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THE SYNTHESIS OF [9](2,4)PYRROLOPHANES

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Abstract—Two methods utilized in the synthesis of [9](2,4)pyrrolophanes are reported. The first, an application of the Paal–Knorr cyclization, involved the condensation of ammonia with 3-formylcyclododecanone. The second method employed the condensation of 3-chlorocyclododec-2-en-1-one with diethyl aminomalonate.

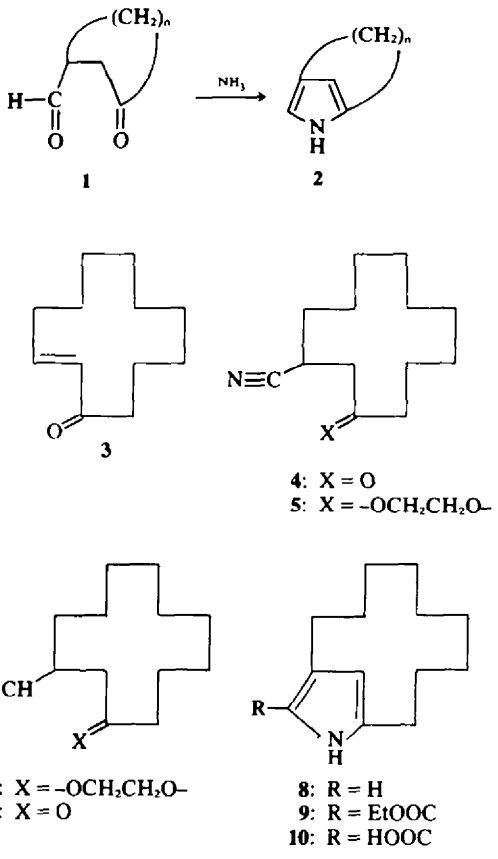
The isolation of meta-fused heterophanes from natural sources[1,2] has prompted recent investigations into general methods for the synthesis of these meta-bridged systems. Prominent among studies in this area has been the work of Nozaki *et al.* on the preparation of various types of heterophanes.[3] In this paper we are reporting results of our studies on the synthesis of the [9](2,4)pyrrolophane system† which is present in the C-25 bacterial pigment, metacycloprodigiosin.[1] As is outlined below, two general synthetic routes to meta-fused pyrroles have been developed. In each case, the pyrrole ring is annelated to an existing 12-membered ring.

The first method represents an application of the classical Paal–Knorr cyclization,[4] involving the condensation of ammonia with a 1,4-dicarbonyl compound (e.g. **1**→**2**). 2-Cyclododecenone **3**‡ was utilized as the starting material.

Conjugate addition of hydrogen cyanide to the unsaturated ketone **3** was accomplished with potassium cyanide in hot N,N-dimethylformamide[6] yielding the cyano ketone **4** (40%). Ketalization to give **5** was accomplished (86%) by heating a mixture of the ketone **4**, ethylene glycol, and benzene at reflux temperature with a catalytic amount of *p*-toluenesulfonic acid. The nitrile **5** was reduced with diisobutylaluminum hydride (DIBAL) yielding the aldehyde **6**[7] (86%). Hydrolysis of the ketal group in **6** with *p*-toluenesulfonic acid in aqueous acetone yielded the 1,4-dicarbonyl compound **7** which was immediately heated with ammonium carbonate in aqueous N,N-dimethylformamide to give the [9](2,4)pyrrolophane **8** (40% from **6**).

The key compounds in the second route to meta-fused pyrroles are the *cis*- and *trans*-isomers of 3-chlorocyclododec-2-en-1-one **11**.

