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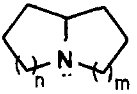
SYNTHESIS OF PYRROLIZIDINE AND INDOLIZIDINE RING SYSTEMS VIA N-CHLORAMINE REARRANGEMENT

Fred M. Schell*, Rathindra N. Ganguly, Kim S. Percell
Department of Chemistry, The University of Tennessee
Knoxville, TN 37916

Julian E. Parker, III
Department of Chemistry, The College of Charleston
Charleston, S. C. 29401

Summary: The silver ion induced rearrangement of bicyclic N-chloramines is reported. In addition to the expected reaction, oxidation of the rearrangement products was observed in two cases.

The wide occurrence of bicyclic systems 1 a-d in a variety of alkaloid structures makes the development of new methods for their synthesis worthwhile. One approach to such heterocycles is the rearrangement of appropriate N-haloamines in analogy with the pioneering work of Gassman in other systems.[1]



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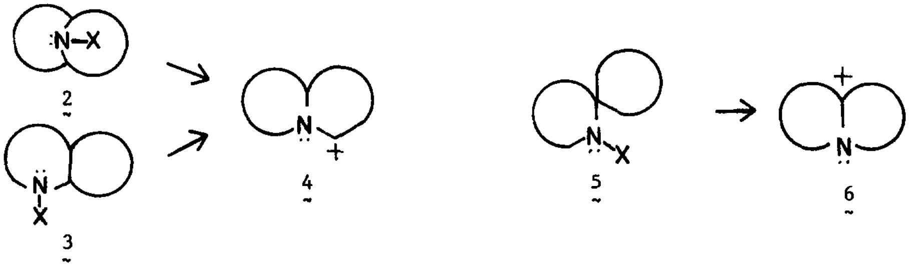
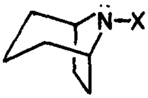
a n=1, m=1
b n=1, m=2
c n=1, m=3
d n=2, m=2

Three basic methods of producing derivatives of these systems can be envisioned. With appropriately sized rings, bicyclic N-haloamines of the type 2 or 3 would provide immonium ions such as 4, while spirocycles 5 could lead to 6. We wish to report our first attempts to explore this strategy in cases related to 2 and 3.



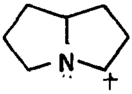
When N-chloronortropane(7a)[2] was exposed to refluxing, methanolic silver nitrate solution, copious precipitation of silver chloride occurred. No attempt was made to isolate the expected immonium salt 8 or its chloride or methanol adducts. After precipitation of excess silver ion with lithium chloride, the reaction mixture was filtered and immediately treated with sodium cyanoborohydride in acid according to the procedure of Borch et al.[3] After alkaline work-up and acetic anhydride treatment, N-acetylnortropane(7b) was isolated in 45% yield and pyrrolizidine(1a)[4] in 35% yield (64% based on nortropane recovered as 7b). Both products can be assumed to arise from nitrenium ion 9.[5] Thus, spin inversion to the triplet state followed by hydrogen atom abstractions[7,8] would provide nortropane, and rearrangement to 8 would provide 1a upon hydride reduction. However, the production of nortropane from radicals generated by homolytic cleavage of 7a can not be dismissed.[6]



7

a X=Cl

b X=Ac



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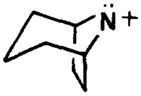

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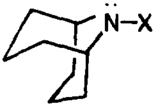
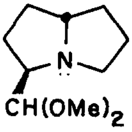
In anticipation of a similar conversion of the granatanine skeleton to indolizidine(1b), N-chlorogranatanine(10a)[2] was submitted to the identical reaction conditions. An alteration in the reaction course was indicated by formation of silver metal in addition to silver chloride in the first stage of the sequence. Although N-acetylgranatanine(10b) was isolated as expected (50% yield), no indolizidine(1b) was produced. However, a dimethoxy compound, whose spectral characteristics (pmr (CDCl$_3$), δ 3.39 (s,3H), 3.41 (s,3H), 4.11 (d,J = 7Hz,1H); cmr, CH$_3$ carbons δ 54.7, 53.8; CH$_2$ carbons δ 55.4, 32.0, 31.9, 29.7, 26.8; CH carbons, δ 109.1, 68.6, 65.5; ms (70eV), m/e 185 (M$^+$), 110 (base peak = – CH(OCH$_3$)$_2$) are consistent with structure 11 was isolated in 25% yield. This material was converted to an unstable aldehyde (pmr (CDCl$_3$) δ 9.42 (d,J = 2.5 Hz,1H); cmr, CHO δ 202.9; ir (CHCl$_3$) 1718 cm^{-1}) in refluxing 20% HCl.



10

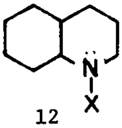
a X=Cl

b X=Ac



11

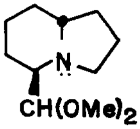
Similarly, silver induced rearrangement of N-chloro-trans-decahydroquinoline(12a) provided trans-decahydroquinoline isolated as its acetamide derivative 12b (45% yield) and acetal 13 (26% yield; pmr (CDCl$_3$) δ 3.33 (s,6H), 4.48 (d,J = 7Hz,1H); cmr, CH$_3$ carbons δ 53.2 (2C); CH$_2$ carbons, δ 49.5, 30.0, 29.3, 22.8, 20.7, 19.8; CH carbons, δ 103.2, 55.6, 54.8; ms (70eV), m/e 199 (M$^+$), 124 (base peak = – CH(OCH$_3$)$_2$).



12

a X=Cl

b X=Ac



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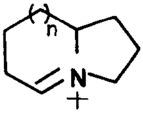
Acetals 11 and 13 resemble products of β-haloenamine rearrangement[9] and they may arise in part from chlorination of enamines 15a,b in the reaction mixture. However, silver oxidation is clearly implicated. Using 2 equivalents of silver nitrate in the rearrangement of 10a provided 0.91 equivalents of Ag° relative to 11. Thus, radical cations 16 could be formed by silver oxidation[10] of 15a,b or via hydrogen atom abstraction from 14a,b by triplet nitrenium ion or other amino radical. Reaction with solvent and further oxidation by silver or chloramine, etc. would provide aziridinium ions 17 which would rapidly add methanol to produce the observed acetals.[13] The lack of similar oxidation after rearrangement of 9 is probably due to rapid trapping of 8 as its chloro or methoxy adduct.



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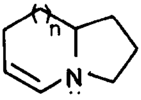

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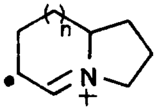

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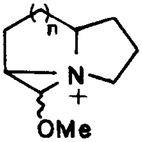

17

a n=1 b n=2

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References and Notes.

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2. The N-chloramines used in this study were produced in essentially quantitative yield from the corresponding secondary amines with N-chlorosuccinimide and were used immediately without extensive purification.

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4. Identical to an authentic sample produced according to L. R. Kray, M. A. Reinecke, J. Org. Chem., 32, 225 (1967).

5. Although silver ion induced heterolytic cleavage of nitrogen-chlorine bonds has been questioned,[6] a recent comparison of homolytic and heterolytic cleavage clearly indicates the intermediacy of nitrenium ions in similar reactions.[7]

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