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THE APPLICATION OF NITRENE INSERTION REACTIONS TO THE FUNCTIONALIZATION OF TRICYCLO[3.3.0.$0^{2,6}$]OCTANE

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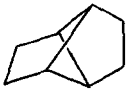
Tricyclo[3.3.0.$0^{2,6}$]octane (1), built up from four equivalent methylene and four equivalent methine groups, is one of the most readily obtainable bicyclo[2.1.1]hexane derivatives.[2] At the same time, 1 can be viewed as a small-ring analog of adamantane (2), the tricyclic C_{10} hydrocarbon built up from six equivalent methylene and four equivalent methine groups. In connection with our interest in the chemistry of bicyclo[2.1.1]hexanes,[3] we have sought convenient methods for the functionalization of 1. Some reactions leading to attack at the methylene positions of this hydrocarbon will be described elsewhere.[4] We wish now to report the first successful functionalization of 1 which results in attack at both the methylene and the methine positions. These results open the way to the synthesis of tricyclo-[3.3.0.$0^{2,6}$]octyl analogs of the important new anti-viral agent, 1-aminoadamantane hydrochloride (3).[5]



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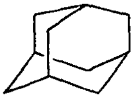

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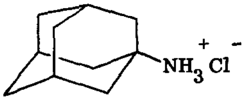

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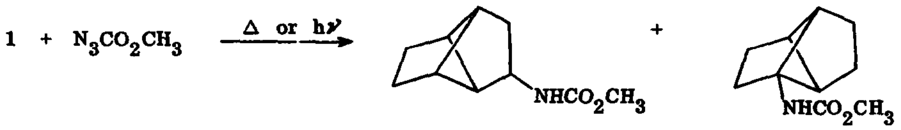
We chose to study nitrene insertion reactions of 1 since (1) there have been several examples of such insertions in simple alkanes and cycloalkanes,[6] (2) these reactions might be expected to favor methine over methylene attack,[7] and (3) the symmetry of our starting hydrocarbon permits the formation of only two isomeric C-H insertion products.

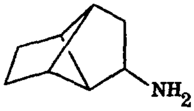
When dilute solutions of methyl azidoformate (4) in 1 were either irradiated or heated to 120°, nitrogen was evolved in nearly quantitative yield. After removal of excess 1 and short path distillation of the residue, there was obtained a 45% yield of a 2:1 mixture of the methyl urethanes 5 and 6. It is interesting that in spite of the observed 3:1 preference for methine over methylene attack in acyclic hydrocarbons,[7] an essentially statistical mixture of isomeric urethanes is formed from the tricyclooctane 1. Nevertheless,



4 5 6

a bridgehead substituted derivative of 1 becomes available for the first time by this technique.

The isomeric urethanes could be separated and purified by spinning band distillation, column chromatography, and fractional crystallization. The major isomer 5 (isolated in 20% yield), mp 87-89°, was shown to contain a hydrogen geminal to nitrogen by the appearance of an nmr signal (broad triplet, 1H) at 5.87 τ. The rest of the nmr spectrum contains a singlet methoxyl absorption at 6.42 τ, a broad N-H absorption at 4.9 τ, a complex series of peaks from 7.6-8.6 τ (6H), and a singlet at 8.27 τ corresponding to the four C_7 and C_8 hydrogens. The infrared spectrum (CCl_4) has characteristic bands at 2.88 and 5.78 μ. The mass spectrum exhibits a parent peak at *m/e* 181 and a rational fragmentation pattern. Structure 5 for the major isomer was confirmed by base hydrolysis to the amine 7, which was prepared by an independent route and shown to have identical infrared and nmr spectra.[4]



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The minor isomer 6 (isolated in *ca.* 6% yield), mp 85-86°, has a simpler nmr spectrum than the less symmetrical 5. A singlet methoxyl absorption at 6.44 τ and a broad N-H absorption at 4.9 τ appear downfield, with no absorption in the 5.9 τ region. Peaks at 7.94 τ (2H), 8.28 τ (2H), and 8.40 τ (4H), and a series of broad peaks from 8.0 - 8.2 τ (3H) comprise the high field absorption. The infrared spectrum of 6 is similar to that of 5. The mass spectrum of 6 shows a parent peak at *m/e* 181 and a fragmentation pattern consistent with its assigned structure. Further discussion of these spectral data will be presented in a future publication.

These nitrene insertion reactions open the way to an extensive study of the chemistry of C_1 and C_3 substituted tricyclo[3.3.0.0^{2,6}]octanes. We are now subjecting the resulting urethanes and their derived amines to a variety of deamination procedures[8] known to produce alcohol derivatives,[9,10,14] olefins,[9-11,14] ketones,[12] and diazo compounds.[13] We are also examining the application of this technique to other bridged hydrocarbons to determine the factors influencing the relative reactivities of C-H bonds,[15] and to explore the possible usefulness of nitrene insertion reactions as a general method for direct bridgehead functionalization.

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FOOTNOTES AND REFERENCES

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