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7-MONOOXYGENATED 2,3-DIAZABICYCLO[2.2.1]HEPTANES[1]

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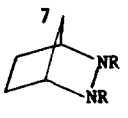
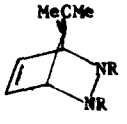
Even though the 2,3-diazabicyclo[2.2.1]heptyl system has been known for some time,[2] the synthesis of the corresponding 7-monooxygenated derivatives, potential precursors of the 5-substituted bicyclopentanes, has remained an elusive goal. During the course of our research, two approaches to 7,7-disubstituted 2,3-diazabicyclo[2.2.1]heptyl compounds have been described;[3,4] however, these compounds could not be converted to the desired 7-monosubstituted systems under a myriad of reaction conditions.[5]

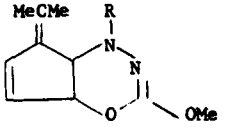
We should like to report the successful synthesis of 7-monooxygenated derivatives of I. The reaction of dimethylfulvene with dimethyl azodicarboxylate gives rise to an adduct (IIa) which isomerizes readily in polar solvents, or under acidic conditions, to afford a mixture of rearranged products, one component of which on the basis of spectroscopic data, appears to be IIIa.[6]



I

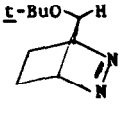


II



III

IV



V

(a) R = CO_2Me

(b) R = CO_2Et

(c) R = Me

The Diels-Alder adduct IIa can be selectively hydrogenated[4] (5% $Pd/BaSO_4$, ethyl acetate) to saturate the endocyclic double bond and give dihydro-IIa. Ozonization of dihydro-IIa in methanol, followed by in situ reduction with sodium borohydride leads to the production of the desired 2,3-dicarbomethoxy anti-2,3-diazabicyclo[2.2.1]heptan-7-ol (IVa) (nmr ($CDCl_3$) δ 4.25

(broad s, 2), 4.12 (broad s, 1), 3.78 (s, 6), 1.6-2.1 ppm (m, 4)) in 90% overall yield. The viscous oil IVa was converted into the corresponding acetate with sodium acetate in acetic anhydride (Anal. calcd. for $C_{11}H_{16}N_2O_6$: C, 48.52, H, 5.92; N, 10.29. Found: C, 48.36; H, 6.23; N, 10.66) which displayed the expected one-proton signal (CCl_4, TMS) at δ 4.85 ppm, attributable to H-7.

An anti-stereochemistry can be assigned to IVa for several reasons. Reduction of IVa with lithium aluminum hydride gives the corresponding dimethylhydrazine IVc, dilute solutions of which showed only absorption due to free hydroxyl (i.e. 1.415 μ) in the first overtone region for hydroxyl stretching in the near infrared,[7] whereas the alternative syn-epimer would be expected to exhibit strong intramolecular hydrogen bonding. Moreover, the dicarbomethoxy alcohol IVa also indicates only free hydroxyl absorption (i.e. 1.411 μ) in this region. In addition, the hydroxyl proton signal observed in the nmr spectrum of IVc shifts upfield from δ 5.35 to δ 2.67 ppm as the concentration is varied from 2.0 M to 0.125 M in deuteriochloroform, a consequence anticipated for the anti-epimer but not for the strongly intramolecularly hydrogen bonded syn-isomer.[8]

An nmr double irradiation experiment carried out on anti-7-t-butoxy-2,3-diazabicyclo[2.2.1]-hept-2-ene (V) prepared by the acid catalyzed addition of isobutylene to IVa, followed by hydrolysis and oxidation,[9] indicated that the broad singlet attributed to the 7-proton at δ 3.43 ppm ($CHCl_3$, TMS) sharpens to a triplet (J = 2 Hz)* when decoupled at the frequency of the endo-protons. The small magnitude of this long range coupling (i.e. less than 1 Hz) of the endo protons to the 7-proton in V is matched in the carbocyclic series. We found nearly identical behavior for anti-bicyclo[2.2.1]hept-2-ene-7-ol and its methanesulfonate.

The ozonization of IIa in methanol should proceed via the molozonide[10] to the 7-ketone VI according to Path 1 (Chart 1).** Path 2 appears less likely since we have found, along with others,[3-5] that the generation of positive charge at C-7 is an unfavorable process in this system. Thus, we have found that the methanesulfonate of IVa is remarkably resistant to solvolysis in acetic acid. This can be ascribed to the combined action of inductive and field

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*This triplet stems from the coupling between the two bridgehead protons and the H-7 proton.

**The reorganization of the molozonide to the ozonide can not be excluded. Reduction of the ozonide would also most likely produce IVa through the intermediacy of the 7-ketone.

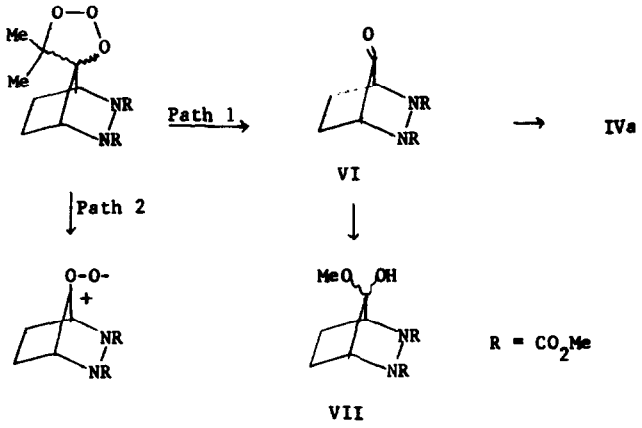

Chart I

effects attributable to the carbamate moieties. The ketone, once formed, would likely proceed, in a reversible process, to the hemiketal stage in methanol. The anti-stereochemistry observed for IVa can be attributed either to the carbamate moities exerting a specific directive effect on the reduction, or to steric factors influencing the direction of approach of the borohydride. This point clearly requires further elaboration.

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