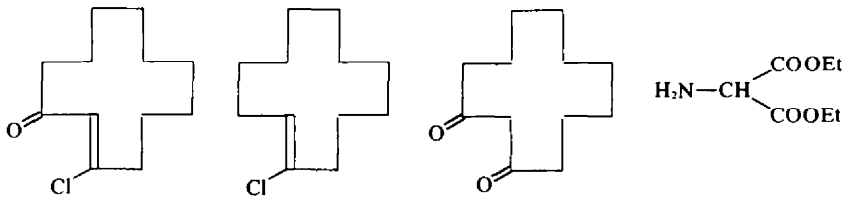
The *cis* and *trans* material **11** was prepared by a route reported earlier by Schank and Eistert[8] from cyclododecanone, through the vinyl chloride **12**. Allylic bromination of **12** followed by conversion to the β-chloro-α,β-unsaturated alcohol, and then oxidation,[8] yielded **11**. It was our original intention to prepare the meta-fused pyrrolophane **9** by conversion of the chlorovinyl ketone **11** to the 1,3-diketone **13**[8] followed by treatment with diethyl oximinomalonate under reducing conditions according to the general procedure of Kleinspehn.[9] In our hands, however, this procedure was not successful, and we therefore resorted to the direct condensation of **11** with diethyl aminomalonate **14**.[10] Heating the mixture of ketones **11** with **14** at 100° in the presence of sulfuric acid yielded 11-carbethoxy[9](2,4)pyrrolophane **9**. Hydrolysis of **9** with potassium hydroxide in aqueous methanol gave the carboxylic acid **10** which could be decarboxylated to [9](2,4)pyrrolophane **8** by heating at 135°. Alternatively, pyrrolophane **8** could be obtained directly from 11-carbethoxy[9](2,4)pyrrolophane **9** by pyrolysis under vacuum with soda-lime at 300–350°.



The two methods described above allow for relatively easy and versatile entry into the meta-fused pyrrole system. The application of the first method to natural product synthesis is shown in an accompanying paper[11] in which the preparation of ±1-9-ethyl[9](2,4)pyrrolophane is described.

†For a discussion of the nomenclature and numbering of such compounds, see F. Vogtle and P. Neumann, *Tetrahedron Letters* 5329 (1969).

‡This compound has been prepared either from cyclododecane epoxide[5a] or from cyclododecanone.[5b] We have synthesized a mixture of the *cis*- and *trans*-isomers of **3** by each of the reported routes. Since our results starting from cyclododecane epoxide are different from the reported procedure, we have included details on this transformation in the Experimental.



11 12 13 14

EXPERIMENTAL

M.ps and b.ps are uncorrected. IR spectra were recorded on either a Perkin–Elmer, Model 421 Recording Infrared Spectrometer or a Perkin-Elmer, Model 237 Grating Spectrophotometer. NMR spectra were taken on a Varian Model A60-A Spectrometer. Chemical shifts are reported in τ units using TMS as internal reference. Mass spectra were recorded on a CEC, Model 21-103, a AEI, model MS-9, or a Hitachi-Perkin Elmer instrument. UV spectra were recorded on a Cary, Model 11-S or on a Bausch & Lomb, Model 550 recording spectrometer. Microanalyses were performed by Dr. R. Rittner of the Olin Mathieson Chemical Company, New Haven, Connecticut, and by Alfred Bernhardt, Muhlheim, Germany. Gas-liquid chromatographic analyses and sample collections were made on a Varian Aerograph, Model A90-P3 instrument. A 5' × 1/4" 20% Silicon Gum Rubber (SE-30) on 60/80 mesh Chromosorb W column was used for analytical purposes, and a 12' × 3/8" 20% SE-30 on Chromosorb W column was used for preparative purposes unless otherwise noted. The helium flow rate was 200 cm³/min unless otherwise noted.

