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A SYNTHETIC ROUTE TO 1,2,4,5-TETRAHYDRO-3H-BENZ[e]INDOLES

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We describe here the synthesis in two steps from the appropriately substituted β-tetralones of 3-methyl-1,2,4,5-tetrahydro-3H-benz[e]indole, 1a, and of its 8,9-dimethoxy analog, 1b. Insofar as we are aware, no compounds belonging to the 1,2,4,5-tetrahydrobenz[e]indole class have been previously reported (1) and the synthetic route to be described should be of general utility in their preparation.

Some years ago, Cloke (2,3) reported that imines of aryl cyclopropyl ketones undergo a thermal, acid-catalyzed ring expansion to 2-aryl-Δ^1-pyrrolines. More recently, Stevens (4,5) and we (6) have found the method can also be applied to the preparation of 1-alkyl-Δ^2-pyrrolines from the N-alkyl imines of 1-arylcyclopropanecarboxaldehydes. Having need of 1a and 1b for a synthetic study, we decided to attempt their preparation by an extension of this general approach.

The β-tetralones 2a and 2b were prepared according to literature methods (7,8). The conversion of the tetralones to the 1,1'-spirocyclopropane derivatives, 3a and 3b, was accomplished in yields of 50% and 30% respectively by the alkylation of the tetralone anion with 1,2-dibromoethane in dry dimethyl sulfoxide at 55-60° and using either potassium t-butoxide or dimsyl sodium as the base. Since in both cases the alkylation product did not

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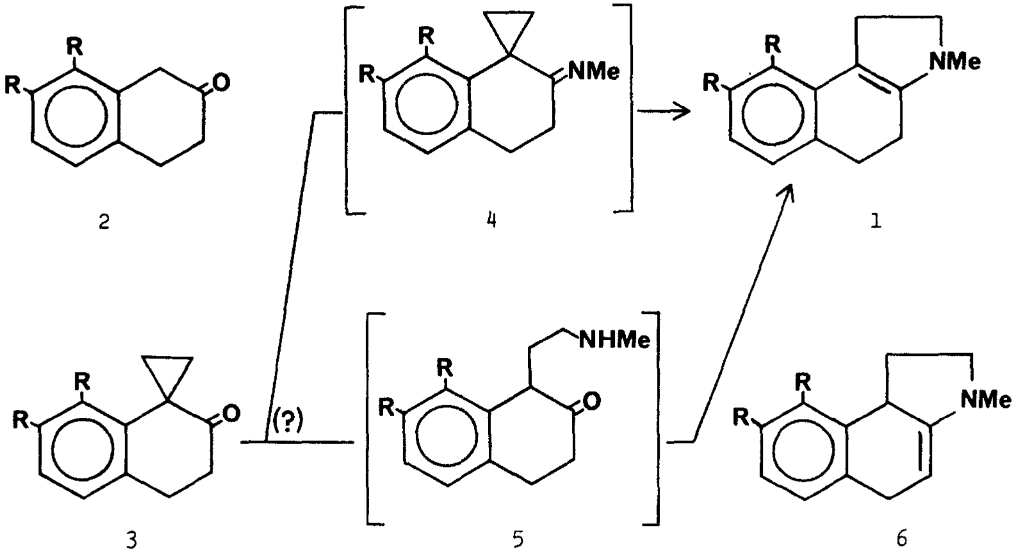
*NASA Predoctoral Trainee, 1966 to date.

form a bisulfite adduct under the same conditions as did the tetralone precursor, the separation of these, the two major components of the reaction mixture, was not difficult.



a, R = H; b, R = OMe

Attempts to prepare 4a by the condensation at room temperature of 3a with a large excess of methylamine in an ether-benzene solution in the presence of calcium oxide were unsuccessful, very little reaction appearing to occur under these conditions even over a two week period. When, however, the same reactants but with benzene alone as the solvent, were heated in a stainless steel bomb for seven days at 110°, the direct conversion of 3a to the tetrahydrobenz[e]indole 1a was accomplished in 70% yield. Ketone 3b was converted to 1b in the same yield under the same reaction conditions in either the stainless steel bomb or in a sealed glass tube. Whether or not this transformation involves the formation and subsequent rearrangement of imine 4 has not been established. Previous studies (4,5,6) have shown, however, that in the absence of added acid catalyst this type of rearrangement is extremely sluggish if it takes place at all. This suggests that the conversion may occur, at least to some extent, by another route such as that involving the cleavage of the cyclopropane ring of 3 by methylamine in a nucleophilic displacement step (9) to yield, after appropriate proton transfers, 5 which subsequently undergoes an intramolecular condensation producing 1.*

The absence of appreciable amounts of enamine tautomer 6a in equilibrium with 1a is apparent from spectral evidence. The nmr spectrum ($CDCl_3$ solution) of 1a, for example, shows no more than traces of absorption in the τ 5.0-6.3 ppm region which would be characteristic of the olefinic proton of 6a. This observation is in accord with that on related nonaromatic systems for which it was found the more stable enamine of a tautomeric pair contained the more highly substituted double bond (10) and also with the expectation that the conjugative interaction of the enamine double bond with the aromatic ring, possible only in 1a, would stabilize 1a with respect to 6a. In the case of tautomeric pair 1b and 6b, the spectroscopic evidence is again in accord with conjugated enamine 1b as the major species present. The nmr spectrum ($CDCl_3$ solution) of this substance does show, however, a small amount of absorption in the τ 6.05-6.35 ppm region which appears almost entirely as small shoulders on the two methyl singlets. This absorption could be at least partly owing to the olefinic proton of 6b. Even if this is the case, it is difficult to ascertain with any accuracy from the nmr spectrum the quantity of unconjugated enamine 1b to which it corresponds

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*The spectral and combustion analysis data on all compounds are in accord with the assigned structures. Although correct combustion analysis data on benz[e]indoles 1a and 1b were obtained only after a number of attempts, all mass spectra obtained on purified samples of these compounds showed the expected molecular ion (m/e at 185 and 245, respectively) as the base peak of each spectrum. While the combustion analysis on 3b was correct, the mass spectrum of this substance shows low abundance peaks above the molecular ion (m/e at 232) probably indicative of the presence of small amounts of dimeric material.

but the uv and ir data suggest it must be small.

Despite the fact that, as anticipated, enamine 1 is more stable than 6, low concentrations of 6 may be in mobile equilibrium with it and the enamine reactions of each tautomeric pair could yield products derived principally from 6. Work bearing on both this point and on the potential of these substances as intermediates for use in the synthesis of more complex molecules is presently in progress.

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