

A NOVEL BENZO[a]QUINOLIZIDINE REARRANGEMENT
INVOLVING INTRAMOLECULAR CARBAMYL-CHLORIDE-INDUCED
CLEAVAGE OF A TERTIARY AMINE

Bruce E. Maryanoff* and Albert J. Molinari
Research Division, McNeil Pharmaceutical
Spring House, Pennsylvania 19477 USA

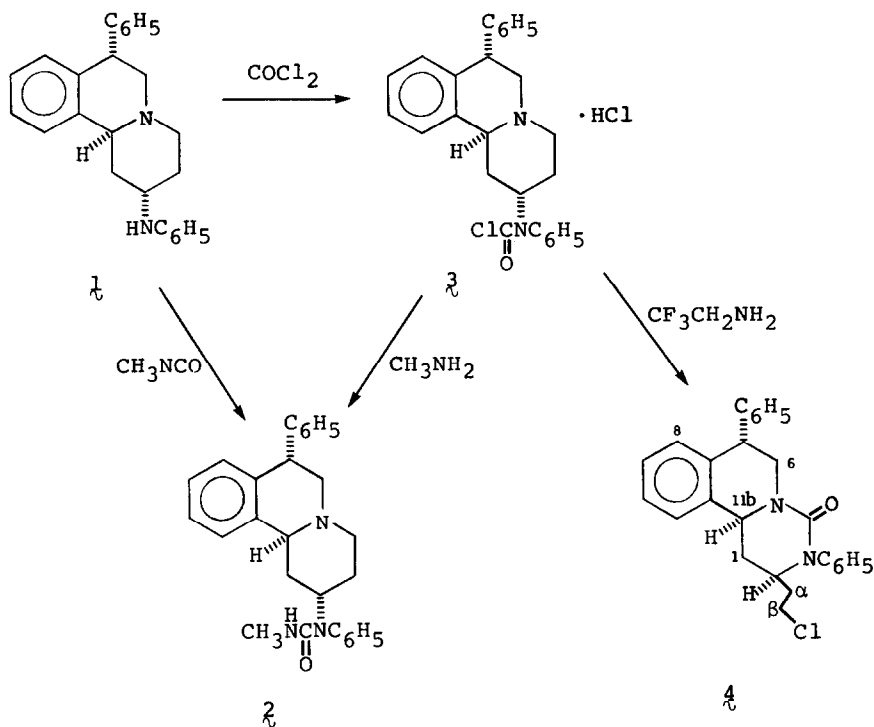
Gary P. Wooden and R. A. Olofson
Department of Chemistry, The Pennsylvania State University
University Park, Pennsylvania 16802 USA

Summary: The free base of benzoquinolizidine **3** undergoes a facile rearrangement to pyrimidoisoquinoline **4**, the structure of which was confirmed by x-ray crystallography. The regioselectivity of this novel rearrangement is governed by stereoelectronic factors.

The cleavage of tertiary amines with acyl halide reagents, such as phosgene, chloroformates, and cyanogen bromide, has been performed by organic chemists over the past 80 years.¹ However, intramolecular variants of this N-dealkylation process have received little recognition.² We report herein a carbamyl-chloride-induced cleavage of a tertiary amine which occurs with remarkable facility and high regioselectivity.

As an extension of our work on propionyl derivatives of **1**, and its diastereomers,³ we prepared several urea congeners (e.g., **2**) by a conventional route, the reaction of **1** with phosgene, followed by a primary or secondary amine. However, use of 2,2,2-trifluoroethylamine in the reaction sequence did not lead to the expected urea product; instead, a non-basic, chlorine-containing substance [mp 165-167°C (ethyl ether); ν_{\max} (CO) 1635 cm^{-1} ; m/z (^{35}Cl) 416; elemental analysis for $\text{C}_{26}\text{H}_{25}\text{ClN}_2\text{O}$] was obtained in good yield (61%, analytical purity). Specifically, aniline **1** was reacted with COCl_2 in CH_2Cl_2 to afford **3** as an off-white powder on evaporation of solvent. An IR spectrum of **3** (KBr) showed an NH^+ band at 2430 cm^{-1} and a carbonyl absorption at 1727 cm^{-1} . The identity of **3** was further substantiated by conversion with methylamine to **2**, a compound prepared independently from **1** and methyl isocyanate. Treatment of **3** with an excess of $\text{CF}_3\text{CH}_2\text{NH}_2$ generated only the new product, and this transformation was complete in ca. 8 h ($t_{1/2}$ = ca. 2.3 h) at 23°C. Other amines were examined with **3**: pyridine and N,N-dimethylaniline gave no reaction (within 2 h at 23°C), but triethylamine readily produced the new compound.