A. *Preparation of* [9](2,4)*pyrrolophane* **8** *from* 2-*cyclododecenone* **3**

2-*Cyclododecenol.* The starting material for this procedure, modeled after the method of Kirchhof,[12] was cyclododecane epoxide (114 g, 0.62 mol) which was dissolved in xylene (110 ml) in a 3-neck round-bottomed flask equipped with a nitrogen inlet tube, a mechanical stirrer, an addition funnel, and a reflux condensor. Diisobutyl-aluminum hydride (DIBAL) (90 g, 0.635 mol) was placed in the addition funnel under nitrogen, xylene (90 ml) was added to the aluminum hydride, and the mixture was swirled to effect solution. The xylene solution of the epoxide was then heated at 120° with stirring while the DIBAL solution was added dropwise over the course of 1 h. After addition was complete, the reaction mixture was stirred for an additional 3·5 h at 120°. The solution was then allowed to cool, and the aluminum salts were decomposed by the dropwise, cautious addition of 10% aqueous sulfuric acid. The organic layer was separated, washed with water (100 ml), and dried ($MgSO_4$). The xylene was removed *in vacuo* leaving a clear oil which was distilled (6" Vigreux column) to yield 54 g of a 60:40 mixture of 2-cyclododecenol and cyclododecanol, b.p. 83–90° (0.1 mm). The separation and identification of these two compounds is discussed below. The mixture containing 1-cyclododecenol was found to be suitable for use in the next step of the synthesis.

Isolation of cyclododecanol. A solution of the mixture of 2-cyclododecenol and cyclododecanol in acetic acid was cooled to 15°, and bromine added dropwise until the color persisted. The acetic acid solution was poured into excess aq. NaOH, the resultant solution cooled, and then extracted with 3 portions of ether. The ether extracts were combined, washed with water, sat NaCl soln, and dried ($MgSO_4$). The solvent was removed *in vacuo* leaving an oil which was distilled to yield a liquid which solidified on standing, b.p. 95–100° (0.05 mm). The solid was crystallized from acetone to yield cyclododecanol: m.p. 78–79° [lit[12] 80°]; IR (CCl_4) 3620, 3500, 2940, 2850, 1470, 1440 cm⁻¹; NMR (CCl_4) 6.3 (m, τ 1 H), 7.8 (s, 1 H), 8.6 (broad s, 22 H). This material was shown to be identical (m.m.p., IR, NMR) with an authentic sample of cyclododecanol prepared by lithium aluminum hydride reduction of cyclododecanone.

2-*Cyclododecenone* **3.** The mixture of 2-cyclododecenol and cyclododecanol (75%) in ether (760 ml) was placed in a 3-neck, round-bottomed flask equipped with a mechanical stirrer, an addition funnel, and a reflux condenser. In a procedure similar to that used by Brown,[14] a solution of sodium dichromate (82 g, 0.274 mol) and conc H_2SO_4 (95 ml) in water (630 ml) was added dropwise with stirring to the alcohol mixture at a rate sufficient to maintain moderate reflux. After addition was complete, the reaction mixture was stirred for 2 h. The layers were then separated and the aqueous layer extracted with 5 portions of ether (250 ml). The ether extracts were combined, washed with water (250 ml), 1 N Na_2CO_3 (250 ml), 3 portions of water (250 ml), and sat NaCl soln (250 ml). The ether solution was dried ($MgSO_4$) and the ether removed *in vacuo* to yield an oil (67 g). Analysis by NMR, IR and GLC indicated that the product consisted of a 60:40 mixture of 2-cyclododecenone **3** and cyclododecanone. Preparative GLC (180°) afforded a pure sample of 2-cyclododecenone **3**: λ_{max} (EtOH) 230 nm (ϵ 9700); IR (CCl_4) 2950, 2880, 1692, 1666, 1628, 1465, 1445, 900 cm⁻¹; NMR (CCl_4) τ 3.30 (hex, 1 H), 3.80 (d, 1 H), 7.70 (m, 4 H), 8.1–9.0 (m, peaking at 8.7, 18 H). Preparative GLC also yielded a pure sample of cyclododecanone, identified by comparison of its NMR and IR with those of an authentic sample (Aldrich Chemical Co.). The mixture of 2-cyclododecenone and cyclododecanone was found to be suitable for use in the next step of the synthetic sequence.

