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TRANSAMIDATION REACTIONS IN THE FORMATION OF MACROCYCLIC LACTAMS. A TOTAL SYNTHESIS OF CELACINNINE.

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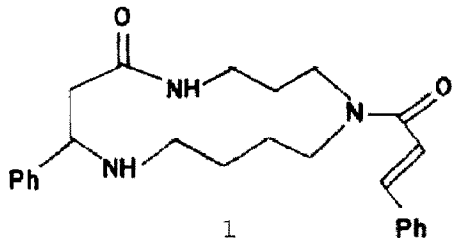
SUMMARY: The macrocyclic spermidine alkaloid, celacinnine, has been synthesized by methods involving successive ring expansion reactions. One route starts with 4-phenyl-2-azetidinone; another, with piperidazine.

Celacinnine (1) is a member of a family of plant products derived from polyamine units which show notable biological activity.[1,2] We have recently investigated the application of transamidation reactions to the synthesis of macrocyclic lactams, and now report a total synthesis of 1 involving successive expansions of smaller rings to form the 13-membered system. The ring expansion procedures applied here suggest new routes toward the formation of other large ring systems incorporating spermine or spermidine units.



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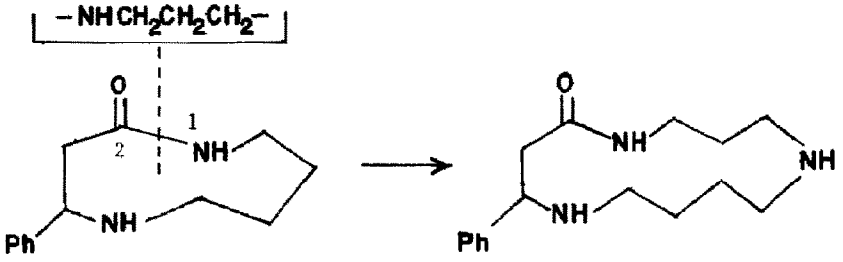

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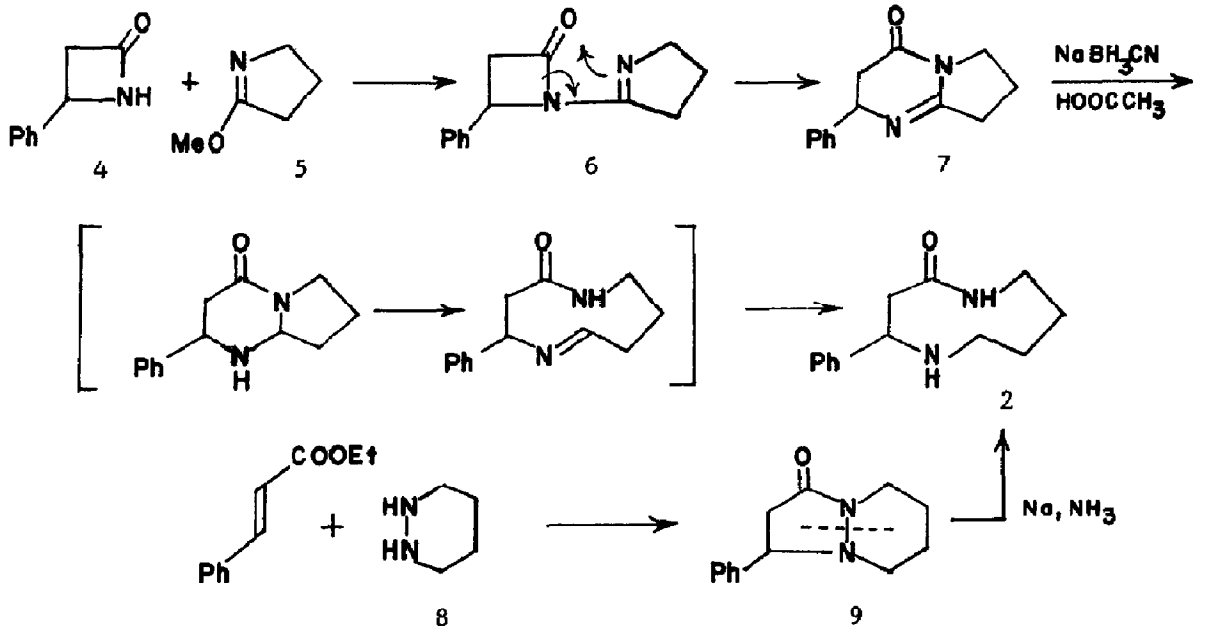
The first step in the synthesis involved construction of lactam 2, incorporating nine members of the celacinnine ring skeleton. Conversion of 2 to 3 (the precursor of 1) requires insertion of an aminopropyl residue between N-1 and C-2 as shown. We were able to accomplish this second-stage ring expansion by an alkylation-transamidation sequence.[14]

