

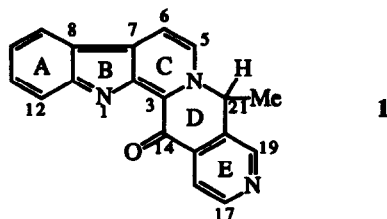
MAXONINE: STRUCTURE CORRECTION AND SYNTHESIS

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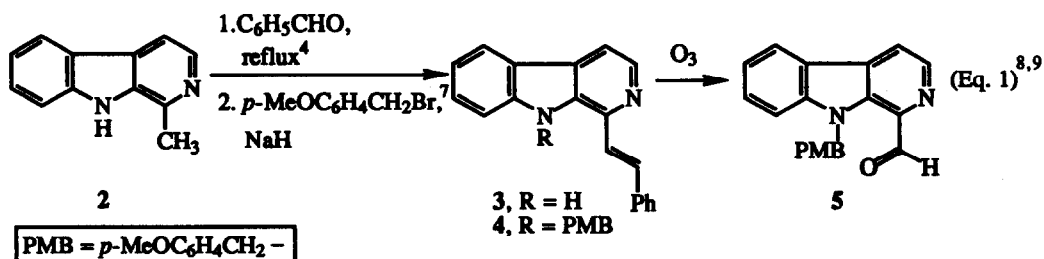
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Abstract: The structure for the pentacyclic alkaloid maxonine is revised from 1 to 17. Compound 17 was prepared by total synthesis and shown identical to the natural product.

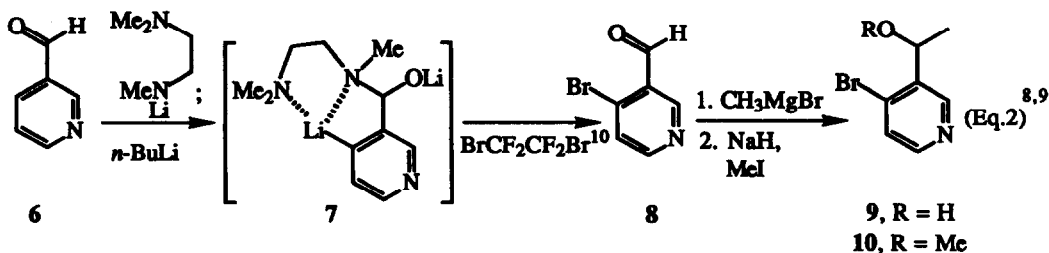
In 1989 Delle Monache et al. reported¹ the isolation and structural characterization of an alkaloid that had been obtained from the roots of a plant (*Simira maxonii*) endemic to the Costa Rican tropical forest. They named the alkaloid maxonine and assigned it structure 1. Our interest in the synthesis of heterocyclic natural products² combined with a desire to verify the structure assignment led us to undertake the synthesis of 1.



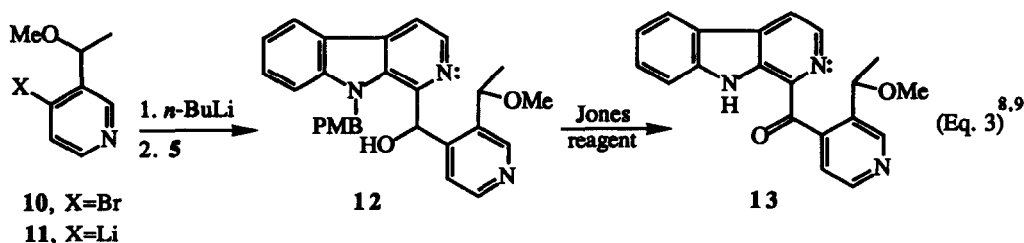
Harmane³ (2) was elaborated (Equation 1) to aldehyde 5 by conversion to its benzal derivative 3,⁴ protection and ozonolysis. The E-ring unit 10 was prepared as outlined in Equation 2. Our⁵ previously



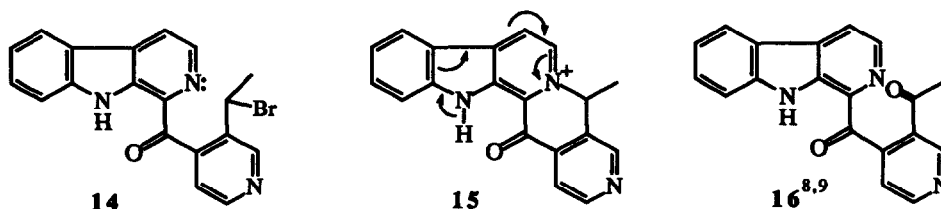
developed application of the Comins method⁶ to the regiospecific lithiation of nicotinaldehyde (6) gave bromide 8 via 7. Reaction of 8 with methylmagnesium bromide followed by methylation generated 10.