3-*Cyanocyclododecanone* **4.** Following the procedure of Nagata,[6] a mixture of 2-cyclododecenone **3** and cyclododecanone (67 g), potassium cyanide (47 g, 0.66 mol), ammonium chloride (25 g, 0.47 mol), dimethyl formamide (450 ml) and water (45 ml) was placed in a 3-neck, round-bottomed flask equipped with a nitrogen inlet tube, a mechanical stirrer, and a reflux condenser. The mixture stirred at 110° for 12 h. The dark brown reaction mixture was cooled, poured into NH_4Cl soln (1500 ml) and the resultant aqueous mixture extracted with 5 portions of ether (250 ml). Caution: The odor of hydrogen cyanide was evident during the work-up. The combined ether extracts were filtered through infusorial earth to remove tars which had formed during the reaction. The filtrate was washed with 3 portions of water (250 ml), and one portion of sat NaCl soln (250 ml). The ether solution was then decolorized with activated charcoal, dried ($MgSO_4$), and concentrated *in vacuo* leaving a dark oil which was distilled "12" Vigreux column). The first fraction (b.p. 80–96°/0.4 mm) consisted mainly of cyclododecanone identified by comparison of its NMR and IR with those of an authentic sample (Aldrich Chemical Co.). The second fraction (32.7 g, 18.2% from cyclododecane epoxide) consisted mainly of 3-cyanocyclododecanone **4**, b.p. 140–143° (0.4 mm). A portion of the distilled cyanide was crystallized from methanol: m.p. 73.5–75.5° (lit.[15] 73–74°); IR (CCl_4) 2950, 2875, 2860, 2240, 1712, 1470, 1445, 1360 cm⁻¹; NMR (CCl_4) τ 6.7–7.8 (m, 5 H), 8.1–9.0 (m, peaking at 8.46 and 8.67, 16 H). (Found: C, 74.74, 75.00; H, 10.12, 10.43; N, 6.55, 6.52. Calc. for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76%).

3-*Cyanocyclododecanone ethylene ketal* **5.** A mixture of ketone **4** (60 g, 0.29 mol), ethylene glycol (180 g, 2.9 mol), *p*-toluenesulfonic acid monohydrate (5.5 g, 0.029 mol) and benzene (550 ml) was placed in a flask equipped with a Dean Stark water separator and a reflux condenser and the mixture heated at reflux temperature for 72 h during which time 8 ml of water was collected. The reaction mixture was cooled, poured into 500 ml of 0.1 N $NaHCO_3$, and the layers separated. The aqueous layer was extracted with two portions of ether (750 ml) and the combined organic extracts washed with three portions of water (200 ml) and one portion of NaCl soln (250 ml). The solution was dried ($MgSO_4$) and the organic solvents removed *in vacuo* leaving a solid which was crystallized from methanol to yield 62.5 g (86%) of

3-cyanocyclododecanone ethylene ketal **5**: m.p. 106–108°; IR (CCl_4) 2950, 2875, 2245, 1470, 1450, 1120, 1075, 1055 cm^{-1}; NMR (CCl_4) τ 6.07 (m, 4 H), 7.45 (m, 1 H), 7.8–8.9 (m, peaking at 8.61, 21 H). (Found: C, 71.66; H, 9.77; N, 5.56. Calc. for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57%).

