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A Reported "New Synthesis of Lysergic Acid" Yields Only The Derailment Product: Methyl 5-Methoxy-4,5-dihydroindolo[4,3-*f*,*g*]quinoline-9-carboxylate

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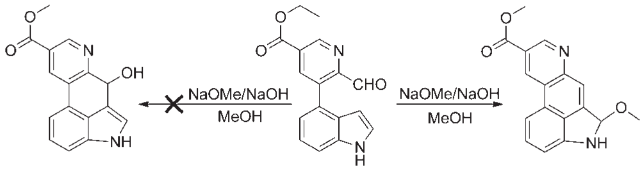
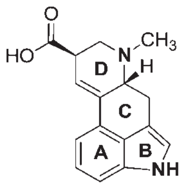
ABSTRACT



3 2 4

The treatment of ethyl 6-formyl-5-(1*H*-indol-4-yl)pyridine-3-carboxylate (2) with NaOMe or NaOH in methanol solution at room temperature under the reported reaction conditions afforded solely product 4 in 80% yield, rather than anticipated product 3.

In the course of our studies on hallucinogenic agents,[1] we wished to complete a total synthesis and to characterize A-ring substituted derivatives of the potent hallucinogenic agent, lysergic acid diethylamide (LSD). We therefore began synthetic studies directed toward appropriate A-ring-substituted derivatives of lysergic acid **1** (Figure 1).



lysergic acid, 1

Figure 1. Structure of lysergic acid.

We found the short and facile total synthesis of lysergic acid published in this journal by Wang and Hendrickson[2] to be particularly attractive. It was envisioned that by starting with ring-substituted indoles we could ultimately obtain the desired A-ring-substituted lysergic acid derivatives.

We began our work by attempting to reproduce exactly the published lyergic acid synthesis, so as to optimize conditions for our eventual use of substituted indoles in the sequence. We proceeded to the preparation of compound **2**, obtained without difficulty as outlined in the reported synthesis, but using the ethyl ester instead of the methyl ester to avoid the formation of various ester mixtures in the Suzuki-coupled product **2**. This change had no effect, as we obtained **4** in comparable yields from either the methyl or the ethyl ester.

Surprisingly, however, the anticipated intramolecular cyclization of **2** to produce **3** was unsucessful under the reported conditions[2] using 2 mol % of 0.5 M NaOMe/MeOH at rt for 2 h. When we attempted the cyclization at 50 °C, using the same amount of base, we observed only decomposition of the starting material. After considerable experimentation, intramolecular cyclization appeared to

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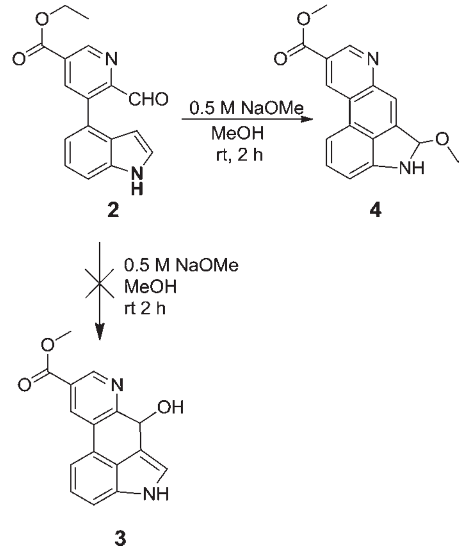
[1] (a) Chambers, J. J.; Kurrasch-Orbaugh, D. M.; Parker, M. A.; Nichols, D. E. *J. Med. Chem.* **2001**, *44*, 1003. (b) Monte, A. P.; Marona-Lewicka, D.; Cozzi, N. V.; Nichols, D. E. *J. Med. Chem.* **1993**, *36*, 3700. (c) Nichols, D. E.; Frescas, S.; Marona-Lewicka, D.; Kurrasch-Orbaugh, D. M. *J. Med. Chem.* **2002**, *45*, 4344. (d) Oberlender, R.; Pfaff, R. C.; Johnson, M. P.; Huang, X. M.; Nichols, D. E. *J. Med. Chem.* **1992**, *35*, 203. (e) Monte, A. P.; Marona-Lewicka, D.; Kanthasamy, A.; Sanders- Bush, E.; Nichols, D. E. *J. Med. Chem.* **1995**, *38*, 958.

[2] Hendrickson, J. B.; Wang, J. *Org. Lett.* **2004**, *6*, 3.

10.1021/ol203048q

proceed using 10 mol % NaOMe in MeOH at rt for 2 h. These conditions led to the expected formation of a reported "yellow crystalline product," anticipated to be **3**, but upon isolation this material had a much higher melting point (> 260 °C) than reported (234.6−235.8 °C). Furthermore, and most disturbing, the NMR spectrum was not consistent with expected structure **3**. In particular, we noted the absence of an absorption for the indole NH, reported[2] as 8.55 ppm, as well as a new peak at 3.29 ppm that integrated for three protons. This reaction was repeated by two different investigators many (> 30) times, with varying mole ratios of NaOMe, use of NaOH instead of NaOMe, and varying reaction temperatures and times, to no avail; all efforts ultimately led either to decomposition or to the exact same product, which we finally identified as **4** (Scheme 1).

