1H) *dd* (9 Hz, 2·5 Hz) (H-7); 7·81 (1H) *s* (H-2); 7·84 (1H) *d* (9 Hz) (H-8); 8·36 (1H) *d* (2·5 Hz) (H-5); 10·70 (1H) *s* (NH).

O-ethylaristololactam AII and O-ethylaristololactam AIII. The mixture of aristololactam AII and aristololactam AIII (15 mg) isolated as described above, was treated in MeOH with ethereal diazoethane in the usual way. The solvent was evaporated *in vacuo* to give a residue which, on TLC (system 3) revealed two components (R_f 0·68 and 0·59), the procedure used to isolate them was the same as described for compounds **3** and **4**.

O-ethylaristololactam AII (**11**). The solid residue obtained from the R_f 0·68 band was crystallized from *n*-PrOH-petrol. (3·7 mg); m.p. 193–195°. Parent mass 293; calc. for $C_{18}H_{15}NO_3$, 293. IR cm^{-1} 3247 (NH); 1706 (CO); 1385; UV max 232 nm (log ε 4·48); 264 (4·40); 276 (4·46); 287 (4·46); 318 (3·87); 385 (3·81).

O-ethylaristololactam AIII (**12**). From the R_f 0·59 band a solid residue was obtained which crystallized from *n*-PrOH (4·2 mg); m.p. 223–224°. Parent mass 323; calc for $C_{19}H_{17}NO_4$, 323. IR cm^{-1} 3289 (NH); 1709 (CO); 1316; 1256; 1053; UV max 236 nm (log ε 4·51); 255 (4·35); 262 (4·36); 281 (4·26); 293 (4·30); 314 (3·98); 321 (3·98); 400 (3·77).

Aristololactams BII (**3**) *and BIII* (**4**). Fractions 8–12 yielded aristololactam I (62·5 mg), identified as described in a previous publication.[1] Examination of the mother liquors by TLC showed two spots identical to the *O*-methyl derivatives of aristololactams AII and AIII. In order to confirm unequivocally their structures these products were isolated by preparative TLC and from the corresponding bands aristololactam BII (13·8 mg) and BIII (2 mg) were obtained in crystalline form. Both were identical to the synthetic products by m.m.p., IR and TLC.

Synthesis of reference compounds. 6-Bromo-3,4-dimethoxyphenylacetic acid (**5a**). It was prepared by the usual way, m.p. 115–117°, in 60% yield (lit.[7] m.p. 113–114°).

2-Bromo-4,5-dimethoxy-2′-nitro-cis-stilbene-α-carboxilic acid (**7a**). A mixture of **5a** (10 g) and *o*-nitrobenzaldehyde (5·5 g) in Ac_2O (90 ml) and NEt_3 (45 ml) was refluxed for 16 hr. The reaction mixture was then poured into H_2O (500 ml) and refluxed 10 min. By cooling **7a** crystallized out (9·56 g), m.p. 195–198°, which was recrystallized from MeOH–H_2O, m.p. 197–199°. IR cm^{-1} ($CHCl_3$) 1700 (COOH); 1530, 1350 (NO_2). PMR ($CDCl_3$): δ 3·64

[7] KAMETANI, T. (1964) *Chem. Abstr.* **61**, 12351.

(3H) *s* (OMe); 3·87 (3H) *s* (OMe); 6·50 (1H) *s* (aromatic or olefinic); 7·03 (1H) *s* (aromatic or olefinic); 8·32 (1H) *s* (aromatic or olefinic); 7·05–8·25 (4H) *m* (aromatic protons). (Found: C, 50·20; H, 3·82; N, 3·68. Calc. for $C_{17}H_{14}BrNO_6$: C, 50·01; H, 3·45; N, 3·43%.)

2-Bromo-4,5-dimethoxy-2'-amino-cis-stilbene-α-carboxylic acid (**8a**). A suspension of $Fe(OH)_2$ was prepared by adding NH_3 (124 ml) to a well-stirred soln of $FeSO_4.7H_2O$ (49·4 g) in H_2O (140 ml). The suspension was heated at 85° and, while stirring, **7a** (9·32 g) in aq. NH_3 (1:1; 140 ml) was added gradually. After the addition was complete, the reaction was heated at 95° for an additional 15 min and while the reaction mixture was still hot it was filtered. The ferric oxide sludge was washed with diluted NH_3 (400 ml). The combined filtrates were decolorized with charcoal. Acidification of the cold solution with conc. HCl yielded a pale yellow solid (7·97 g) which was used directly in the next step. IR cm^{-1} ($CHCl_3$) 1690 (COOH); no bands at 1530, 1350 (NO_2).

