

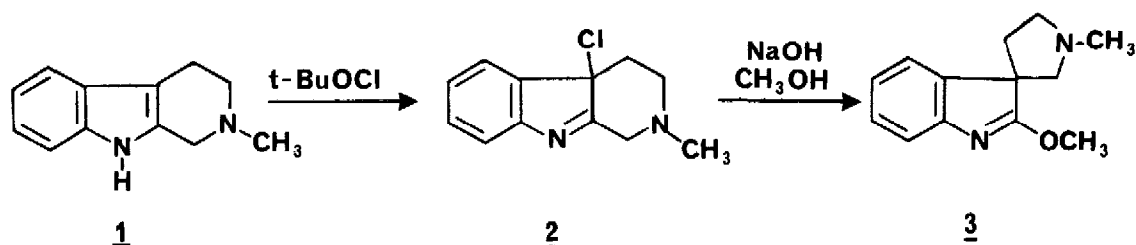
REARRANGEMENTS OF CHLOROINDOLENINES DERIVED FROM TETRAHYDRO- γ -CARBOLINES. 1.

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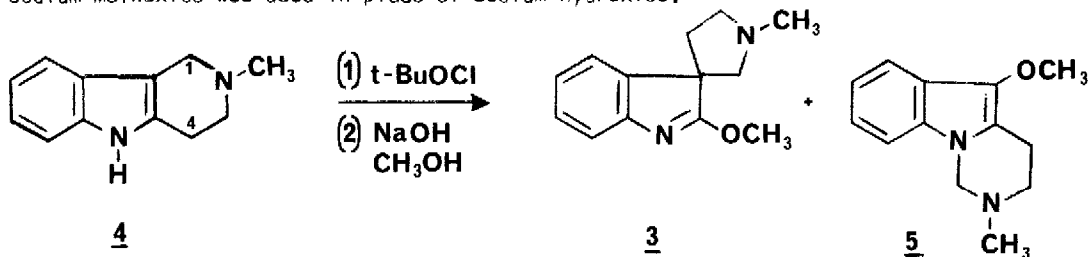
Summary: The reaction of *N*-methyltetrahydro- γ -carboline with *t*-butyl hypochlorite followed by methanolic sodium hydroxide yields two rearrangement products: a β -spiro-[pyrrolidinoindolenine] and a tetrahydropyrimido-[1,6-*a*]-indole.

The reaction of tetrahydro- β -carboline with *t*-butyl hypochlorite followed by treatment of the intermediate chloroindolenine with various nucleophiles is a synthetic sequence that is frequently encountered in the preparation of indoles and indole alkaloids.¹ Finch and Taylor first described the reaction of chloroyohimbine, obtained from yohimbine and *t*-butyl hypochlorite, with methanolic potassium hydroxide.² We have subsequently used this reaction in the preparation of spiro-pyrrolidinoindolines, and found that treatment of the tetrahydro- β -carboline, **1**, with *t*-butyl hypochlorite followed by reaction of the intermediate chloroindolenine, **2**, with methanolic sodium hydroxide resulted in the formation of the rearranged iminoether, **3**, in high yield as the sole product.³



During these studies, we wondered if replacement of **1** with the isomeric tetrahydro- γ -carboline, **4**, would furnish the same product from this sequence of steps. As far as we knew, this question had never been answered in the literature, and it was of some importance since the reduced γ -carboline are synthetically more accessible (Fischer indole reaction of *N*-methyl-4-piperidone and phenylhydrazine).⁴

Treatment of N-methyltetrahydro- γ -carboline, 4, with *t*-butyl hypochlorite followed by methanolic sodium hydroxide, using the same reaction conditions that were employed in converting 1 into 3,³ produced a mixture of products. Chromatographic separation of this mixture on silica gel using medium-pressure liquid chromatography furnished two major products: the rearranged spiro-pyrrolidinoindolenine, 3, and a new compound, 5. The same compounds could be obtained in somewhat higher yields (27% vs 15% of 3, and 25% vs 12% of 5) when sodium methoxide was used in place of sodium hydroxide.