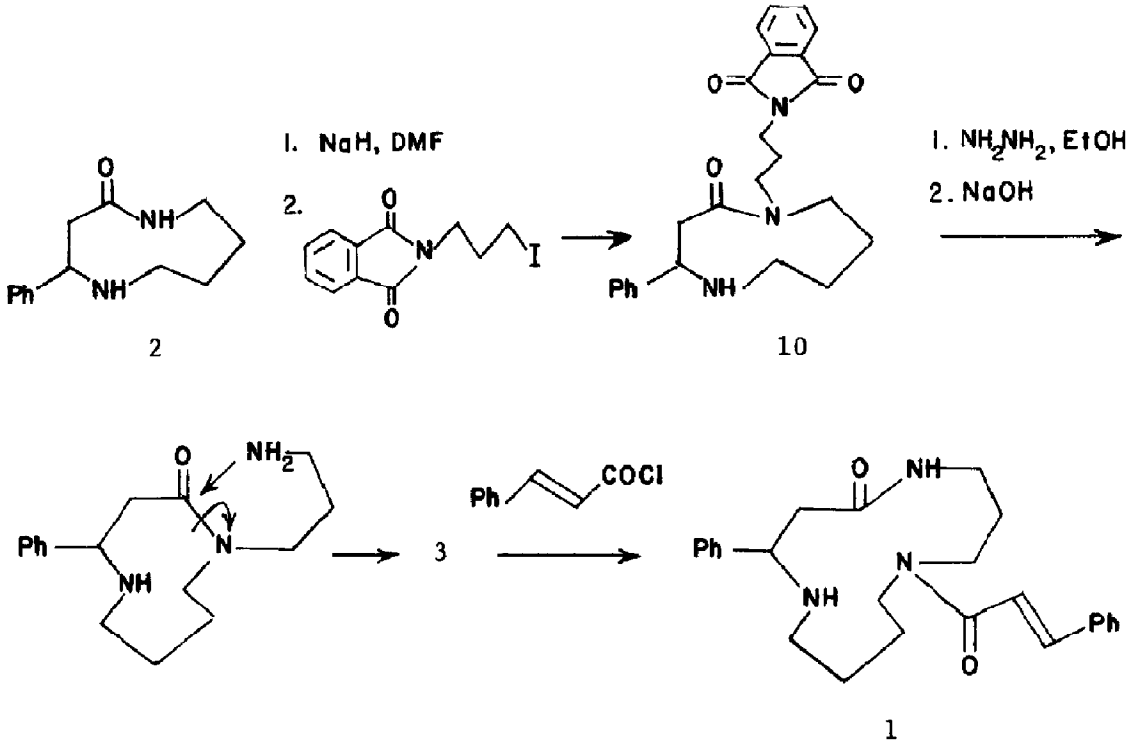
Two methods were developed for the formation of the nine-membered lactam (2). The first made use of the bicyclic 4-oxo-tetrahydropyrimidine (7) prepared by heating 4-phenylazetidinone (4) with 2-methoxypyrroline (5). This reaction, reported earlier by Bormann[3] appears to involve intramolecular ring opening of an intermediate N-pyrrolinyl-β-lactam (6).[4] Reductive cleavage[5] of 7 took place by reaction with excess $NaBH_3CN$ in the presence of HOAc (20°, 24 hr) followed by work up in aqueous NaOH forming 2, m.p. 87-88° (31%).[6,7,8]



An alternative route to 2, starting with piperidazine (8), proved to be more efficient. Thus, heating 8 with ethyl cinnamate for 27 hr generated 2-oxo-4-phenyl-1,5-diazabicyclo[4.3.0]nonane (9) 71%, m.p. 65-66°.[7,9] Fission of the N-N bond in 9 took place with Na/NH_3 (2.5 equiv, reflux 1.25 hr) yielding 2 (80%).[10]

Selective alkylation of the amide NH group (25%) was achieved by treatment of 2 with NaH (1.5 equiv) in DMF at 50° followed by addition of N-(3-iodopropyl)-phthalimide (1.1 equiv) at 25°. The product (10),[7,11] m.p. 122-123° was heated to reflux in ethanol with $H_2N-NH_2 \cdot H_2O$ (5 equiv) followed by warming in 1N NaOH at 50°[12] to yield 3 (70%) from 10 as a white solid, m.p. 128-131°.[13,14] Lactam 3 was then converted to celacinnine (1) (40%) by acylation with trans-cinnamoyl chloride as reported by Ganem.[2] The synthetic celacinnine is identical in all respects (NMR, IR, TLC behavior) with the authentic material.[15]

We are continuing to investigate the use of transamidation reactions in the synthesis of other macrocyclic lactams in the polyamine field.