1-Bromo-3,4-dimethoxyphenanthrene-10-carboxylic acid (**9a**). Amyl nitrite (10 ml) was added gradually to a well stirred suspension of **8a** (13·8 g) in 15% ethanolic HCl solution (200 ml), the temperature being kept at −5°. After the addition was complete, dry Et_2O (300 ml) was added when a yellow solid precipitated, which was filtered and dried (9·8 g), m.p. 95–98° (dec.). IR cm^{-1} 2230 (diazo group); 1700 (COOH). The crude diazonium salt was suspended in dry acetone (80 ml) and with stirring Cu powder (360 mg) was added. N_2 evolution took place and when finished the suspension was filtered off. The filtrate was then poured into ice-H_2O (300 ml) and extracted with Et_2O. The dried Et_2O extracts were evaporated to dryness *in vacuo* to yield a solid residue (6·22 g), which was crystallized from EtOH (5 g), m.p. 165–167°. An analytical sample was recrystallized from EtOH, m.p. 168–169°. IR cm^{-1} ($CHCl_3$) 1700 (COOH); UV max 210 nm (log ε 4·42); 263 (4·68); 308 (4·04). PMR ($CDCl_3$): δ 3·92 (3H) *s* (OMe); 4·04 (3H) *s* (OMe); 7·20–7·90 (3H) *m* (H-6, H-7, H-8); 7·67 (1H) *s* (H-2); 8·06 (1H) *s* (H-9); 9·51 (1H) *m* (H-5). (Found: C, 56·90; H, 3·70. Calc. for $C_{17}H_{13}BrO_4$: C, 56·54; H, 3·62%.)

1-Bromo-3,4-dimethoxy-10-phenanthrylamine (**10a**). NaN_3 (60 mg) was gradually added to a cold and well stirred mixture of **9a** (100 mg) in $CHCl_3$ (2 ml) and conc. H_2SO_4 (1 ml). The mixture was stirred for an additional hour at 0° and then poured into a mixture of ice and $CHCl_3$ (10 ml). With good stirring this mixture was made alkaline with NH_3 and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed, dried and evaporated to dryness. The oily residue (12 mg) was dissolved in EtOAc and HCl passed through when a solid salt precipitated. The hydrochloride was filtered (14 mg), m.p. 231–238°. The free base that was recovered as a solid by neutralizing an aq. suspension of the hydrochloride with NH_3, extracting with $CHCl_3$, and evaporating the $CHCl_3$ was used for the next step without further purification. PMR($CDCl_3$): δ 3·84 (3H) *s* (OMe); 4 (3H) *s* (OMe); 4·22 (2H) broad singlet which disappears after equilibration with D_2O (NH_2); 6·80 (1H) *s* (H-9); 7·20–7·70 (3H) *m* (H-6, H-7, H-8); 7·55 (1H) *s* (H-2); 9·45 (1H) *m* (H-5).

Lactam of 10-amino-3,4-dimethoxyphenanthrene-1-carboxylic acid (**3**). *n*-Butyl lithium (0·5 ml of 11% hexane solution) was added gradually to a stirred soln of **10a** (125 mg) in Et_2O (4 ml) at 0° and under N_2. After being stirred for 15 min, the reaction mixture was poured over powdered Dry Ice. The Li salts were then decomposed by the addition of 10% HCl and the product was extracted with Et_2O. The combined Et_2O extracts were washed, dried and evaporated to leave an oily residue (40 mg). The above oil was rechromatographed on silica plates in $CHCl_3$–EtOH (94:6). The blue fluorescent band was eluted to give a yellow solid (4·1 mg) which recrystallized from *n*-BuOH melted at 252–253°. Identical with *O*-methylaristololactam AII (m.m.p., IR and TLC).

2-Bromo-4-ethoxy-5-methoxyphenylacetic acid (**5b**). It was prepared as compound **5a**; m.p. 122° (from C_6H_6). (Found: C, 45·70; H, 4·85. Calc. for $C_{11}H_{13}BrO_4$: C, 45·69; H, 4·53%.)

