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A VERSATILE NEW SYNTHESIS OF 1H-AZEPINES[1]

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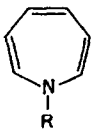
Derivatives of 1H-azepine (1), the 8π electron azalog of the unstable cycloheptatrienide anion, were first reported in 1963.[4] These interesting heterocycles are produced in good to excellent yield by the reaction of benzene with nitrenes generated in situ by thermolysis or



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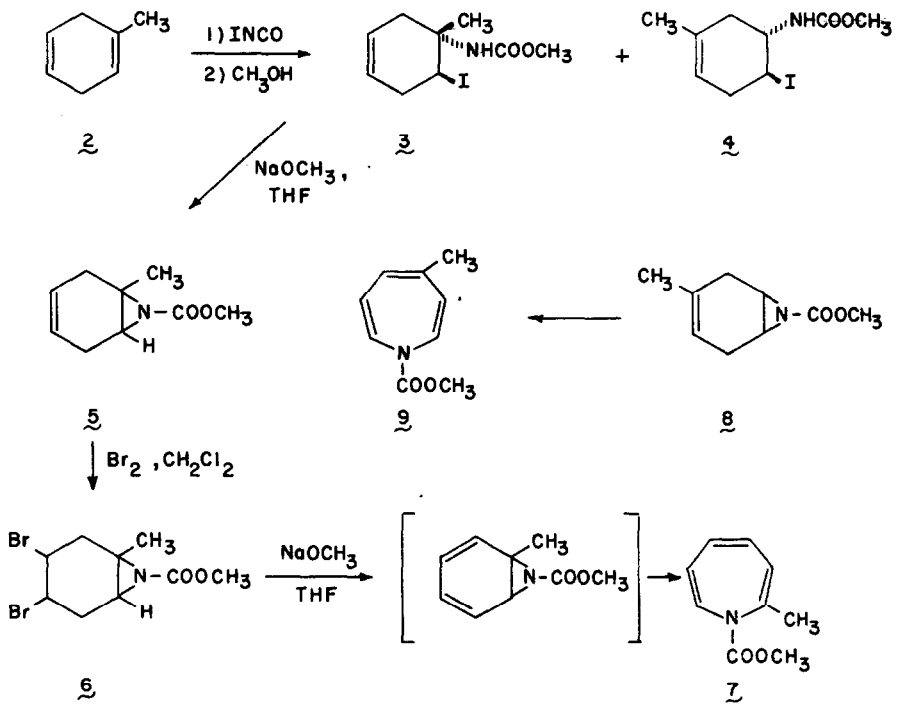
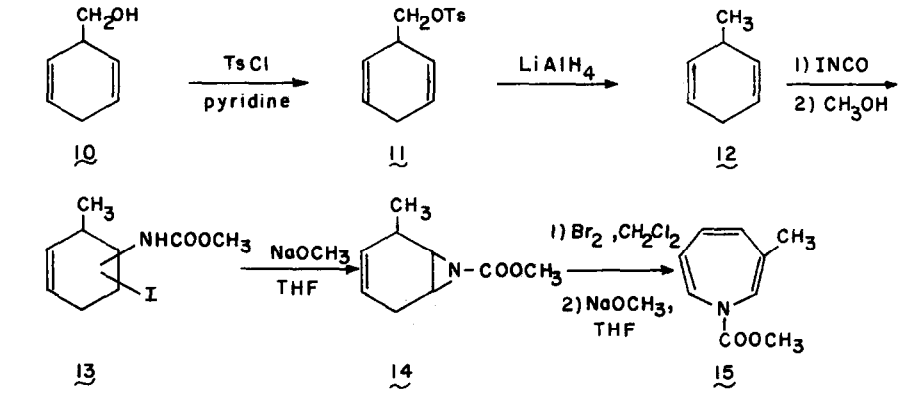
photolysis of appropriate azides.[5] When the reaction is extended to substituted aromatics such as toluene, bromobenzene, and anisole, however, there results a mixture of isomeric 1H-azepines which, in general, defy preparative scale vpc separation.[6] Due to such circumstances, various studies of the ground- and excited-state properties of substituted derivatives of 1 have not heretofore been capable of realization. As part of our continuing interest in heteroatomic 8π electron systems,[7] we have developed a new synthesis of 1H-azepines which allows for the specific introduction of one or more substituents at the three different ring positions of 1. This preliminary report will be concerned solely with monomethyl derivatives.

