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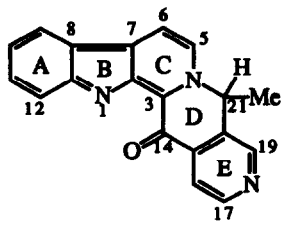
MAXONINE: STRUCTURE CORRECTION AND SYNTHESIS

T. Ross Kelly*, Wei Xu and Jayashree Sundaresan

Department of Chemistry, E. F. Merkert Chemistry Center, Boston College, Chestnut Hill, MA 02167

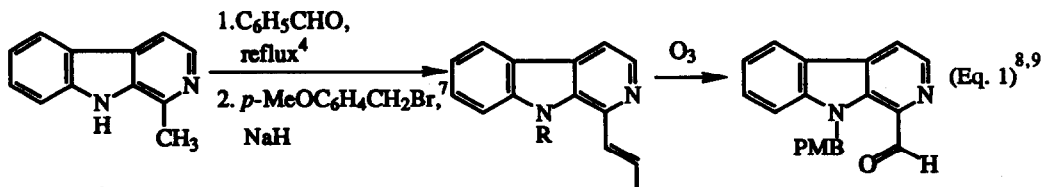
Abstract: The structure for the pentacyclic alkaloid maxonine is revised from **1** to **17**. Compound **17** was prepared by total synthesis and shown identical to the natural product.

In 1989 Delle Monache et al. reported[1] 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 products[2] combined with a desire to verify the structure assignment led us to undertake the synthesis of **1**.



1

Harmane[3] (**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. Our[5] previously



(Eq. 1)[8,9]

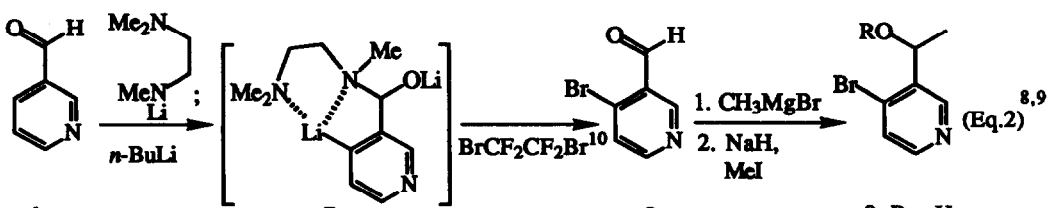
2

3, R = H
4, R = PMB

5

PMB = *p*-MeOC$_6$H$_4$CH$_2$ –

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



(Eq.2)[8,9]

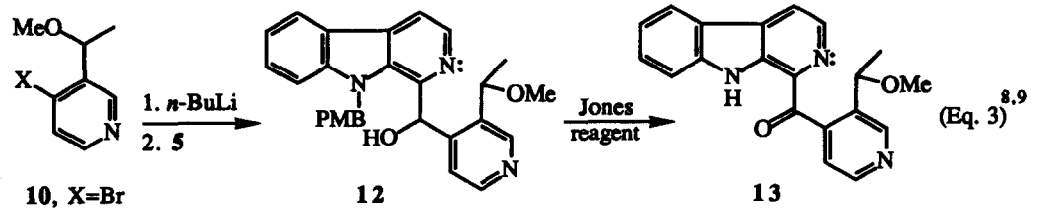
6

7

8

9, R = H
10, R = Me

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**.



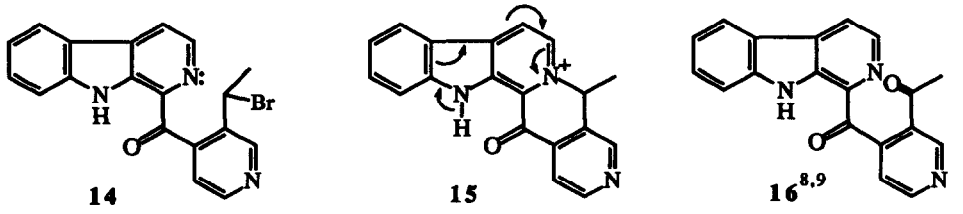
10, X=Br
11, X=Li

12

13

(Eq. 3)[8,9]

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.