2-Bromo-4-ethoxy-5-methoxy-2'-nitro-cis-stilbene-α-carboxylic acid (**7b**). The procedure used to prepare **7b** was the same as described above for compound **7a**. M.p. 184–186° (from EtOH). IR cm^{-1} 1690 (COOH); 1520, 1300 (NO_2). PMR ($CDCl_3$): δ 1·40 (3H) *t* (OCH_2–$\underline{CH_3}$); 3·70 (3H) *s* (OMe); 4·20 (2H) *q* ($O\underline{CH_2}$–Me); 6·50 (1H) *s* (aromatic or olefinic); 7·05 (1H) *s* (aromatic or olefinic); 8·30 (1H) *s* (aromatic or olefinic); 7·05–8·23 (4H) *m* (aromatic protons). Found: C, 51·40; H, 3·95; N, 3·50. Calc. for $C_{18}H_{16}BrNO_6$: C, 51·21; H, 3·82; N, 3·32%.)

2-Bromo-4-ethoxy-5-methoxy-2'-amino-cis-stilbene-α-carboxylic acid (**8b**). The procedure used to prepare **8b** was the same as described above for compound **8a**. From **7b** (4·4 g), **8b** was obtained (3 g). IR cm^{-1} 1700 (COOH); no bands at 1520, 1300 (NO_2). It was used directly in the next step.

1-Bromo-3-ethoxy-4-methoxyphenanthrene-10-carboxylic acid (**9b**). The procedure to prepare **9b** was the same as described above for compound **9a**. From **8b** (550 mg), **9b** was obtained (240 mg), m.p. 185° (from *n*-PrOH). IR cm^{-1} 1710 (COOH); UV max 210 nm (log ε 4·59); 263 (4·78); 307 (4·10). PMR ($CDCl_3$): δ 1·53 (3H) *t* (OCH_2–$\underline{CH_3}$); 3·94 (3H) *s* (OMe); 4·23 (2H) *q* ($O\underline{CH_2}$ Me); 7·63 (1H) *s* (H-2); 7·50–8 (3H) *m* H-6; H-7; H-8); 8·04 (1H) *s* (H-9); 9·60 (1H) *m* (H-5). (Found: C, 57·50; H, 3·95. Calc. for $C_{18}H_{15}BrO_4$: C, 57·62; H, 3·62%.)

1-Bromo-3-ethoxy-4-methoxy-10-phenanthrylamine (**10b**). The procedure used to prepare **10b** was the same as described above for compound **10a**. From **9b** (600 mg), **10b** was obtained (234 mg), m.p. 134° (from C_6H_6–petrol.). PMR ($CDCl_3$): δ 1·57 (3H) *t* (OCH_2–$\underline{CH_3}$); 3·87 (3H) *s* (OMe); 4·22 (2H) *q* ($O\underline{CH_2}$–Me); 4·69 (2H) *s* which disappears after equilibration with D_2O ($\underline{NH_2}$); 6·77 (1H) *s* (H-9); 7·15–7·55 (3H) *m* (H-6, H-7, H-8); 7·50 (1H) *s* (H-2); 9·40 (1H) *m* (H-5). Picrate; m.p. 148–152° (from EtOH). (Found: N, 9·92. Calc. for $C_{17}H_{16}BrNO_2.C_6H_3N_3O_7$: N, 9·73%.)

Lactam of 10-amino-3-ethoxy-4-methoxyphenanthrene-1-carboxylic acid (**11**). The procedure used to prepare **11** was the same as described above for compound **3**, except that dioxane, instead of Et_2O, was used as solvent. From **10b** (100 mg), **11** was obtained (1 mg), m.p. 198° (from *n*-PrOH–petrol.). Identical with *O*-ethylaristololactam AII (m.m.p., IR and TLC).

2-*Nitro*-4-*methoxybenzaldehyde* (**7b**). It was prepared by the method of Suvorov *et al.*, m.p. 96–98° (lit.[8] m.p. 95–96°).