We supposed that a rearrangement of the free base of **3** had transpired, via the intermediacy of III, giving rise to one of three possible products: **4**, **5**, or **6** (Scheme). Although high-field ^1H and ^{13}C NMR data were interpretable in terms of either structure **4** or **6**, **6** was unlikely on the basis of a negative AgNO_3 test. The new compound was unambiguously identified as **4** by single-crystal x-ray analysis (Figure).^{4,5}



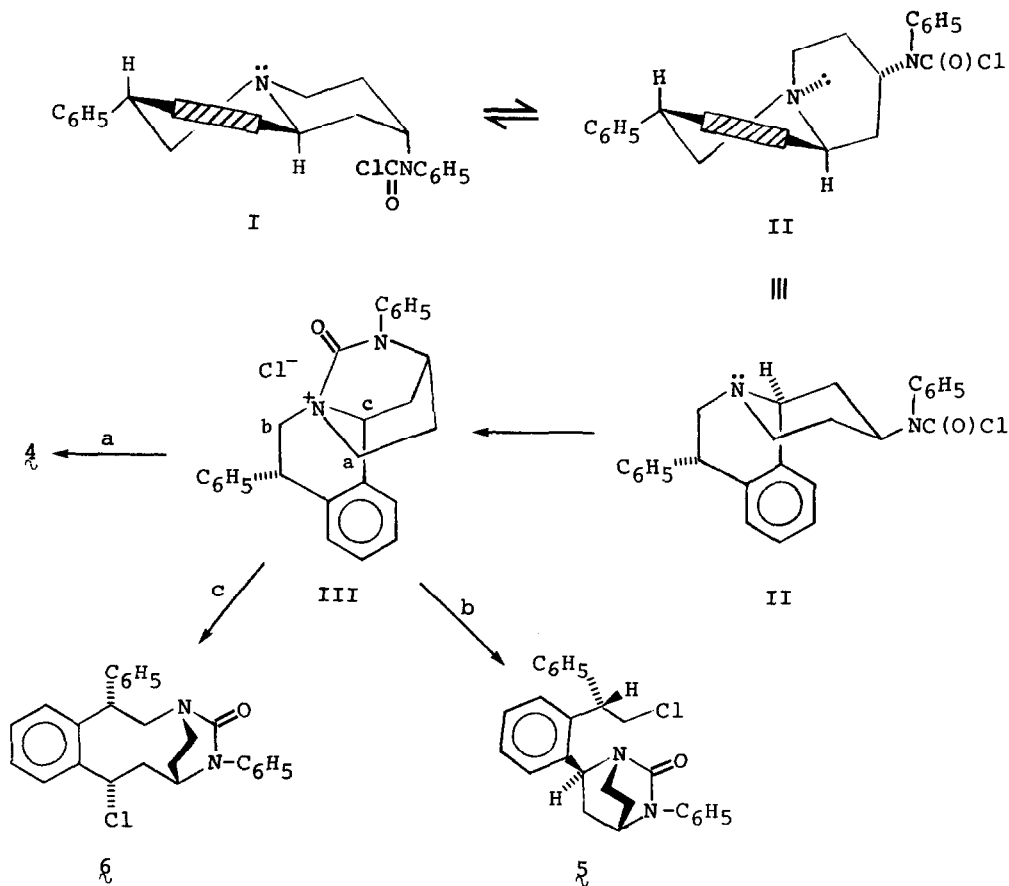
For the rearrangement of **2** to **4** to take place, bicyclic ammonium intermediate III must be formed (Scheme). Three possible modes of cleavage (a, b, and c) are available to III, but only pathway a is observed. The normally favored benzylic cleavage (pathway c) does not occur. This preference for pathway a is probably associated with the development of maximum amide resonance in the transition state for N-dealkylation. The proposed intramolecular nature of the rearrangement is consistent with the imposition of stringent stereoelectronic controls leading to high regioselectivity.

The necessary bicyclic ammonium intermediate, III, can be generated directly from cis-fused quinolizidine conformer II, but not from trans-fused conformer I.⁶ The conformational equilibrium is expected to be strongly biased (90-95%) toward cis-fused conformer II, based on our work with congeneric propionyl derivatives.³ Thus, the facility of the rearrangement may be attributed to the high population of conformer II in the carbamyl chloride free base.

Given the above rationale for the ease of the rearrangement, one might suggest that diastereomers of the free base of **2**, devoid of a high population of cis-fused conformer, should rearrange more sluggishly. Work is in progress to test this idea.

Acknowledgments. We wish to thank Dr. Cynthia A. Maryanoff for helpful discussions, and Mr. David F. McComsey for technical assistance.

