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UNUSUAL BRIDGEHEAD HYDROXYLATIONS VIA SELENOXIDES: EVIDENCE FOR BRIDGEHEAD CARBOCATIONS

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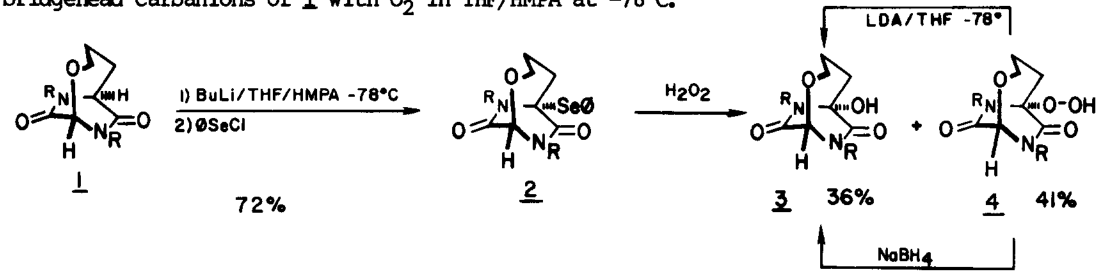
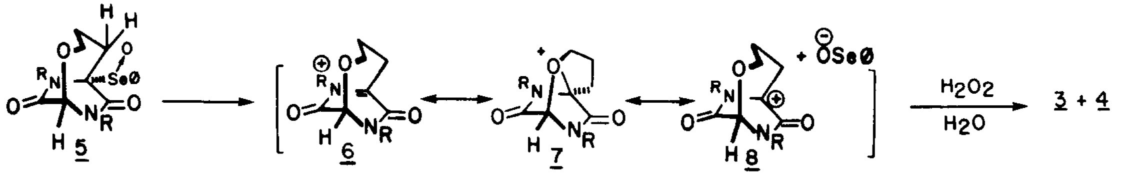
Summary: Treatment of C-6-phenylselenyl bicyclo[4.2.2]piperazinediones with H_2O_2 affords the C-6-peroxy and C-6-hydroxy bicyclic piperazinediones and is rationalized on the basis of intermediate bridgehead carbocations.

During the course of our studies[1] on the chemistry of the 8,10-diaza-2-oxabicyclo[4.2.2]-decane-7,9-dione nucleus present in the novel antibiotic bicyclomycin, we discovered an unusual bridgehead hydroxylation reaction via selenoxides.

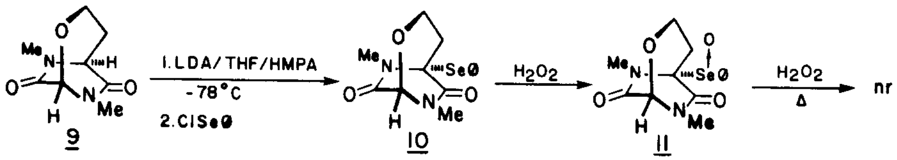
Quenching the bridgehead carbanion of bicyclic piperazinediones 1 with phenylselenenyl chloride according to our previously described protocol[1a] afforded the bridgehead selenides 2.[2] Treatment of 2 with 6 equiv of 30% H_2O_2 in THF for 15 h at 25°C followed by evaporation and PTLC on silica gel afforded the bridgehead alcohol[3] 3 (36%) and the novel peroxide 4 (41%).[4] Reduction of the peroxide with $NaBH_4$ in CH_3OH afforded the corresponding alcohol 3 (98%). We also found that peroxide 4 is readily reduced[5] to 3 in the presence of LDA in THF at -78°C (quant). Authentic samples of 3 were prepared[1] by quenching the regioselectively generated bridgehead carbanions of 1 with O_2 in THF/HMPA at -78°C.



