

THE BROMINATION OF 2,3-DIMETHYLINDOLE

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ABSTRACT:

The product of bromination-hydrolysis of 2,3-dimethylindole, previously reported to be 3-hydroxymethyl-2-methylindole, has now been shown to be the known dimer of 2,3-dimethyl-3-hydroxyindolenine. A mechanistic interpretation of this result is presented and a simple preparation of 3-methoxyindolenines is described.

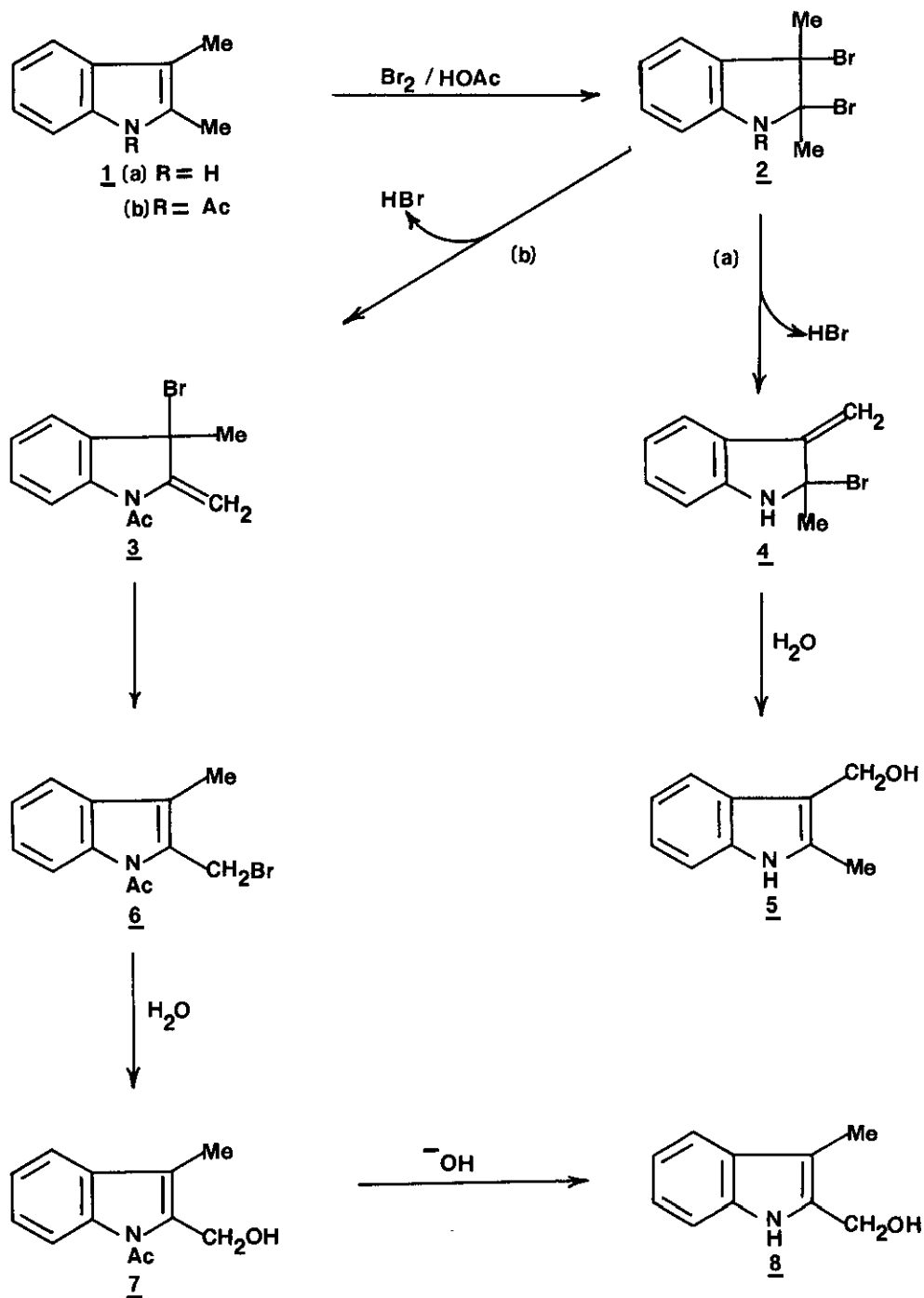
The bromination of 2,3-dimethylindole 1(a) and N-acetyl-2,3-dimethylindole 1(b) was first studied many years ago by Plant and Tomlinson (1). It was reported that treatment of 2,3-dimethylindole with an equimolar amount of bromine in acetic acid immediately followed by aqueous workup yielded a crystalline product m.p. 225°, elemental analysis of which suggested the molecular formula $C_{10}H_{11}NO$. Based on the mechanistic interpretation illustrated in Scheme 1, it was suggested that this product was 3-hydroxymethyl-2-methylindole 5. Similar treatment of N-acetyl-2,3-dimethylindole 1(b) yielded a product, $C_{12}H_{13}NO_2$, assigned structure 7. Alkaline hydrolysis then gave a product isomeric with 5 and assumed to be 2-hydroxymethyl-3-methylindole 8.