3-Formylcyclododecanone ethylene ketal **6**. The procedure, a modification of that used by Zakharkin,[7] started with 56 g, (0.22 m) of the ketal in ether (500 ml) in a 3-neck round-bottomed flask equipped with a nitrogen inlet tube, a mechanical stirrer, a 250 ml addition funnel, and a reflux condenser. Diisobutylaluminum hydride (DIBAL) (40 g, 0.28 mol) was placed in the addition funnel under nitrogen. Ether (100 ml) was added to the DIBAL, the mixture swirled, and the solution then added dropwise with stirring to the cyanide over the course of 1 h.[7] After addition was complete the reaction mixture was heated at reflux for an additional h. It was then allowed to cool, and the aluminum salts were decomposed by the dropwise addition of 10% H_2SO_4. The layers were separated and the aqueous layer extracted with 3 portions of ether (150 ml). The combined ether extracts were washed with 0.5 N $NaHCO_3$ soln (200 ml), 3 portions of water (200 ml), and one portion of NaCl soln (200 ml). The ether solution was dried and the ether removed *in vacuo* yielding 48 g (86%) of crude 3-formylcyclododecanone ethylene ketal **6**. A portion of the aldehyde was purified by sublimation; m.p. 66.5–68°; semicarbazone m.p. 198–200°; IR (CCl_4) 2950, 2860, 2820, 2720, 1728, 1470, 1440, 1110, 1070, 1050 cm^{-1}; NMR (CCl_4) τ 0.49 (d, 1 H), 6.23 (m, 4 H), 7.65 (m, 1 H), 8.0–8.9 (m, peaking at 8.61, 21 H). (Found: C, 61.98; H, 9.66; N, 13.39. Calc. for $C_{16}H_{29}N_3O_3$ (semicarbazone): C, 61.71; H, 9.39; N, 13.49%).

3-Formylcyclododecanone **7**. A solution consisting of 5 g (0.0196 mol) of ketal **6** and *p*-toluenesulfonic acid monohydrate (0.3 g 0.0016 mol) in acetone–water (38:15) was stirred for 8 h. It was then poured into water (100 ml), and the aqueous mixture was extracted with 4 portions of ether (50 ml). The ether extracts were combined and washed with 3 portions of water (100 ml) and one portion of NaCl soln (100 ml). The solution was dried ($MgSO_4$) and the ether removed *in vacuo* to yield 3.8 g (92%) of crude 3-formyl-cyclododecanone **7**. Analysis by IR, NMR and GLC (190°) indicated that the product was contaminated with 10% of the starting material. A sample was purified by sublimation: IR (CCl_4) 2945, 2880, 2815, 2712, 1729, 1709, 1470, 1445 cm^{-1}; NMR (CCl_4) τ 0.25 (s, 1 H), 7.2 (m, 3 H), 7.5 (m, 2 H), 8.0–8.9 (m, peaking at 8.67, 16 H). (Found: C, 73.75; H, 10.29. Calc. for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54%).

[9](2,4)*Pyrrolophane* **8**. The ketoaldehyde **7** (3.8 g, 0.018 mol) was heated at 120° for 3 h with an excess of ammonium carbonate in N,N-dimethylformamide (60 ml) and water (10 ml) under nitrogen. The reaction mixture was poured into 1000 ml of water and the aqueous mixture extracted with ether. The combined ether extracts were dried ($MgSO_4$) and the solution concentrated *in vacuo* to yield 1.4 g (40%) of crude [9](2,4)pyrrolophane **8** as an oil which solidified on cooling. Crystallization from carbon tetrachloride followed by sublimation under reduced pressure gave an analytical sample: m.p. 90–92°; IR (KBr) 3489, 3390, 2925, 2850, 1464, 1445, 1428, 1106, 715, 683 cm^{-1}; NMR (CCl_4) τ 2.72 (broad, 1 H), 3.76 (t, 1 H), 4.18 (t, 1 H), 7.62 (m, 4H), 8.3–9.2 (m, 12 H), 9.7 (m, 2 H); MS *m/e* (rel intensity) 192(15), 191(100), 190(53), 162(27), 148(45), 134(39), 120(27), 108(33), 106(60), 95(50), 94(75), 93(60), 80(69). (Found: C, 81.95; H, 11.27; N, 7.28. Calc. for $C_{13}H_{21}N$: C, 81.61; H, 11.06; N, 7.32%).