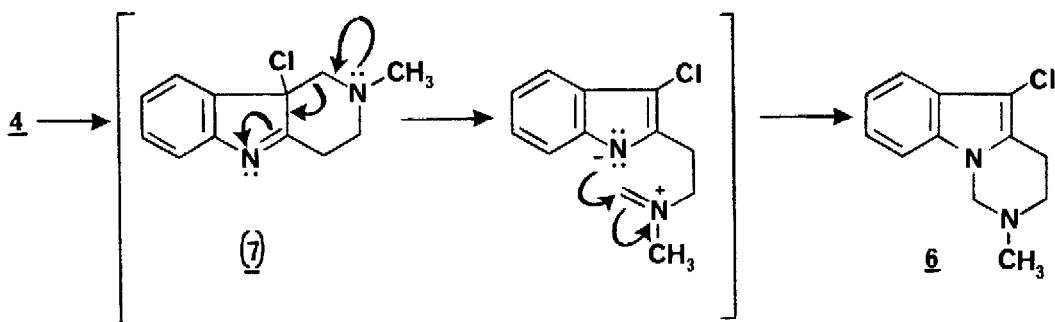


The basis for the structure assignment of 5 was as follows: the high resolution mass spectrum of 5 contained a peak for the molecular ion at m/e 216.1259 (C₁₃H₁₆N₂O; calcd., 216.1262). The UV spectrum resembled that of the starting indole, 4, and not the indolenine, 3; however, the IR spectrum failed to display a N-H stretching band (3480 cm⁻¹ in 4). The PMR spectrum of 5 (60 MHz; CDCl₃ solution) contained, in addition to the aromatic signals at δ 6.9 - δ 7.7, an A₂B₂ multiplet centered at δ 2.98 (two adjacent CH₂ groups), and singlets at δ 2.55 (NCH₃), δ 3.92 (OCH₃), and δ 4.63 (NCH₂N). While this latter methylene signal in 5 appeared as a sharp singlet (width at half-height of 1.3 Hz), the methylene group in 4 corresponding to the protons at C-1 appeared as a singlet with a width at half-height of 3.1 Hz. Furthermore, irradiation of the signal for the methylene group at C-4 (δ 2.66) resulted in the sharpening of the C-1 methylene singlet, indicating the presence of homoallylic coupling between the protons at C-1 and C-4 in the parent tetrahydro- γ -carboline. Since this was not observed in the isolated methylene in 5, it can be taken as evidence for a rearrangement of the parent heterocyclic system. The CMR spectrum of 5 also reflected this change in structure from that found in the starting carboline. While the C-1 carbon in 4 appeared at δ 51.8, the isolated methylene carbon in 5 was found to resonate at δ 65.8.

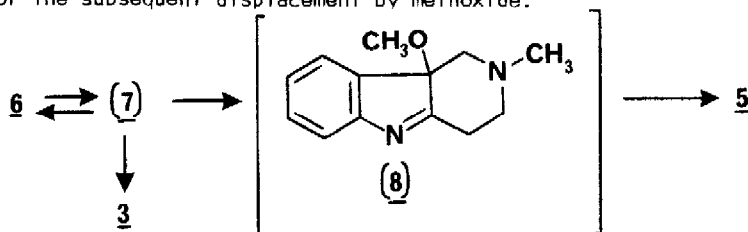
On examination of the reaction of 4 with *t*-butyl hypochlorite alone, we found that within two hours at 5^o, the starting carboline was converted into the tetrahydropyrimido-[1,6-*a*]-indole, 6, in 69% yield. Once again, the spectral characteristics of this compound confirmed that a rearrangement had taken place. Heating a methylene chloride solution of 6 to reflux for several hours failed to effect any further structural changes. When 6 was subsequently treated with sodium methoxide (reflux in methanol for 2 days), a mixture of 3 and 5 was obtained in 81% yield, in a ratio of 1.3 to 1, respectively (ratio is based on the

integration of the OCH_3 and NCH_3 singlets in the PMR). From this study, it appears that 6 is the intermediate in the two step conversion of 4 into 3 and 5.

The mechanistic explanation for the formation of 6 from the tetrahydro- γ -carboline, 4, has some literature precedent.⁵⁻⁸ Ebnoter and coworkers were first to report such a rearrangement⁵ and Bhandari and Snieckus subsequently described the conversion of 4 into the bromo analog of 6 with N-bromosuccinimide.⁸ In our case, the rearrangement involves a retro-Mannich reaction of the initially formed chloroindolenine (7) with subsequent reclosure to afford the pyrimido[1,6-a]indole, 6.



Treatment of 6 with methoxide, resulting in the formation of both 3 and 5, can be interpreted as follows: equilibration of 6 with the chloroindolenine (7) occurs under reaction conditions and is followed by the nucleophilic displacement of the allylic halide in (7) by methoxide. The resultant indolenine (8) is then able to rearrange to the pyrimido-[1,6-a]-indole, 5, via the retro-Mannich reaction. The formation of the spiro-pyrrolidinoindolenine, 3, can be envisioned to occur from (7) in a manner analogous to the rearrangement observed in the tetrahydro- β -carboline system.^{3,9} The need to invoke such an equilibration of 6 and (7) arises from the concern that nucleophilic displacement of 3-haloindoles is generally an unfavored reaction. By reverting back to the more reactive halide in (7), it is easier to account for the subsequent displacement by methoxide.



Studies on the reactions of compound 6 with other nucleophiles, such as cyanide ion, will be reported in the near future.

Acknowledgement: We wish to thank the Searle Spectroscopy Department for the spectral data reported and Dr. Jeremy Hribar for the high resolution mass spectra.

References and Notes

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(Received in USA 3 April 1980)