

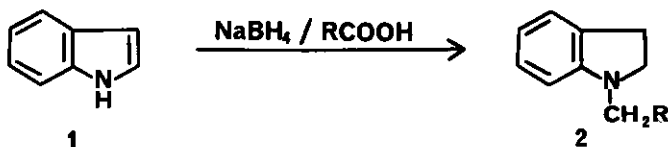
ON THE REACTION OF INDOLE WITH SODIUM BOROHYDRIDE IN FORMIC ACID¹

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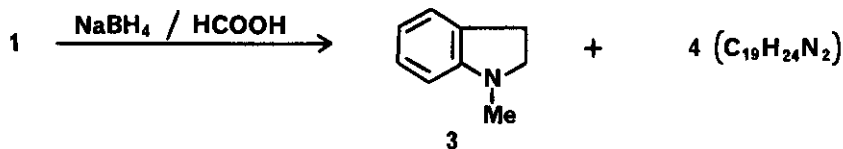
Abstract - The reaction of indole (1) with sodium borohydride in formic acid yields N-methylindoline (3) and a product derived from "indole dimer", 3-(2-(2-N,N-dimethylaminophenyl)ethyl)-1-methylindoline (4), whose structure is proved by independent synthesis.

Several years ago we reported² the novel reaction of indole (1) with sodium borohydride (NaBH_4) in neat carboxylic acids. This reagent combination effects reduction of the indole double bond and N-alkylation, affording an excellent one-flask synthesis of N-alkylindolines (2).



But in contrast to the other carboxylic acids studied,² formic acid, in addition to its more vigorous reaction with NaBH_4 , gave somewhat erratic results and invariably produced another product, in addition to the expected N-methylindoline (3). In this paper we describe the structure of this by-product.

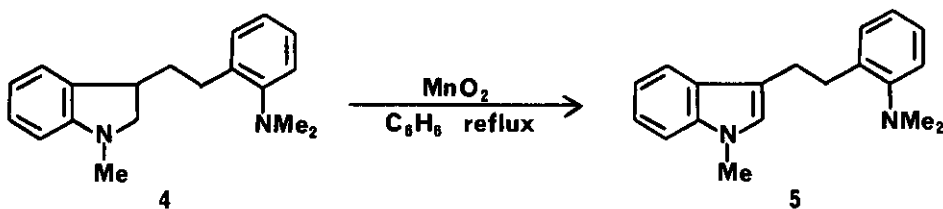
Thus, treating a solution of 1 (8.5 mmol) in 97% formic acid (45 ml, redistilled) under nitrogen at 0-5° with NaBH_4 pellets (75 mmol) (Ventron), followed by a standard work-up³, gives a mixture consisting of two major products by thin layer chromatography. Column chromatography (basic alumina, hexane elution) gives 3 in 16% yield, identical (TLC, IR, $^1\text{H-NMR}$, UV) to a sample prepared⁴ from N-methylindole, and 4 (oil; crystallizes in freezer) in 32% yield, having the molecular formula $\text{C}_{19}\text{H}_{24}\text{N}_2$ by mass spectrometry ($m/e = 280.1923$; calcd $m/e = 280.1939$).



The UV spectrum (95% EtOH) of 4 (217, 252, 296 nm) is very similar to that of 3 (212, 253, 300 nm) and the IR spectrum (CHCl_3) of 4 is similar to that of 3, showing strong bands at 2960-2810 (C-H stretch), 1610, 1490, and 1450 (phenyl C=C stretch) cm^{-1} , but no N-H absorption. The $^1\text{H-NMR}$ spectrum of 4 reveals singlets at δ 2.65 (6H; N-Me) and 2.70 ppm (3H; N-Me) and multiplets between 2.3-3.5 (7H) and 6.4-7.4 ppm (8H).

Further structural information on 4 was obtained by treating it with activated manganese dioxide, a reagent known to oxidize indolines to indoles⁵. This gives 5 (oil; 87% yield) which displays 1,3-dialkylindole UV absorption (226, 289 nm) and a mass spectrum consistent with $\text{C}_{19}\text{H}_{22}\text{N}_2$ (m/e 278 (21%), 144 (100%), 134 (9%)). The $^1\text{H-NMR}$ spectrum of 5 shows singlets at δ 2.60 (6H; N-Me), 3.00 (4H; CH_2CH_2), and 3.55 ppm (3H; N-Me), and multiplets at 6.8-7.3 (8H) and 7.5 ppm (1H; indole H-4).

All of these data and mechanistic considerations (*vide infra*) suggest 3-(2-(2-N,N-dimethylaminophenyl)ethyl)-1-methylindoline as the structure of 4 and 3-(2-(2-N,N-dimethylaminophenyl)ethyl)-1-methylindole as the structure of 5.