It would seem plausible that the geometric constraints imposed by the bicyclic ring system preclude the normal syn-elimination of the selenoxides 5 with the β-hydrogens of the C-5 methylene; in this case a highly strained bridgehead olefin would be produced and is considered an unlikely intermediate. The bridgehead disposition of the selenoxide also precludes bimolecular (S_N2) displacement of the selenate by H_2O or H_2O_2 to afford 3 and 4, respectively. A third possibility involves homolysis of the C-Se bond to form a bridgehead radical which could combine with O_2 to form the peroxide 4. The radical could also recombine with ·OSeØ to form a hydrolytically labile selenate leading to 3. However, performing the reaction in O_2-degassed H_2O_2 afforded exactly the same results as that above. This result and the abscence of reduced 1 would tend to cast doubt on the intermediacy of free radicals. Finally, expulsion of the selenate by participation of the N-10 amide nitrogen to form a bridgehead iminium/carbocationic species (6/7/8) could be trapped by H_2O or H_2O_2 to give the observed products.[6] Although



efficient overlap of the N-10 amide lone pair with C-6 is not possible, an inductively stabilized and partially pyramidal carbocation at C-6 cannot be ruled out. The additional participation of the oxonium canonical structure 7 requiring a 5-5-5 tricyclic transition state is geometrically accessible and possibly significant. If 6/7/8 were an intermediate, we reasoned that the corresponding bicyclo[3.2.2] analog 9^{1b} would be considerably less capable of passing through an analogous carbocation at C-5. In the same fashion,[1] the C-5-phenylselenenyl bicyclo[3.2.2] piperazinedione (10) was prepared from 9 (43%) and treated with 30% H_2O_2. The resulting selenoxide (quant) was found to be completely stable at reflux temperature for several days. Absolutely no evidence for the formation of bridgehead alcohol or peroxide could be obtained from this substrate. From these observations, we conclude that the bicyclo[4.2.2] system is geometrically and electronically capable of supporting a positive charge at C-6, whereas the smaller, more highly strained bicyclo[3.2.2] system is not. These considerations must also be compared to the strikingly similar bridgehead carbanion chemistry which both systems display.[1]



References and Footnotes

1. a) Williams, R. M.; Dung, J-S.; Josey, J.; Armstrong, R. W.; Meyers, H. J. Am. Chem. Soc. (1983) **105**, 3214; b) Williams, R. M.; Anderson, O. P.; Armstrong, R. W.; Josey, J.; Meyers, H.; Eriksson, C.; ibid (1983) **104**, 6092; c) total synthesis: Williams, R. M.; Armstrong, R. W.; Dung, J-S. ibid (1984) **106**, 5748; d) 188th National ACS Meeting, Division of Organic Chemistry, Philadelphia, PA, August 1984, Abstract 92.
2. Satisfactory spectroscopic and analytical data were obtained for this compound.
3. Spectroscopic and analytical data for 1 (R=CH_3, CH_2Ph) and 3 (R=CH_3) are reported in reference 1b; data for 3 (R=CH_2Ph) is reported elsewhere, Williams, R. M.; Armstrong, R. W.; Dung, J-S. submitted for publication.
4. Data for 4 (R=CH_3): ^1H NMR (270 MHz) ($CDCl_3$) δ TMS: 1.55-1.86(1H, m), 1.87-1.92(1H, m), 1.98-2.02(2H, m), 3.06(3H, s), 3.12(3H, s), 3.48(1H, m), 3.90(1H, m), 5.14(1H, s), 9.51(1H, s, D_2O exch); IR(NaCl, neat): 3240, 1675, 1450, 1400, 1310, 1250, 1065 cm^{-1}; mp 200°C (sublimes). Anal. ($C_9H_{14}N_2O_5$) C, H, N.
5. It is of interest that 4 is not observed in the bridgehead carbanion quench of 1 with O_2; this putative, reactive peroxide is reduce in situ to 3 with either HMPA or diisopropylamine.
6. A somewhat related piperazinedione (cyclo-pro-pro) peroxide reaction via sulfides has been reported: Ohler, E.; Tataruch, F.; Schmidt, V. Chem. Ber. (1973) **106**, 165.
7. This work was financially supported by the National Institutes of Health Grant RO1AIGM18957.

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