2-*Bromo*-4-*ethoxy*-5-*methoxy*-2′-*nitro*-4′-*methoxy*-cis-*stilbene*-α-*carboxylic acid* (**7c**). The procedure used to prepare **7c** was the same as described above for compounds **7a** and **7b**. From **5b** (24·2 g) and **6b** (15·9 g), **7c** was obtained (32·2 g), which after purification through a silicic acid column melted at 235–237° (from EtOH–H_2O). IR cm^{-1} ($CHCl_3$) 1695 (COOH); 1530, 1350 (NO_2). By treatment of **7c** with an ethereal solution of CHN_2 the corresponding methyl ester was prepared, m.p. 103–104° (from *n*-PrOH). PMR (CCl_4): δ 1·50 (3H) *t* (OCH_2–$\underline{CH_3}$); 3·60 (3H) *s* (OMe); 3·80 (3H) *s* (OMe); 3·95 (3H) *s* (OMe); 4·05 (2H) *q* ($O\underline{CH_2}$–Me); 6·50 (1H) *s* (olefinic or aromatic); 6·90 (3H) broad singlet (aromatic); 7·50 (1H) broad singlet (aromatic); 8·00 (1H) *s* (aromatic). (Found: C, 52·04; H, 4·57; N, 2·88. Calc. for $C_{20}H_{20}BrNO_7$: C, 51·75; H, 4·32; N, 3·00%.)

2-*Bromo*-4-*ethoxy*-5-*methoxy*-2′-*amino*-4′-*methoxy*-cis-*stilbene*-α-*carboxylic acid* (**8c**). The procedure used to prepare **8c** was the same as described above for compounds **8a** and **8b**. From **7c** (9·47 g), **8c** was obtained (8·1 g). It was used directly in the next step.

1-*Bromo*-3-*ethoxy*-4,6-*dimethoxyphenanthrene*-10-*carboxylic acid* (**9c**). Freshly distilled isoamyl nitrite (8 ml) was added gradually in 3 hr and 30 min to a well stirred soln of **8c** (8 g) in a mixture of DMF (88 ml) and 50% H_3PO_2 (32 ml), the temp. being kept at 15°. After the addition was complete the mixture was heated at 50–60° for 30 min and poured into a mixture of ice–H_2O. The solid precipitate was filtered and recrystallized from EtOH (1·14 g), m.p. 215–218°. Parent mass 405; calc. for $C_{19}H_{17}BrO_5$, 405. UV max 220 nm (log ϵ 4·47); 266 (4·75); 326 (4·21). PMR (d_6-DMSO): δ 1·45 (3H) *t* (OCH_2–CH_3); 3·93 (3H) *s* (OMe); 3·97 (3H) *s* (OMe); 4·29 (2H) *q* (OCH_2–Me); 7·36 (1H) *dd* (9 Hz, 2·5 Hz) (H-7); 7·83 (1H) *s* (H-2); 7·93 (1H) *s* (H-9); 8·01 (1H) *d* (9 Hz) (H-8); 9·03 (1H) *d* (2·5 Hz) (H-5).

1-*Bromo*-3-*ethoxy*-4,6-*dimethoxy*-10-*phenanthrylamine* (**10c**). The procedure used to prepare **10c** was the same as described above for compounds **10a** and **10b**. From **9c** (200 mg), **10c** was obtained as picrate (170 mg), m.p. 154° (from EtOH). (Found: C, 47·50; H, 3·54. Calc. for $C_{18}H_{18}BrNO_3 \cdot C_6H_3N_3O_7$: C, 47·61; H, 3·49%.) PMR of the free base ($CDCl_3$): δ 1·54 (3H) *t* (OCH_2–CH_3); 3·87 (3H) *s* (OMe); 3·93 (3H) *s* (OMe); 4·35 (2H) broad singlet (NH_2); 6·93 (1H) *s* (H-9); 7·13 (1H) *dd* (9 Hz, 2·5 Hz) (H-7); 7·50 (1H) *d* (9 Hz) (H-8); 7·56 (1H) *s* (H-2); 8·98 (1H) *d* (2·5 Hz) (H-5).

Lactam of 10-*amino*-3-*ethoxy*-4,6-*dimethoxyphenanthrene*-1-*carboxylic acid* (**12**). The procedure to prepare **12** was the same as described above for compounds **3** and **11**. From **10c** (95·5 mg, free base) **12** was obtained (4 mg). Identical with the *O*-ethylderivative of aristololactam AIII (m.m.p., IR, TLC).

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