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AN UNUSUAL FRAGMENTATION PROCESS DISCOVERED DURING THE COURSE OF CLEAVAGE OF A CAMPHANIC ACID AMIDE

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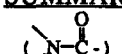
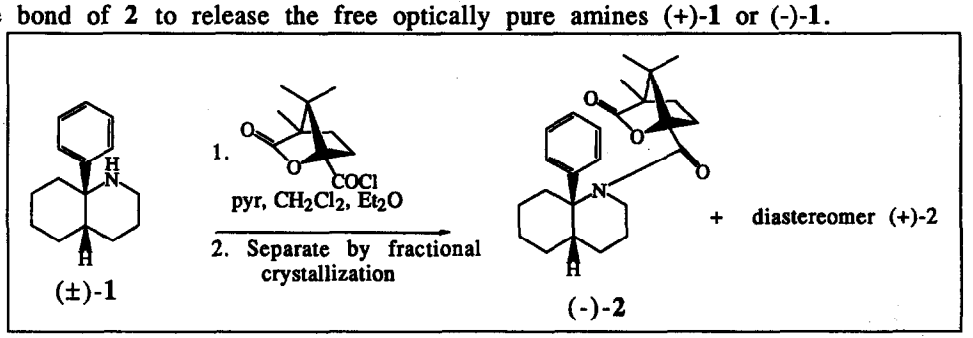
SUMMARY: An unusual fragmentation reaction that affords a carbamoyl anion  discovered during the course of the synthesis of rigidified PCP analogues is reported.

During synthetic efforts relating to the preparation of certain rigidified analogues of phencyclidine for use in studying both the modulation of the NMDA receptor complex and the topography of the associated PCP binding sites,[1] we discovered an unusual fragmentation process which we report in this Letter.

The 8a-phenyldecahydroquinoline **1** was prepared in racemic form by established methods.[2] As we wished to examine the binding affinity of the optically pure isomers of **1**, a variety of methods to effect the chemical resolution of the racemate were examined. The diastereomeric amides **2** prepared from **1** by reaction with (1*S*)-(-)camphanic chloride were found to be easily separated by fractional crystallization from 10% ethyl acetate in hexane. The structure of the pure (+)-amide obtained by X-ray analysis is presented in Figure 1.[3] Having successfully solved the separation problem, all we needed to accomplish at this point was hydrolysis of the amide bond of **2** to release the free optically pure amines (+)-**1** or (-)-**1**.



While numerous acidic and basic conditions were examined to bring about this hydrolysis reaction, we found the amide bond to be quite reluctant to undergo hydrolytic cleavage, a consequence, presumably, of the steric congestion about the carbonyl group. Eventually, Gassman's conditions involving the use of potassium *tert*-

butoxide (8 equiv.) plus water (4 equiv.) in ether were examined.[4] Surprisingly, we found that the formamide **5** could be isolated in good yield under these reaction conditions! The free base was obtained in turn from this formamide by reaction with phenyllithium in ether.[5]

