Amidinium Cation as a Mimic of Allylic Carbocation: Synthesis and Squalene Synthetase Inhibitory Activity of an Amidinium Analog of a Carbocation Intermediate

Mahavir Prashad

Sandoz Research Institute, 59 Route 10, East Hanover, New Jersey 07936

Received December 14, 1992

Because of its strategic location in the cholesterol biosynthesis pathway, squalene synthetase enzyme is an attractive target for inhibition. Squalene synthetase catalyzes the conversion of farnesyl pyrophosphate (FPP) to squalene in two steps.[1] The first step is the condensation of the two molecules of FPP to presqualene pyrophosphate (PSPP), and the second step involves the reductive rearrangement of PSPP to squalene. Both steps have been hypothesized to involve several putative carbocation intermediates.[2] Ammonium and sulfonium ion analogs that mimic the electrostatic properties of the putative carbocation intermediates have been reported[2-4] to inhibit the first and second steps of the FPP to squalene conversion.

In a program to synthesize squalene synthetase inhibitors as agents for the treatment of hypercholesterolemia, we sought to design an analog of the carbocation I (Figure 1), a carbocation that may undergo reaction with NADPH to produce squalene in the second step of squalene biosynthesis from FPP. One of the shortcomings of the ammonium and sulfonium ions is that they mimic only the positive charge of the carbocation and fail to resemble its shape, which may be an important property to mimic. We wanted to design an analog of carbocation I which would not only mimic the electrostatic properties of the positive charge but also its shape and delocalization. We envisioned that an amidinium cation[5] would fulfill all the requirements necessary to mimic an allylic carbocation. This analysis led to structure II (Figure 1), which is an exact mimic of the allylic carbocation I.

Amidinium cation II would be generated at physiological pH by the protonation of *N*-homogeranyl-*N*-methyl-*N'*-farnesylformamidine (1). Retrosynthetic analysis revealed that 1 could be prepared from condensation of *N,N*-dimethyl-*N'*-farnesylformamidine (2) with *N*-methylhomogeranylamine (3). The required formamidine 2 (Scheme I) was prepared by the reaction[6] of dimethyl sulfate with *N,N*-dimethylformamide at 90 °C followed by treatment of the resulting intermediate with farnesylamine[7] in 65% yield. *N*-Methylhomogeranylamine (3) was prepared from homogeranyl iodide[8] in three steps. Treatment of homogeranyl iodide with trifluoroacetamide in the presence of potassium carbonate and tetrabutylammonium bromide in DMF at 80 °C furnished *N*-homogeranyltrifluoroacetamide (4) in 31% yield. *N*-Methylation of 4 with methyl iodide in DMF using sodium hydride as base yielded *N*-methyl-*N*-homogeranyltrifluoroacetamide (5) in 98% yield. Hydrolysis of 5 with potassium hydroxide in refluxing aqueous methanol furnished 3 in 77% yield. Treatment of 2 and 3 in refluxing toluene[6] in the presence of ammonium sulfate yielded the desired compound 1 in 53% yield.

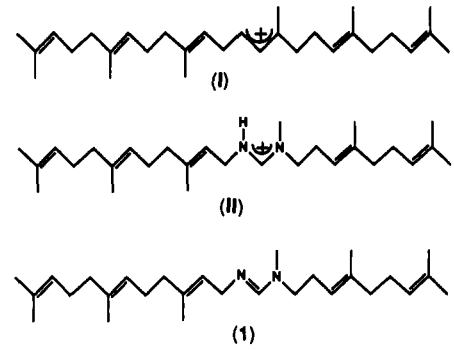
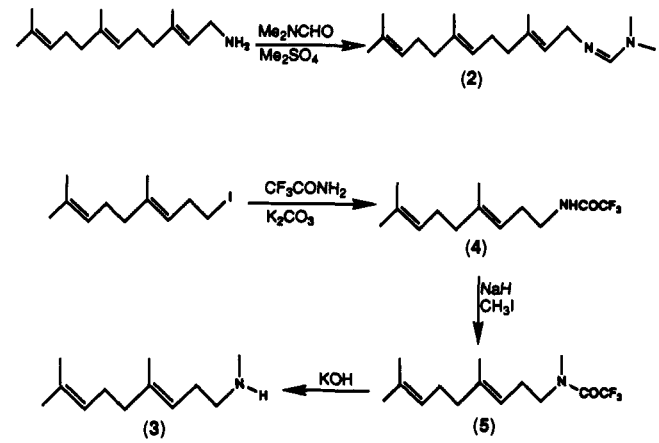


Figure 1.

Scheme I



Compound 1 was tested in a rat liver microsomal assay, and it inhibited squalene synthetase with an IC_{50} of 6.9 μM. When 1 was tested in the presence of inorganic pyrophosphate (PP_i) it showed an IC_{50} of 0.1 μM. Such an enhancement in the activity in the presence of added PP_i was first reported by the Poulter group[3] and serves as good evidence for both the involvement of the cation in the rearrangement and its existence as a tight ion pair with PP_i in the active site. This analog is thus much more active than those reported by Poulter et al., which were active only in the presence of PP_i. These results suggest that an amidinium cation is a suitable mimic of the allylic carbocation. To the best of our knowledge this is the first report[9] on the utility of an amidinium cation as a mimic of the allylic carbocation.

Acknowledgment. We thank Prof. T. Scallen (University of New Mexico) for biological data and Professors J. Knowles (Harvard University), P. Bartlett (University of California, Berkeley), and R. Abeles (Brandeis University) for their useful comments.

Supplementary Material Available: Procedures for the synthesis of 1-5 are available (2 pages). Ordering information is given on any current masthead page.

References

(1) Poulter, C. D.; Rilling, H. C. In *Biosynthesis of Isoprenoid Compounds*; Porter, J. W., Spurgeon, S. L., Eds.; Wiley: New York, 1981; Vol. 1, Chapter 8.
(2) Oehlschlager, A. C.; Singh, S. M.; Sharma, S. *J. Org. Chem.* **1991**, *56*, 3856 and references cited therein.
(3) (a) Poulter, C. D.; Capson, T. L.; Thompson, M. D.; Bard, R. S. *J. Am. Chem. Soc.* **1989**, *111*, 3734. (b) Capson, T. L.; Thompson, M. D.; Dixit, V. M.; Gaughan, R. G.; Poulter, C. D. *J. Org. Chem.* **1988**, *53*, 5903. (c) Sandifer, R. M.; Thompson, M. D.; Gaughan, R. G.; Poulter, C. D. *J. Am. Chem. Soc.* **1982**, *104*, 7376.
(4) Steiger, A.; Pyun, H. J.; Coates, R. M. *J. Org. Chem.* **1992**, *57*, 3444.
(5) Hafelinger, G. In *The Chemistry of Amidines and Imidates*; Patai, S., Eds.; John Wiley and Sons: New York, 1975, Chapter 1.

0022-2623/93/1836-0631$04.00/0

(6) Meyers, A. I.; Edwards, P. D.; Reiker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270.
(7) Coppola, G.; Prashad, M. *Synth. Commun.* In Press.
(8) Knochel, P.; Chou, T. S.; Chen, H. G.; Yeh, M. C. P.; Rozema, M. J. *J. Org. Chem.* **1989**, *54*, 5202.
(9) We thank Prof. R. Abeles (Brandeis University) for pointing this out to us. For an amidine analog of D-glucose which resembles the flattened chair conformation of glucosyl cation in the glycosydase inhibitor area, see: Tong, M. K.; Papandreou, G.; Ganem, B. *J. Am. Chem. Soc.* **1990**, *112*, 6137.