Compounds **5** and **10** were linked (Equation 3) by lithium/halogen exchange of **10** with *n*-BuLi (to give **11**) followed by addition of **5** to **11** to provide **12**. Oxidation of **12** was accompanied by cleavage of the *para*-methoxybenzyl group, giving **13**.

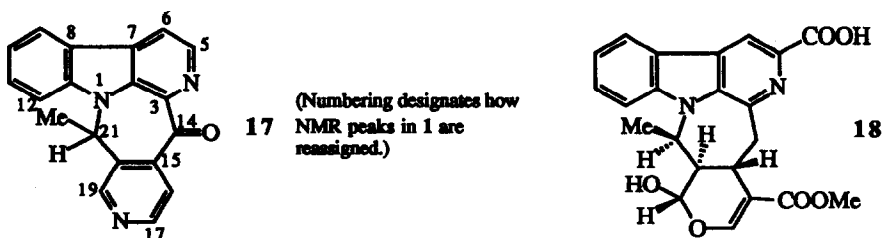


Ether **13** was then exposed to a solution of 48% HBr in acetic acid at reflux. It had been our expectation that **13** would be converted to **14** (or a protonated form thereof) and that **14** would undergo intramolecular *N*-alkylation to furnish **15**. Deprotonation of **15** would then (note arrows in **15**) provide **1**. Since Dr. Delle Monache had generously supplied a sample of authentic maxonine, it was easy to monitor the outcome of reactions intended to convert **13** to maxonine. But numerous attempts to achieve the conversion of **13** to **1** failed to give even a trace of maxonine; diketone **16** was frequently obtained as a reaction product.



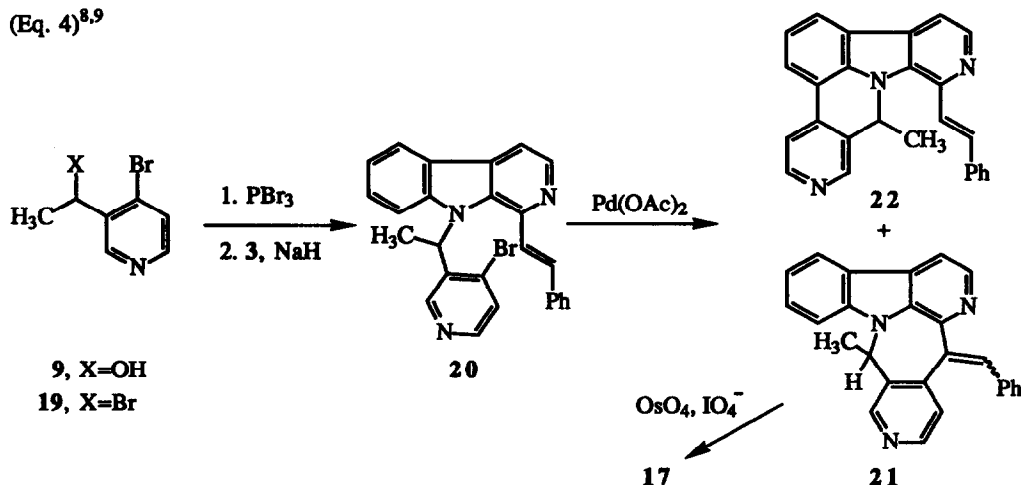
Our inability to convert **13** or functionally equivalent compounds to maxonine led us to reexamine the structure assignment for the natural product. Due in part to maxonine not only being noncrystalline, but also to a total of less than 20 mg having been isolated, the structure assignment rested heavily on 2D NMR spectroscopy. Structure **1** is in good agreement with the NMR data reported by Delle Monache et al. But reconsideration of that data suggested that structure **17** is also in accord with the data reported for maxonine. Moreover **17**, like **1**, is consistent with standard pathways of monoterpene indole alkaloid biosynthesis.¹¹ In fact, the same basic skeleton as **17** is found in deoxyadifoline (**18**).¹²