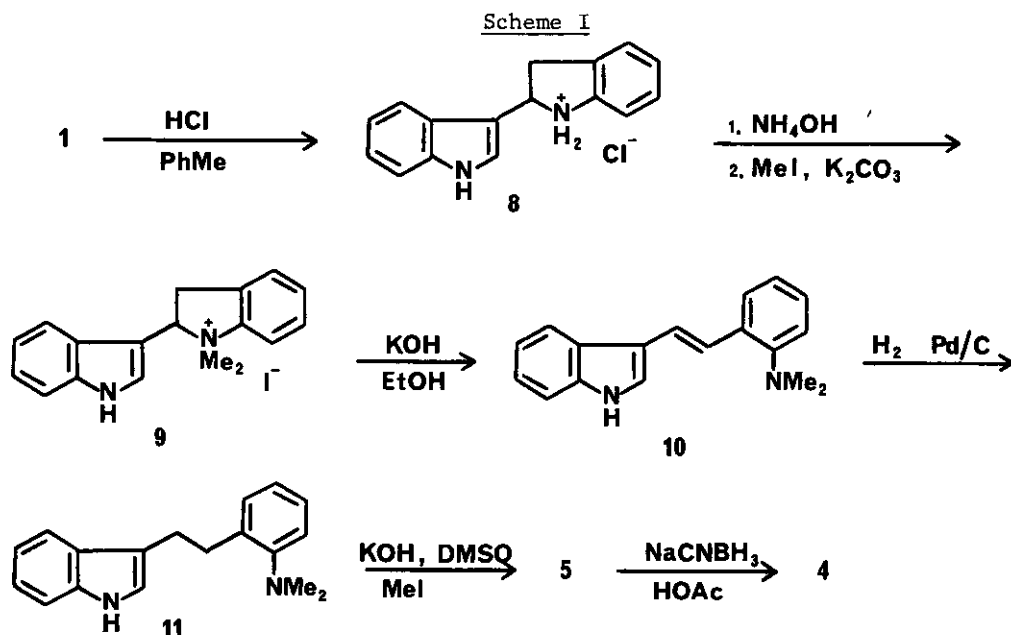


The two very conspicuous peaks in the mass spectrum of 5, m/e 144 (100%) and 134 (9%), can be ascribed to fragment ions 6 and 7, respectively.



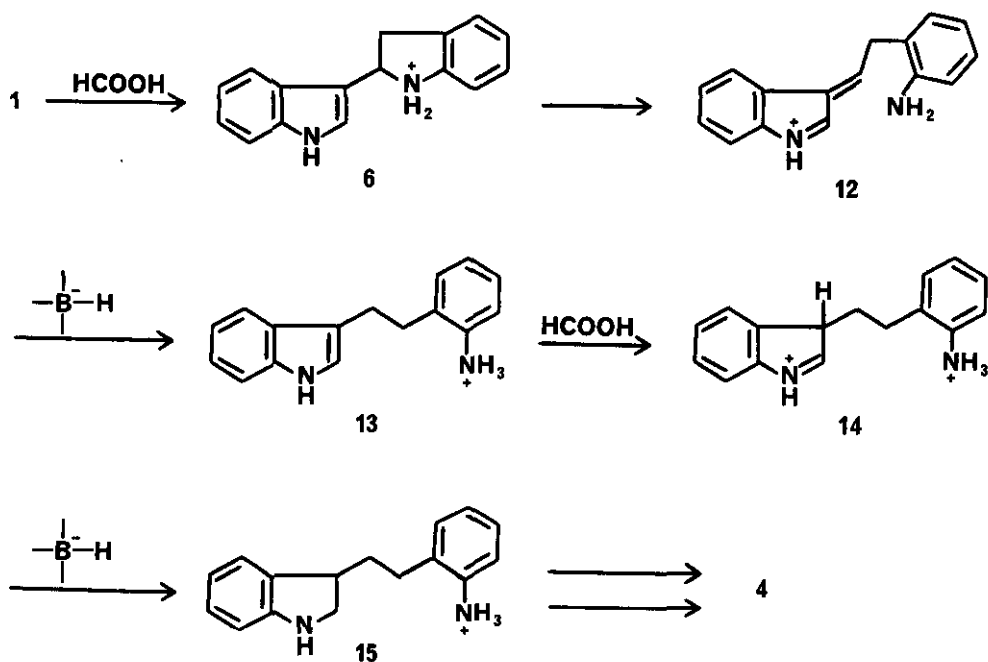
To confirm 4 as the structure of this by-product, we independently synthesized this compound as shown in Scheme I. Dimerization of 1 to the well-known "indole

dimer" hydrochloride⁶ (8) (88% yield) was followed by conversion to methiodide 9 using a procedure modified from that reported.⁷ Thus, slowly adding a benzene solution of the free base of 8 to a refluxing benzene solution of excess methyl iodide in the presence of potassium carbonate gave 9. This crude material was subjected to a Hofmann degradation as previously described⁷ and the resulting 3-vinylindole (10) was hydrogenated⁸ to 11 (35% yield from 8). Selective indole N-methylation of 11 was readily accomplished⁹ to give an oily product (50% distilled yield; bp 165°/0.075 torr) that was identical (TLC, IR, ¹H-NMR, UV) to 5, as prepared above from 4. Reduction⁴ of this material gave a product (93% yield) which was identical (TLC, IR, ¹H-NMR, UV) to 4, as obtained from 1. Thus, the structure of 4 is secured as proposed.



A plausible pathway for the formation of 4 is depicted in Scheme II. Formation of the indole dimer 6 (as its formate salt) is followed by an acid-induced gramine-type cleavage¹⁰ to give 3-alkylideneindolenine (12), which is reduced to indole (13) by a presumed¹¹ formoxyborohydride species. Intermediate 12 has been implicated in the formation of an indole trimer from indole (1) and indole dimer 6.¹² Subsequent protonation of the indole double bond in 13 and reduction of the protonated indolenine (14) lead to indoline (15). Finally, triple N-methylation³ by the presumed formoxyborohydride reagent would give the bis-tertiary amine (4).

Scheme II



Further studies are needed to understand the difference between formic acid and the other carboxylic acids in their reactions with NaBH_4 .

Acknowledgments

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References and Notes

1. This paper is Part XI in the series "Reactions of Sodium Borohydride in Acidic Media." For Part X, see G. W. Gribble, J. L. Johnson, and M. G. Saulnier, Heterocycles, in press.
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