Scheme 1



The original PhD thesis describing this work[3] was not informative with respect to alternate reaction conditions or the possibility of derailment products, nor was there any evidence of an error in transcription of the thesis text to the published paper or the Supporting Information. Contact with the corresponding author revealed that any original spectra from the project were no longer available.

The structure of **4** was assigned on the basis of a combination of COSY, TCOSY, HMBC, and HMQC NMR experiments. COSY revealed that H-2 (6.52 (H)) of compound **4** is coupled to two adjacent protons H-1 (5.24 (H)) and H-4 (7.98 (H)). The NH pair's chemical shift at 5.24 ppm (H) and 83.4 ppm (15N) are consistent with structure **4**, but not **3**. HMBC revealed that the H-2 (6.52 (H)) proton correlated with the OCH_3 carbon (51.2 (C)), also consistent with aromaticity. Ultimately, extensive ^1H and ^{13}C NMR analysis firmly established the product of the cyclization reaction to be **4** (Figure 2).

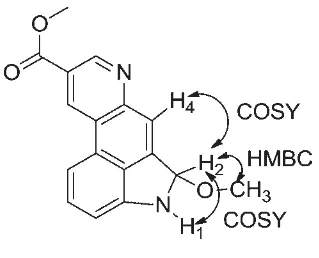
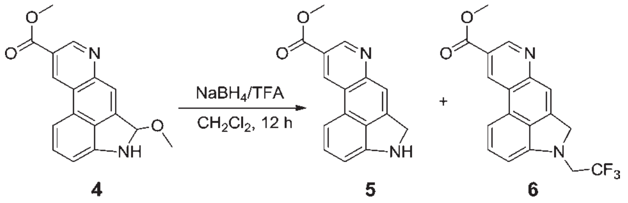


Figure 2. 2D NMR studies.

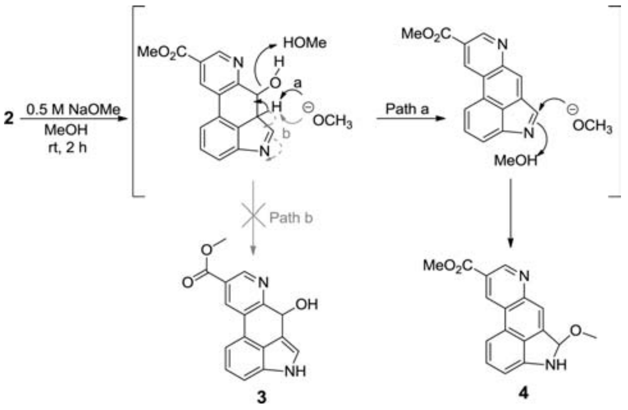
Product **4** can be reduced with diborane, but the product is not, however, the one described in the publication.[2] Reduction of **4** using $NaBH_4$/TFA,[4] as described in the published report,[2] resulted in a mixture of products **5** and **6** (Scheme 2). The structures of these compounds also were determined by NMR studies and support the formation of **4** in the cyclization reaction. It might be noted that the ethyl ester of **5** had been reported in a 1956 patent but was obtained through a completely different synthetic approach.[5]

Scheme 2



Once the actual product was determined to be **4**, the reason for the derailment became evident (Scheme 3). The tricyclic aromatic indoloquinoline system of **4** has significant resonance stabilization, resulting in the driving force for the formation of **4** via path a, rather than the reported path b, as illustrated in Scheme 3.

Scheme 3



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(3) Wang, J. PhD Dissertation, Brandeis University, 2002

It also is probably important that the dihedral angle between the C(3) proton of the indole and the C–O bond in the bracketed intermediate in Scheme 3 is 160°, almost ideally disposed to undergo an E2 type elimination under base catalysis. Once the double bond has been installed into the 2a,3 position to provide the aromatic benzo[*f*]quinoline moiety, there is no obvious way to reduce this bond selectively and restore the 2,3-bond of the indole ring. Instead, the indolic nitrogen is protonated, and the imminium species then adds methoxide.

We considered possible ways to remedy this problem, such as the use of less polar solvents, or different bases, but initial attempts were not promising. It seemed fairly evident that any reaction that proceeded through the postulated cyclization intermediate would likely suffer the same fate: collapse to the ACD ring aromatic derailment product.

Based on the facile conversion of **2** to **4**, and the evident stability of **4**, we cannot envision a set of reaction conditions that would instead have resulted in the formation of **3**. We are forced to conclude, therefore, that the published synthesis[2] is simply not viable.

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Supporting Information Available. Experimental details and copies of 2D NMR spectral data of **4**, **5**, and **6**. This information is available free of charge via the Internet at http://pubs.acs.org.

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(4) Gribble, G. W.; Leese, R. M.; Evans, B. E. *Synthesis* **1977**, 172.

(5) Sandoz Ltd., British Patent 759,105, Oct 10, 1956.