Treatment of N-acetyl-2,3-dimethylindole with an equimolar amount of bromine in acetic acid without aqueous workup yielded a crystalline monobromo derivative assumed to be N-acetyl-2-bromomethyl-3-methylindole 6.

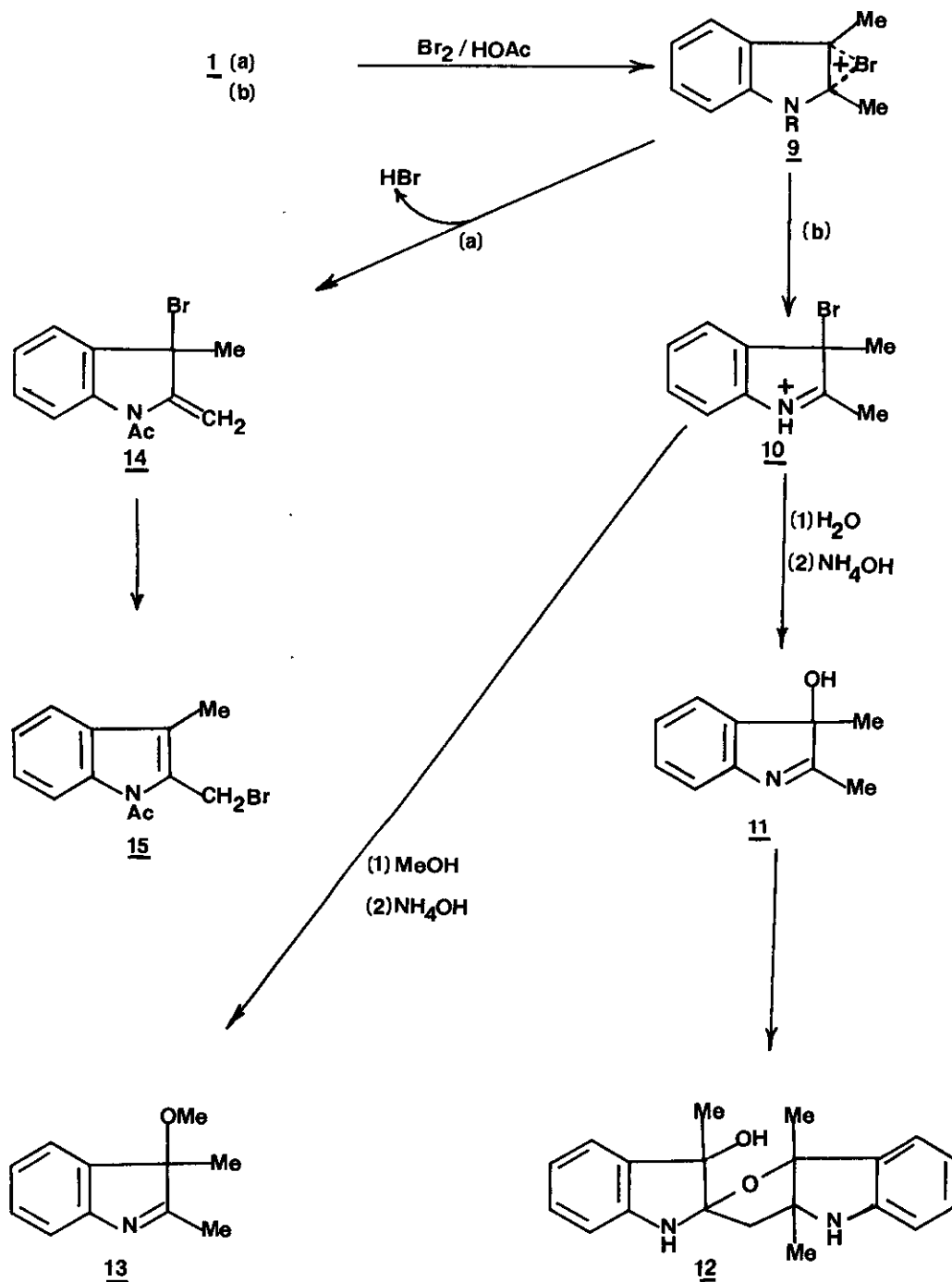
In light of the present knowledge of the chemistry of 2,3-dialkylindoles, the reaction sequences of Scheme 1 are quite unusual. For example, compound 6 remains the only known side chain brominated indole produced by direct halogenation of a 2,3-dialkylindole derivative (2). Furthermore, there is no known mechanistic analogy for the sequence leading to the alcohol 5 from the dibromide 2.

