Tetrahedron Letters Vol. 21, pp 2475 - 2476
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0040-4039/80/0622-2475$02.00/0

THE CHEMISTRY OF NATURALLY OCCURRING POLYAMINES. 2.

A TOTAL SYNTHESIS OF THERMOSPERMINE

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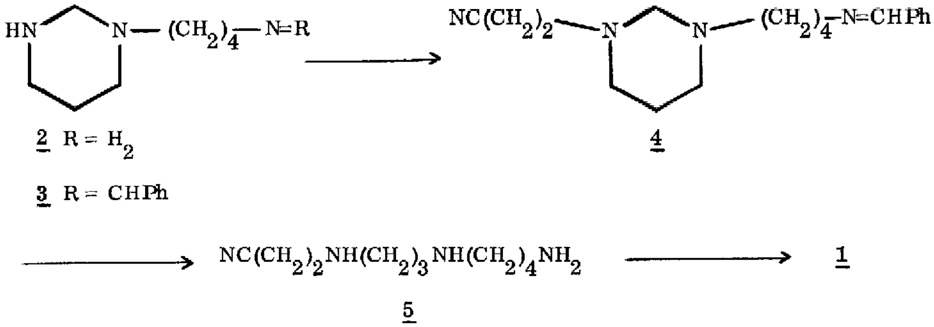
Summary: *De novo* methodology for distinguishing the similar basic sites in spermidine has led to the first synthesis of thermospermine 1.

The biogenic amines putrescine, cadaverine, spermidine and spermine are widespread substances which mediate a host of biophysical and physiological processes both in microorganisms and throughout the plant and animal kingdoms.[2] Several functionalized polyamine derivatives also exhibit marked cytotoxic, antibiotic, antiviral, tumor-inhibitory and anti-hypertensive activity. Recently a new polyamine, required for *in vitro* poly-(U)-directed polyphenylalanine synthesis, was discovered in the extreme thermophile *Thermus thermophilus*, a bacteria which grows normally at 75°C.[3] The structure of this spermine-like tetramine (1,12-diamino-4,8-diazadodecane 1) is shown below, for which the trivial name thermospermine has been proposed. We wish to report a short, convergent synthesis of 1 embodying a new protocol[4] for the regiospecific construction of complex polyamines and their biologically important conjugates.

$$NH_2(CH_2)_3NH(CH_2)_3NH(CH_2)_4NH_2$$

1

Hexahydropyrimidine 2, easily prepared (90% yield) by mixing equivalent amounts of spermidine and formalin solution in water,[4] formed imine 3 with benzaldehyde in quantitative yield [benzene, rt; bp 175° (0.1 torr)].[5] Conjugate addition of 3 to acrylonitrile (1.1 equiv, EtOH, rt, 15h) produced cyanoimine 4 [99% distilled yield, bp 180-184° (0.15 torr); NMR δ ($CDCl_3$) 3.26 (s, 2H $-NCH_2N-$), 3.53 (t, 2H, $=NCH_2-$), 7.33-8.0 (m, 5H), 8.40 (s, 1H, $-CH=N-$); IR λ_{max} (film) 4.44, 6.07 mμ; mass spectrum (electron impact) m/e 298 (M^+)].[5] Simultaneous hydrolysis of both the imine and heterocyclic groups using 2N HCl-CH_3OH (77-79°, 8h) liberated triaminonitrile 5 which could be purified by distillation [50%, bp 165-170° (0.25 torr); m/e 198 (M^+)].[5] Sodium borohydride in the presence of $CoCl_2$ smoothly reduced 5 to thermospermine [70% distilled, bp 105-108° (0.25 torr)] which could be further purified by reprecipitation of its hydrochloride salt (mp > 260°). Synthetic thermospermine exhibited spectral data identical in every respect with those recorded for the natural material.[3] Both ^{13}C-NMR and mass spectrometry were particularly characteristic for 1 and clearly distinguished it from the more commonly occurring symmetric isomer spermine. We believe the 31% overall yield of thermospermine from commercially available spermidine underscores the practicality of this approach.



Acknowledgment: We thank the National Institutes of Health for generous financial support.

REFERENCES AND FOOTNOTES

1. Fellow of the Alfred P. Sloan Foundation, 1978-1980; Recipient of a Camille and Henry Dreyfus Teacher-Scholar Grant, 1978-1983.
2. "Advances in Polyamine Research," Vols 1 and 2, R.A. Campbell, D.R. Morris, D. Bartos, G.D. Daves and F. Bartos, eds., (Raven Press, New York) 1978.
3. T. Oshima, J. Biol. Chem., 254, 8720 (1979).
4. For Part 1 of this series, see J.S. McManis and B. Ganem, "Total Synthesis of Celacinnine, Celabenzine and Maytenine," J. Org. Chem., in press.
5. Satisfactory elemental analysis was obtained for this compound.

(Received in USA 11 March 1980)