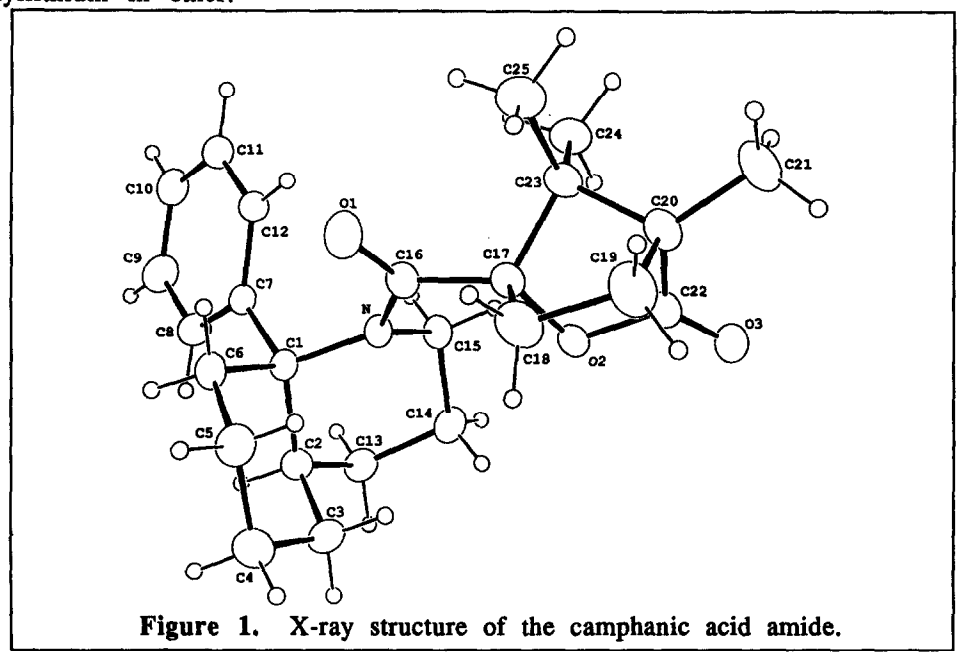
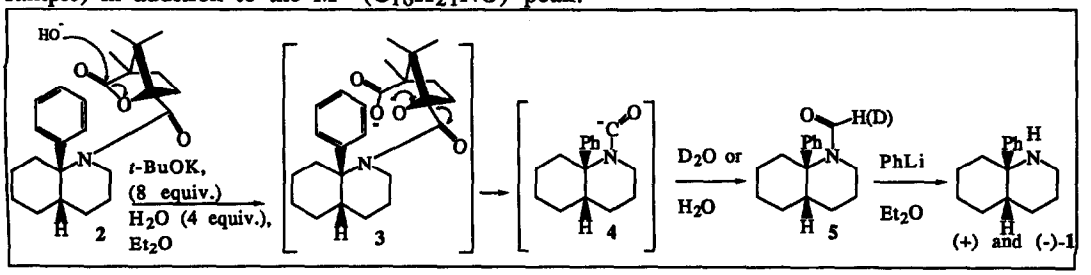
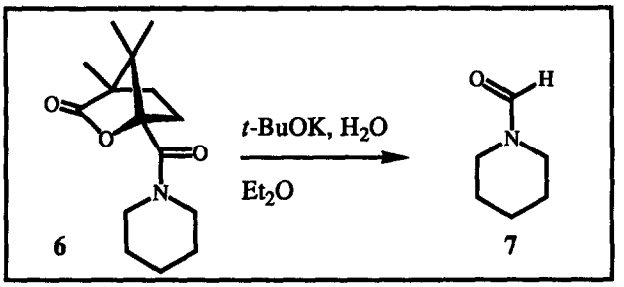


Figure 1. X-ray structure of the camphanic acid amide.

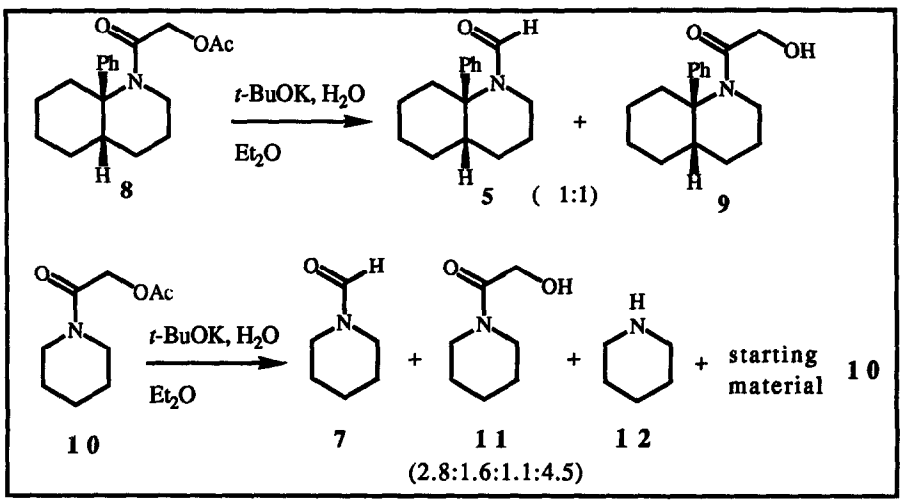
To rationalize the formation of the formamide **5** from amide **2**, we suggest that initial attack by the poorly solvated hydroxide ion occurs at the lactone carbonyl group rather than the more hindered amide carbonyl. The new alkoxide anion released in this process then initiates C-C bond rupture with formation of an intermediate carbamoyl anion **4** which is protonated to provide **5**. Experimental evidence in favor of this reaction pathway was garnered by carrying out the same reaction in the presence of potassium *tert*-butoxide in D_2O. The signal for the formamide proton (δ = 8.5 ppm) was reduced by ~1/2 in the ^{1}H-NMR spectrum, and the mass spectrum exhibited a strong M^++1 peak ($C_{16}H_{20}DNO$, 244, relative intensity 63% in comparison to a 244 peak of 16% relative intensity for the undeuterated sample) in addition to the M^+ ($C_{16}H_{21}NO$) peak.