The present study was undertaken to remove the uncertainties surrounding the structures of the products of Plant and Tomlinson's study and to further probe the apparently anomalous behaviour of 2,3-dimethylindole (4,6). In agreement with Plant and Tomlinson, it has been found that bromination of N-acetyl-2,3-dimethylindole yields a crystalline monobromo derivative. Spectroscopic

SCHEME 1: BROMINATION OF 2,3-DIMETHYLINDOLE (Plant and Tomlinson¹)



SCHEME 2: BROMINATION OF 2,3-DIMETHYLINDOLE (PRESENT STUDY)



analysis of this material confirms that it has structure 6 [$\lambda_{\text{max}}^{\text{CH}_2\text{Cl}_2}$ 290 nm (log ϵ = 4.06); δ (CDCl₃) 2.20 (s, 3H, C₃-CH₃), 2.40 (s, 3H, N-Ac), 5.03 (s, 2H, (CH₂-Br), 7.1 - 7.9 (m, 4H, aromatic H), molecule ions at m/e = 267 (m⁺ Br⁸¹) and m/e = 265 (m⁺ Br⁷⁹)].

On the other hand, bromination-hydrolysis of 2,3-dimethylindole has been found to yield a crude product containing no trace of 3-hydroxymethyl-2-methylindole 5 as evidenced by the NMR spectrum. The major product, which could be crystallized from the crude product, m.p. 225° has been found to be identical with the dimer of 3-hydroxy-2,3-dimethylindole, previously prepared by autoxidation of 2,3-dimethylindole (2). Furthermore, when the bromination of 2,3-dimethylindole was performed in the presence of methanol, the sole product was the known 3-methoxy-2,3-dimethylindolenine 13 previously prepared by Gassman and co-workers (9,10).

All of these observations can now be accommodated by the mechanistic sequences of Scheme 2. When R = H, bromination leads to the formation of the N-protonated 3-bromoindolenine 10 perhaps via the bromonium ion 9. Nucleophilic substitution of bromide ion in 10 by methanol leads to 13 whereas substitution by water gives 11 which dimerizes to 12. When R = Ac, 9 undergoes loss of HBr to give the allylic bromide 14 which undergoes allylic rearrangement to give 15.

The bromination of 2,3-dimethylindole is thus not anomalous. All of the observed products can be rationalized in mechanistic terms which have good analogy in the known chemistry of indoles.

Further studies aimed at testing these mechanistic proposals and exploring the synthetic potential of these reactions are in progress.

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