Although the reported spectral data did not allow a clear distinction between **1** and **17** as the structure for maxonine, two NMR experiments on the authentic sample already in hand were decisive. Delle Monache et al. had shown that irradiation of H-19 caused considerable NOE enhancement of H-21, consistent with both structures **1** and **17**. We found that irradiation of H-21 gave NOE enhancement of H-19 and the methyl resonance, as expected for both **1** and **17**. In addition, NOE enhancement was also seen for H-12, but not H-5, which is consistent with structure **17** but not **1**. Moreover, long range HMQC measurements – which indicated three bond coupling of C-2 with H-6 and H-21, and of C-3 with H-5 (but not H-21) – reinforced the revision of maxonine's structure from **1** to **17**.



Validation of the structure revision was achieved by total synthesis (Equation 4). Alcohol 9 was converted to unstable bromide 19, which was then used immediately to alkylate the indole nitrogen of benzalharmane (3) to produce 20. A palladium-catalyzed intramolecular Heck reaction¹³ then gave both *cis*- and *trans*-21 along with 22.¹⁴ Finally, oxidative cleavage of the stilbene double bond in 21 produced 17 which, except for chiroptical properties, is identical to authentic maxonine by direct comparison.

(Eq. 4)^{8,9}



In summary, the structure of maxonine is established as 17, not 1.

Acknowledgment. We thank Dr. Franco Delle Monache for generously giving us the world's entire (isolated) supply (12 mg) of natural maxonine and for copies of its spectra.

References and Notes

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- Salient experimental details 4: add 0.400 g benzalharmane⁴ to 0.115 g NaH in 10 ml THF; 1 h at 20°; add 0.308 g *p*-MeOC₆H₄CH₂Br⁷ in 10 ml THF; 18 h at 20°; aq workup → 0.500 g 4 (86%). 5: 0.480 g 4 in 5:1 CH₂Cl₂/MeOH + 0.001 g Sudan Red¹⁵ at -78°; pass ozone until pale yellow; 30 min at -78°; add 1 ml Me₂S; 1 h at -78°; 2 h at 20°; remove volatiles in vacuo; flash chromatography (silica, 3:7 EtOAc/pet. ether) → 0.270 g 5 (71%). 8: 1.87 ml Me₂NCH₂CH₂NHMe in 65 ml THF at -78° + 5.63 ml 2.5 M *n*-BuLi in hexane; 15 min at -78°; add 1.16 ml 6; 15 min at -78°; add 6.14 ml 2.5 M *n*-BuLi in hexane at -78°; 4 h at -42°; cool to