Scheme



References and Notes

- (a) H. A. Hageman, *Org. React.*, **7**, 198 (1953); (b) F. Möller, *Meth. Org. Chem. (Houben-Weyl)*, XI/1, 982-988 (1957); (c) R. A. Olofson, R. C. Schnur, L. Bunes, and J. P. Pepe, *Tetrahedron Lett.*, 1567 (1977); (d) J. C. Kim, *Org. Prep. Proced. Intl.*, **2**, 1 (1977); (e) K. C. Rice, *J. Org. Chem.*, **40**, 1850 (1975); (f) references cited in 1a-e.
- An examination of the chemical literature revealed four examples of intramolecular reactions: J. H. Gardner, N. R. Easton, and J. R. Stevens, *J. Am. Chem. Soc.*, **70**, 2906 (1948); R. L. Clarke, A. Mooradian, P. Lucas, and T. J. Slauson, *ibid.*, **71**, 2821 (1949); C. D. Lunsford, A. D. Cale, Jr., J. W. Ward, B. V. Franko, and H. Jenkins, *J. Med. Chem.*, **7**, 302 (1964); C. D. Lunsford and A. D. Cale, Jr., US Patent 3,337,580 (1967).
- B. E. Maryanoff, D. F. McComsey, R. J. Taylor, Jr., and J. F. Gardocki, *J. Med. Chem.*, **24**, 79 (1981).
- (a) ^1H NMR of **4** (270 MHz, CDCl_3) δ 1.65-1.75 (m, $J = 5, 5, 5, 5$ Hz, H_α), 1.92-2.08 (m, 2, H_α , and H_{1a}); H_{1a} is a d of d of d with $J = 11, 11, 13.5$ Hz), 2.77 (d of d of d, $J = 4.0, 4.0, 13.5$ Hz, H_{1e}), 3.04 (d of d, $J = 11.4, 13.5$ Hz, H_{6a}), 3.39 (m, 2, $J = 6, 6$ Hz, H_β), 4.18-4.32 (m, 2, H_2 and H_7), 4.79 (d of d, $J = 5.0, 13.0$ Hz, H_{6e}), 5.01 (d of d, $J = 3.2,$

10.8 Hz, H_{11b}), 6.85 (d, $J = 9.0$ Hz, H_8), 7.07-7.47 (m, 13, arom.). Determination of coupling constants and proton assignments were aided by homonuclear double-resonance experiments, which involved irradiation of H_α , H_{1e} , H_{6a} , H_2/H_7 , H_{6e} , and H_{11b} . (b) ^{13}C NMR of $\mathbf{4}$ (50.3 MHz, CDCl_3) δ 37.17 (C_α , C_1), 40.7 (C_β), 45.5 (C_7), 47.3 (C_6), 53.58 (C_2), 53.90 (C_{11b}), 125.0 (C_{11}), 126.63/126.72/126.94/127.02 (C_9 , C_{10} , 3Ph C_4 , 7Ph C_4 , in any order), 128.66/ 128.70/129.10 (3Ph C_2 , 3Ph C_3 , 7Ph C_2 , 7Ph C_3 , in any order), 129.44 (C_8), 136.6 (C_{11a}), 139.2 (C_{7a}), 141.0 (3Ph C_1), 141.8 (7Ph C_1), 155.3 (C_4). Both proton-decoupled and off-resonance-decoupled ^{13}C spectra were recorded. The off-resonance spectrum exhibited multiplicities due to $^2J_{\text{CH}}$, which assisted in making the assignments for C_6 , C_2 , C_{11b} , C_{11} , C_8 , 3Ph C_1 , and 7Ph C_1 .

5. Crystals of $\mathbf{4}$ (from 1,2-dimethoxyethane/hexane) contain eight molecules per monoclinic unit cell, space group $P2_1/c$ [$a = 32.313$ (6), $b = 13.220$ (3), $c = 11.247$ (13) Å; $\beta = 99.41$ (3)°; $V = 4740$ (8) Å³; $d_{\text{calc}} = 1.17$, $d_{\text{obs}} = 1.20$ g/ml], which comprise two sets of crystallographically independent molecules (4 molecules/set) distinguished by minor conformational differences. The crystal structure was solved by direct methods using MULTAN-78. Atomic positional and thermal parameters (anisotropic C, Cl, N, O; isotropic H) were refined by full-matrix least-squares calculations to $R = 0.125$ over 3878 statistically significant [$I > 2.0\sigma$ (I)] reflections, measured on an Enraf-Nonius CAD-4 automated diffractometer (Mo $K\alpha$ radiation, $\lambda = 0.70926$ Å; θ -2 θ scans).
6. The other cis-fused conformer (not shown), which should be highly unfavored,² cannot form III directly.

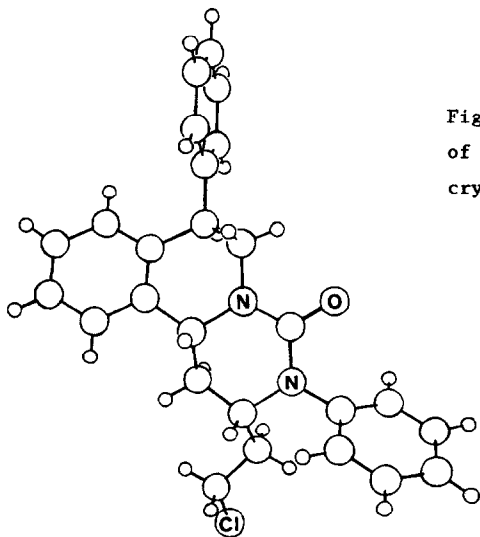


Figure. View of the molecular structure of $\mathbf{4}$ in the solid state (one of the two crystallographically independent molecules).