Treatment of 2,5-dihydrotoluene (2)[8] with freshly prepared silver cyanate and iodine in ether,[9] and finally with methanol, produced a mixture of crystalline iodocarbamates 3 and 4 in yields of 54% and 10%, respectively.[10] Cyclization of 3 with powdered sodium methoxide in dry tetrahydrofuran afforded aziridine 5 in 89% yield. Bromination of 5 in methylene chloride solution at -70° and exposure of the crude dibromide (6) thus formed to powdered sodium methoxide in refluxing tetrahydrofuran solution for 2 hr. led to 1-carbomethoxy-2-methylazepine (7) in 56% yield.



The isomeric 1-carbomethoxy-4-methylazepine (9) was obtained in good yield by a similar sequence of reactions commencing with 4.

When 1,4-dihydrobenzyl alcohol (10)[11] was treated with p-toluenesulfonyl chloride and



pyridine according to the method of Nelson[11] and the non-crystalline tosylate 11 was reduced directly with lithium aluminum hydride, the previously unknown 1,4-dihydrotoluene (12) was obtained in 50% overall yield. Sequential addition of iodine isocyanate and methanol to 12 gave rise to iodocarbamate 13 which, after cyclization, bromination, and dehydrohalogenation in the above manner, was transformed into 1-carbomethoxy-3-methylazepine (15).

Assignment of structure to the various azepines rests not only on the method of synthesis and the individual spectral parameters, but also in certain instances on subsequent interconversion with known substances. For example, catalytic hydrogenation of 7 (10% Pd-C, CH_3OH) and lithium aluminum hydride reduction yielded an amine whose picrate, mp 232-233°, displayed melting point behavior identical with that of authentic 2,N-dimethylhexamethylenimine picrate.[12]

Interestingly, the small structural changes in effect when proceeding from 7→15→9 are accompanied by substantial changes in a variety of physical and chemical properties.[13] For example, whereas pure 7 is very pale yellow in color, 15 is yellow-orange and 9 possesses the dark orange-red hue characteristic of 1-carbomethoxyazepine (1, R = $COOCH_3$).[14] In Table I are summarized the ultraviolet spectra of the various azepines. The proton nmr spectra are recorded in Table II.

Table I

Ultraviolet Absorption Data (n-hexane solution)

Compound	λ_{max}, mμ	ε	λ_{max}, mμ	ε
1 (R = $COOCH_3$)	208	27,580	330	570
7	213	21,870	302	1,020
15	213	23,420	321	640
9	213	22,740	323	670

Table II

Proton Nmr Data (δ values in CCl_4 at 60 Mc)

Compound	CH_3-C	CH_3O-	Vinyl protons
7	2.04 (singlet)[a]	3.63 (singlet)	5.78 and 6.16 (multiplets)
15	1.73 (singlet)[a]	3.68 (singlet)	5.62 and 6.00 (multiplets)
9	1.78 (singlet)[a]	3.72 (singlet)	5.33 and 5.80 (multiplets)

[a]Small long range coupling has not been included.

This new synthetic scheme, which has proven to be reasonably general in scope, now provides ready access to a large number of specifically substituted 1H-azepines.

Acknowledgment. We wish to thank the National Institutes of Health and the Ciba Corporation for grants employed in financial support of this work.

FOOTNOTES AND REFERENCES

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(13) This subject will form the content of future papers.

(14) The parent compound (1, R = $COOCH_3$) has also been prepared by this reaction sequence in good overall yield.