To examine the possible generality of this fragmentation chemistry, we prepared the camphanic acid amide of piperidine and examined its reaction with *t*-BuOK/H_2O/Et_2O. In this case the formamide **7** was again formed as evidenced from ^{1}H-NMR and GC-mass spectral analysis.



To address the question as to whether the observed reaction course is a consequence of the hindered nature of the camphanic acid residue, we prepared the α-acetoxyacetamide derivatives **8** and **10** and subjected these to the *t*-BuOK/H_2O/Et_2O cleavage conditions. In the case of **8**, a ~1:1 mixture of the formamide **5** and the α-hydroxyacetamide derivative **9** was obtained in 65% isolated yield. The formamide **7** was also obtained from the piperidine derivative **10**, however, in this case the reaction mixture was also comprised of piperidine and the α-hydroxyacetamide **11** together with starting material (ratio of **7/11/12/10** = 2.8:1.6:1.1:4.5).



While steric congestion clearly contributes to steering the course of the reaction, this process does nonetheless appear to be somewhat general. We currently know of no other example of a related fragmentation reaction.[6] This novel finding is worthy of further exploration.[7]

Acknowledgement. We are indebted to the National Institute on Drug Abuse for their support of these studies.

References

1. A. P. Kozikowski and Y.-P. Pang, *Molecular Pharmacology*, **37**, 352 (1990); A. P. Kozikowski and Y.-P. Pang, *Synlett*, **1**, 58 (1990). For a discussion of the NMDA receptor subtype, see: A. P. Kozikowski, W. Tückmantel, I. J. Reynolds, and J. T. Wroblewski, *J. Med. Chem.*, **33**, 1561 (1990). For an overview of the PCP field, see: "Sigma and Phencyclidine-Like Compounds as Molecular Probes in Biology", E. F. Domino and J.-M. Kamenka, Eds., NPP Books, Ann Arbor, MI, 1988.

2. E. F. Godefroi, *J. Org. Chem.*, **27**, 3882 (1962).

3. Crystal structure details: $C_{25}H_{33}NO_3$, M_r = 395.55, monoclinic, $P2_1$, a = 11.279 (2), b = 7.803 (2), c = 12.457 (2) Å, β = 94.91 (1)°, V = 1092.3 Å^3, Z = 2, D_x = 1.203 g cm^{-3}, monochromatized radiation λ(Cu Kα) = 1.54184 Å, μ = 0.58 mm^{-1}, $F(000)$ = 428, T = 296 K. Data collected on an Enraf-Nonius CAD4 diffractometer to a 2θ limit of 144° with 1999 observed, $I \geq 3\sigma(I)$, reflections out of 2424 measured. Structure solved by direct methods and refined using full-matrix least-squares on F. All non-hydrogen atoms refined with anisotropic thermal displacements. Hydrogen atom contributions included in calculations. Final agreement statistics are: R = 0.045, wR = 0.047, S = 3.20, $(\Delta,\sigma)_{max}$ = 0.03. Weighting scheme is $1/\sigma^2(I)$. Maximum peak height in final difference Fourier map 0.14(4) eÅ^{-3} with no chemical significance. The atomic coordinates have been deposited with the Cambridge Crystallographic Data Centre.

4. P. G. Gassmann, P. K. G. Hodgson and R. J. Balchunis, *J. Am. Chem. Soc.*, **98**, 1275 (1976).

5. G. A. Olah and M. Arranagh, *Angew. Chem. Int. Ed. Engl.*, **20**, 878 (1981).

6. *The Chemistry of Amides*, J. Zabicky, Ed., Interscience, New York (1970). The deprotonation of tertiary formamides to provide carbamoyllithium compounds is, of course, well precedented and is related to the fragmentation process described herein: U. Schöllkopf and H. Beckhaus, *Angew. Chem. Int. Ed. Engl.*, **15**, 293 (1976). We thank the referee for bringing this point to our attention.

7. Satisfactory ^{1}H and ^{13}C NMR, IR, and high resolution mass spectral data were obtained for all new compounds reported herein.

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