B. *Preparation of* [9](2,4)*pyrrolophane* **8** *from cyclododecanone*

3-Chlorocyclododec-2-en-1-one **11**.[8] A mixture of *cis* and *trans* -3-chlorocyclododec-2-en-1-one **11** was prepared from cyclododecanone in approximately 20% yield according to the procedure described by Schank and Eistert.[8] Analysis by GLC showed two overlapping peaks assumed to be the two isomers of 3-chlorocyclododec-2-en-1-one **11**. Schank and Eistert[8] do not report any purification of this compound, and the crude oil was used directly in the next step of the synthesis. The 2,4-dinitrophenylhydrazone was prepared and characterized, as reported in the next section.

2,4-Dinitrophenylhydrazone of 3-chlorocyclododec-2-en-1-one. Crude 3-chlorocyclododec-2-en-1-one (1 g) was dissolved in absolute ethanol (50 ml) in a 250 ml conical flask, and the 2,4-dinitrophenylhydrazine reagent (50 ml, 0.1 M soln of 2,4-dinitrophenylhydrazine in ethanol/phosphoric acid) was added. An emulsion formed. Heating the solution to boiling cleared the emulsion, which then reformed on cooling. The emulsion was extracted with carbon tetrachloride (in which the excess reagent is almost insoluble) and the extract reduced to an oil on the rotary evaporator. This oil was taken up in ether (10 ml) and a yellow precipitate rapidly formed. After the mixture was cooled overnight in a freezer, 190 mg of the 2,4-DNP derivative was collected by filtration. Recrystallization from ethyl acetate gave orange plates: m.p. 183–186°; MS *m/e* (rel intensity) 395(15), 397(6), 378(trace), 360(100), 341(7), 328(4), 323(3), 243(5), 225(7), 228(5), 198(5), 196(14), 161(25), 81(36), 67(43), 55(70), 43(29), 41(98). (Found: C, 54.72; H, 5.93; N, 14.24. Calc. for $C_{18}H_{23}N_4O_4Cl$: C, 54.75; H, 5.87; N, 14.19%).

11-Carbethoxy[9](2,4)*pyrrolophane* **9**. Crude 3-chlorocyclododec-2-en-1-one (17.0 g, 0.08 mol) was mixed with diethyl aminomalonate (15.5 g, 0.09 mol) and heated in an open, round-bottomed 100 ml flask in an oil bath at 100° with occasional mixing. After 30 min the mixture was made strongly acid with a few drops of conc. H_2SO_4. After a further 30 min water (4 ml) was added, and the mixture heated for 1 hr. The mixture was then repeatedly extracted with hot hexane, the extract dried ($MgSO_4$), and concentrated on the rotary evaporator to about 30 ml. On cooling, white crystals were deposited. Concentration of the mother liquor to about 20 ml and strong cooling overnight gave a second crop of somewhat coloured crystals. The total yield was 5.8 g (27%). Recrystallization from ethanol gave pure white crystals: m.p. 127–129°; λ_{max} (EtOH) 280 nm (log ϵ 4.23); IR (KBr) 3288 (s), 2968 (w), 2950 (sh), 2908 (s), 2840 (s), 1646 (s) cm^{-1}; NMR ($CDCl_3$) τ 0.35 (broad s, 1 H), 3.99 (d, 1 H, J = 3 Hz), 5.70 (quartet, 2 H, J = 7 Hz), 7.18 (t, 2 H, J = 6.5 Hz), 7.44 (t, 2 H, J = 6.25 Hz), 8.60–8.28 (m), 8.65 (t, J = 7 Hz), 9.05–8.60 (m), 9.55–9.05 (m, 4 H) (total of 21 H in the upfield region); MS *m/e* (rel intensity) 263(19), 234(4), 220(3), 218(5), 190(100), 162(5.5), 160(4), 148(3), 146(4.5), 134(6.5), 132(8), 120(7), 118(4.5), 106(8), 104(4), 94(100), 93(9), 91(8), 80(6), 77(7), 67(4), 65(7.5), 55(5), 41(6). (Found: C, 73.00; H, 9.41; N, 5.32. Calc. for $C_{16}H_{25}NO_2$: C, 72.97; H, 9.57; N, 5.35%).