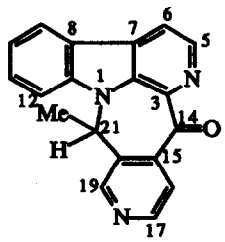
14

15

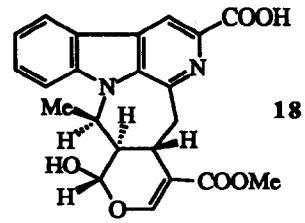
16[8,9]

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 monoterpenoid 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**.



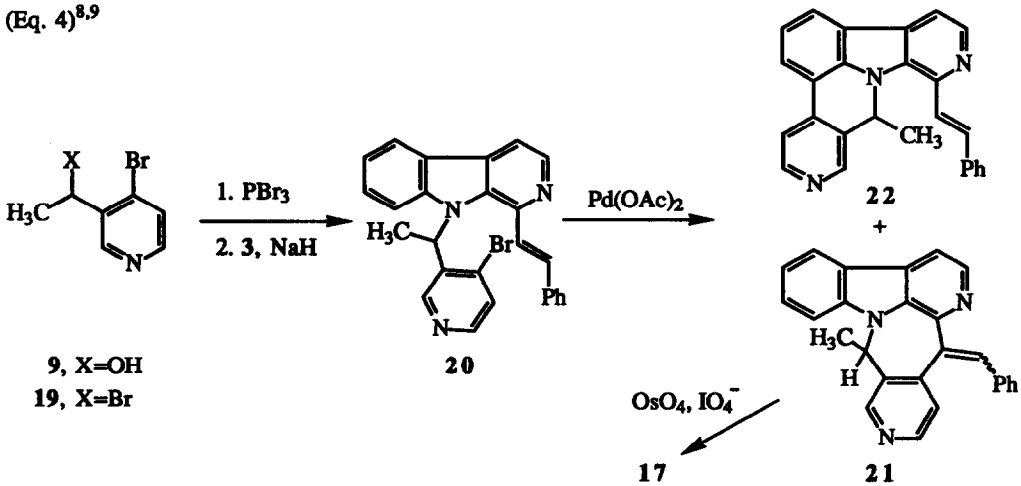
17 (Numbering designates how NMR peaks in 1 are reassigned.)



18

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 reaction[13] 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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8. **Salient experimental details 4**: add 0.400 g benzalharmane[4] to 0.115 g NaH in 10 ml THF; 1 h at 20°; add 0.308 g *p*-$MeOC_6H_4CH_2Br$[7] in 10 ml THF; 18 h at 20°; aq workup → 0.500 g **4** (86%). **5**: 0.480 g **4** in 5:1 CH_2Cl_2/MeOH + 0.001 g Sudan Red[15] at -78°; pass ozone until pale yellow; 30 min at -78°; add 1 ml Me_2S; 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 $Me_2NCH_2CH_2NHMe$ 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 CH_3MgBr in ether at -78°; 18 h at 20°; aq NH_4Cl/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 K_2CO_3/CH_2Cl_2 workup; flash chromatography (silica, EtOAc) → 0.057 g **13** (29%) **16**: 0.057 g **13** + 1 ml 48% aq HBr in 1 ml glacial CH_3COOH; 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 $NaIO_4$ in 0.8 ml dioxane + 0.8 ml H_2O; add 18 µL 0.39 M OsO_4 in CH_3CN; 24 h at 20°; aq $NaHCO_3/CH_2Cl_2$ 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 PBr_3; 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 benzalharmane[4] 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 PPh_3 + 0.001 g $Pd(OAc)_2$ + 15 µL Et_3N in 2 ml CH_3CN; sealed tube under N_2; 20 min at 20°; 28 h at 120°; cool to 20°; aq workup; flash chromatography (silica, EtOAc/pet. ether) → 0.011g **21** (54%) + 0.006 g **22** (16%).

9. **Mp and ^1H NMR ($CDCl_3$ 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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