-78°; add 5.88 ml 1,2-dibromotetrafluoroethane;¹⁰ 4 h at 20°; aq workup; flash chromatography (silica, 1:1 EtOAc/pet. ether) → 1.18 g **8** (52%). **9**: 0.809 g **8** in 25 ml ether + 2.6 ml 3.0 M CH₃MgBr in ether at -78°; 18 h at 20°; aq NH₄Cl/ether workup; flash chromatography (silica, 3:2 EtOAc/pet. ether) → 0.713 g **9** (81%). **10**: add 0.750 g **9** to 1.09 g NaH in 20 ml THF; 10 h at 20°; add 0.26 ml MeI; 12 h at 20°; aq workup; flash chromatography (silica, 1:4 EtOAc/pet. ether) → 0.663 g **10** (83%). **12**: 0.202 g **10** in 5 ml THF at -78° + 0.37 ml 2.5 M *n*-BuLi; 30 min at -78°; add 0.295 g **5** in 10 ml THF; 18 h at 20°; aq workup; flash chromatography (silica, 3:2 EtOAc/pet. ether) → 0.110 g **12** (33%). **13**: 0.200 g **12** in 15 ml acetone at 20° + 5 ml freshly made Jones reagent; 48 h at 20°; aq K₂CO₃/CH₂Cl₂ workup; flash chromatography (silica, EtOAc) → 0.057 g **13** (29%). **16**: 0.057 g **13** + 1 ml 48% aq HBr in 1 ml glacial CH₃COOH; 3 h at 120°; cool to 20°; aq workup; flash chromatography (silica, EtOAc) → 0.050 g **16** (76%). **17** (maxonine): 0.0060 g **21** + 0.012 g NaIO₄ in 0.8 ml dioxane + 0.8 ml H₂O; add 18 μL 0.39 M OsO₄ in CH₃CN; 24 h at 20°; aq NaHCO₃/CH₂Cl₂ workup; flash chromatography (silica, 4:1 EtOAc/pet. ether) → 0.0010 g **17**, (25%), identical (co-TLC, co-NMR) with natural maxonine. **19**: 0.055 g **9** in 0.3 ml pyridine + 1.0 ml PBr₃; 15 min at 100°; 16 h at 20°; cool to -5°; add 3 ml 48% aq HBr; 30 min at 0°; aq workup; flash chromatography (silica, 2:1 EtOAc/pet. ether) → 0.027 g **19** (38%). **20**: add 0.080 g benzalharmane⁴ to 0.023 g NaH in 1 ml THF; 1 h at 20°; add 0.060 g **19** in 2 ml THF at 20°; 1 h at 55°; cool to 20°; aq workup; flash chromatography (silica, 1:1 EtOAc/pet. ether) → 0.085 g **20** (83%). **21**: 0.025 g **20** + 0.006 g PPh₃ + 0.001 g Pd(OAc)₂ + 15 μL Et₃N in 2 ml CH₃CN; sealed tube under N₂; 20 min at 20°; 28 h at 120°; cool to 20°; aq workup; flash chromatography (silica, EtOAc/pet. ether) → 0.011 g **21** (54%) + 0.006 g **22** (16%).