11-Carboxy[9](2,4)*pyrrolophane* **10**. 11-Carbethoxy[9](2,4)pyrrolophane (200 mg, 0.75 mmol) was dissolved in 80% methanol (20 ml) in a round-bottomed flask, and KOH pellets (2 g) added. The flask was heated at 75° with shaking from time to time. Higher temperatures led to decarboxylation of the product. The reaction was followed by TLC, and was complete within 2 h. The solution was diluted with water and adjusted to pH 5–6 with 1 N HCl. The precipitated acid was filtered and dried *in vacuo* yielding a white powder (158 mg, 88%). Analysis by TLC showed it to be pure and free of any decarboxylated product. It could be recrystallized without decarboxylation by cooling a sat soln in chloroform to give crystals of 11-carboxy[9](2,4)pyrrolophane **10** (m.p. variable, with simultaneous decarboxylation above 120°) λ_{max} (EtOH) 276.5 nm (log ϵ 4.19); λ_{max} (0.1 N NaOH) 266.0 nm (log ϵ 4.13); IR (KBr) 3600–2400 (broad band peaking 3250, 3210), 2965 (w), 2925 (s), 2850 (s), 1640 (s), 1610 (s), 1500 (s), 1480 (m), 1460 (w), 1430 (m) cm^{-1}; NMR ($CDCl_3$) τ −0.6 (broad s, 1 H), 0.85 (broad s, 1 H), 3.89 (d, 1 H, J = 2.5 Hz), 7.10 (broad t, 2 H, J = 4 Hz), 7.40 (broad t, 2 H, J = 4 Hz), 9.5–8.15 (m, 14 H); MS *m/e* (rel intensity) 235(20), 216(2), 206(1), 190(100), 162(3), 160(2), 148(3), 146(3), 138(5), 134(4), 132(3), 120(5), 106(5), 101(5), 94(7), 93(4), 91(4), 80(4), 65(3), 41(3), (Found: C, 71.53; H, 8.98; N, 6.35. Calc. for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; N, 5.95%).

[9](2,4)*Pyrrolophane* **8**. (1) 11-Carbethoxy[9](2,4)pyrrolophane (300 mg, 1.1 mmol) was mixed intimately with soda lime (3 g) which had been freshly fired and allowed to cool in a desiccator. A length of glass tubing (25 cm × 8 mm) with a constriction 7 cm from one end was packed with a glass wool plug and fresh soda lime (1.5 g), and the mixture was sealed. The tube was evacuated for 30 min (0.1–0.05 mm) and then the region containing the soda lime was heated to 300–350° in a tube furnace. The [9](2,4)pyrrolophane **8** condensed as white crystals on the cooler portions of the tube (110 mg, 52%). Analysis of the product by TLC and GLC showed it to be pure. Recrystallization from carbon tetrachloride gave white crystals: m.p. 90–91°; IR, NMR and MS

are superimposable on those of the [9](2,4)pyrrolophane produced by the previously described route (Sequence A).

(2) 11-Carboxy[9](2,4)pyrrolophane (10 mg, 0.43 mmol) was heated on a glass slide on a hot-stage m.p. apparatus. At about 135° the sample melted with gas evolution. On cooling the melt, recrystallization occurred to give crystals (8 mg, 95%) which remelted at 89–92°. The product showed identical behavior (on analysis by TLC) with a reference spot of pure [9]-(2,4)pyrrolophane **8**, and gave IR and MS superimposable on those obtained from a sample of **8** prepared by the previously described routes.

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