9. Mp and ¹H NMR (CDCl₃, 300 MHz) data for new compounds. **4**: 127–128 °C, δ 8.51 (d, J=6.0 Hz, 1H), 8.17 (d, J=6.0 Hz, 1H), 7.92 (d, J=4.8 Hz, 1H), 7.71 (d, J=15.6 Hz, 1H), 7.59–7.54 (m, 2H), 7.41 (d, J=8.4 Hz, 1H), 7.35–7.24 (m, 6H), 7.14 (d, J=9.0 Hz, 2H), 6.91 (d, J=9.0 Hz, 2H), 5.73 (s, 2H), 3.79 (s, 3H). **5**: 109–110 °C, δ 10.23 (s, 1H), 8.67 (d, J=4.8 Hz, 1H), 8.22 (d, J=4.8 Hz, 1H), 8.19 (d, J=7.8 Hz, 1H), 7.62 (ddd, J=8.4, 7.2, 0.9 Hz, 1H), 7.53 (d, J=8.4 Hz, 1H), 7.38 (ddd, J=7.8, 7.2, 0.9 Hz, 1H), 6.88 (d, J=8.7 Hz, 2H), 6.71 (d, J=8.7 Hz, 2H), 6.10 (s, 2H), 3.71 (s, 3H). **8**: 47–49 °C, δ 10.39 (s, 1H), 9.0 (s, 1H), 8.57 (d, J=5.4 Hz, 1H), 7.63 (d, J=5.4 Hz, 1H). **9**: 75–78 °C, δ 8.77 (s, 1H), 8.31 (d, J=5.4 Hz, 1H), 7.46 (d, J=5.4 Hz, 1H), 5.25 (q, J=6.6 Hz, 1H), 2.15 (br s, 1H), 1.55 (d, J=6.6 Hz, 3H). **10**: δ 8.64 (s, 1H), 8.30 (d, J=5.1 Hz, 1H), 7.46 (d, J=5.1 Hz, 1H), 4.69 (q, J=6.6 Hz, 1H), 3.30 (s, 3H), 1.46 (d, J=6.6 Hz, 3H). **12**: (mixture of two diastereomers) δ 8.80 (s, 1H), 8.72 (s, 1H), 8.55 (d, J=6.0 Hz, 1H), 8.53 (d, J=3.9 Hz, 1H), 8.27–8.21 (m, 4H), 8.14 (d, J=6.0 Hz, 1H), 8.12 (d, J=3.9 Hz, 1H), 7.52 (t, J=7.2 Hz, 2H), 7.34 (t, J=7.2 Hz, 2H), 7.26–7.23 (m, 3H), 6.74 (s, 8H), 6.40–6.26 (m, 4H), 5.43–5.15 (m, 5H), 4.83 (q, J=6.6 Hz, 2H), 3.74 (s, 6H), 3.14 (s, 6H), 1.54 (d, J=6.6 Hz, 3H), 1.30 (d, J=6.6 Hz, 3H). **13**: δ 10.39 (br s, 1H), 8.82 (s, 1H), 8.69 (d, J=4.8 Hz, 1H), 8.51 (d, J=4.8 Hz, 1H), 8.22–8.17 (m, 2H), 7.67–7.63 (m, 2H), 7.42–7.36 (m, 2H), 4.50 (q, J=6.6 Hz, 1H), 3.04 (s, 3H), 1.52 (d, J=6.6 Hz, 3H). **16**: 229–230 °C, δ 10.35 (br s, 1H), 9.19 (s, 1H), 8.94 (d, J=4.8 Hz, 1H), 8.36 (d, J=4.8 Hz, 1H), 8.16 (d, J=7.8 Hz, 1H), 8.10 (d, J=5.1 Hz, 1H), 7.64–7.62 (m, 2H), 7.51 (d, J=5.1 Hz, 1H), 7.37 (d, J=7.8 Hz, 1H), 2.62 (s, 3H). **17**: identical to authentic maxonine. **19**: δ 8.82 (s, 1H), 8.30 (d, J=5.1 Hz, 1H), 7.49 (d, J=5.1 Hz, 1H), 5.49 (q, J=7.2 Hz, 1H), 2.11 (d, J=7.2 Hz, 3H). **20**: δ 8.97 (s, 1H), 8.53 (d, J=4.8 Hz, 1H), 8.39 (d, J=5.4 Hz, 1H), 8.14 (m, 1H), 7.89 (d, J=4.8 Hz, 1H), 7.68 (d, J=15.6 Hz, 1H), 7.56 (d, J=15.6 Hz, 1H), 7.49–7.45 (m, 3H), 7.43–7.24 (m, 6H), 6.56 (q, J=7.2 Hz, 1H), 2.15 (d, J=7.2 Hz, 1H). **21**: (isomer 1): δ 8.76 (s, 1H), 8.53 (d, J=5.0 Hz, 1H), 8.39 (d, J=5.5 Hz, 1H), 8.16 (d, J=7.5 Hz, 1H), 7.95 (d, J=5.0 Hz, 1H), 7.77 (s, 1H), 7.67 (m, 2H), 7.33 (m, 1H), 7.31–7.24 (m, 5H), 7.21 (d, J=5.5 Hz, 1H), 5.88 (q, J=7.5 Hz, 1H), 2.02 (d, J=7.5 Hz, 3H). **21**: (isomer 2): δ 8.64 (m, 2H), 8.29 (d, J=5.1 Hz, 1H), 8.17 (d, J=7.8 Hz, 1H), 7.9 (d, J=5.1 Hz, 1H), 7.71–7.63 (m, 4H), 7.58–7.52 (m, 2H), 7.49–7.43 (m, 3H), 7.34 (ddd, J=7.8, 5.4, 2.4 Hz, 1H), 7.04 (s, 1H), 5.83 (q, J=7.2 Hz, 1H), 1.97 (d, J=7.2 Hz, 3H). **22**: δ 8.65 (s, 1H), 8.64 (d, J=4.8 Hz, 1H), 8.57 (d, J=5.1 Hz, 1H), 8.09 (dd, J=7.5, 0.6 Hz, 1H), 7.96 (dd, J=7.5, 0.6 Hz, 1H), 7.92 (d, J=15.6 Hz, 1H), 7.90 (d, J=5.1 Hz, 1H), 7.85 (d, J=15.6 Hz, 1H), 7.78 (d, J=4.8 Hz, 1H), 7.70 (dd, J=7.2, 1.5 Hz, 2H), 7.48 (t, J=7.2 Hz, 2H), 7.40 (dd, J=7.2, 1.2 Hz, 1H), 7.36 (t, J=7.5 Hz, 1H), 6.30 (q, J=6.6 Hz, 1H), 1.51 (d, J=6.6 Hz, 3H).

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14. Since the primary purpose of the synthesis was to confirm the revised structure, no particular efforts were directed toward optimizing the yield of **21**.

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