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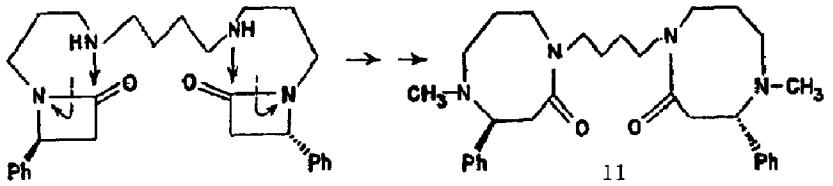
References and Notes

1. (a) S.M. Kupchan, H.P.J. Hintz, R.M. Smith, A. Karim, M.W. Cass, W.A. Court, and M. Yatagai, Chem. Soc. Chem. Commun., 329 (1974); (b) Idem, J. Org. Chem., 42, 3660 (1977).

2. For a recent total synthesis of celacinnine see J.S. McManis and B. Ganem, J. Org. Chem., 45, 2041 (1980).

3. D. Bormann, Chem. Ber., 103, 1797 (1970).

4. We are reporting separately the synthesis of homaline (11), by an intramolecular β-lactam rin opening. H.H. Wasserman and G.D. Berger, to be published. See abstracts of the 180th Am. Che Soc. meeting, San Francisco, California (1980).



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5. Related reductive cleavage reactions of hexahydropyrimidine derivatives are reported by K. Ch trapromma, J.S. McManis and B. Ganem, Tetrahedron Letters, 0000 (1980) and references therein

6. Yields reported refer to products purified by chromatography (silica gel or alumina). NMR wer obtained on a Bruker HX 270 instrument.

7. A satisfactory elemental analysis was obtained.

8. IR ($CDCl_3$) 3341, 1670, 1549 cm^{-1}; NMR ($CDCl_3$) δ 7.40-7.22 (5H, m, phenyl), 6.98 (1H, broad s, CO), 3.86-3.67 (1H, m, CH-N-CO), 3.58 (1H, dd, J=2.2, 12.2 Hz, Ph-CH), 2.90-2.70 (3H, m, CH_2-CH-N-CO), 2.52 (1H, t, J=12.2 Hz, CO-CH), 2.37 (1H, dd, J=2.2, 12.2 Hz, CO-CH), 1.98-1.32 (5H, inner CH_2, NH).

9. IR ($CDCl_3$) 1676 cm^{-1}; NMR ($CDCl_3$) δ 7.44-7.25 (5H, m, phenyl), 4.18 (1H, broad d, J=12.4 Hz, C N-CO), 3.84 (1H, dd, J=8.1, 11.7 Hz, Ph-CH), 3.08-2.98 (2H, m, CH_2-N-N-CO), 2.88 (1H, dd, J=8 16.8 Hz, CO-CH) 2.56 (1H, dd, J=11.7, 16.8 Hz, CO-CH), 2.30-2.21 (1H, m, CH-N-CO), 1.77-1.33 m, inner CH_2).

10. Cleavage of 1,2-diacyl hydrazides with Na/NH_3 has been reported by D.S. Kemp, M.D. Sidell, an T.J. Shortridge, J. Org. Chem., 44, 4473 (1979).

11. IR ($CDCl_3$) 1771, 1713, 1615 cm^{-1}; NMR ($CDCl_3$) δ 7.87-7.66 (4H, m, phth), 7.38-7.20 (5H, m, ph nyl), 4.86-4.75 (1H, m, CH-N-CO), 4.00-3.89 (1H, m, CH-N-CO), 3.78-3.71 (3H, m including t at 3.73, J=7.0 Hz, CH_2-phth, Ph-CH), 3.33-3.26 (1H, m, CH-N-CO), 3.16 (1H, dd, J=11.0, 12.5 Hz, C CH), 3.11-2.76 (3H, m, CH_2-NH, CH-N-CO), 2.59 (1H, d, J=12.5 Hz, CO-CH), 2.05-1.33 (7H, m, in CH_2, NH).

12. J.A. Davies, C.H. Hassall, and I.H. Rogers, J. Chem. Soc., (C), 1358 (1969).

13. IR ($CDCl_3$) 3240, 1638, 1526 cm^{-1}; NMR ($CDCl_3$) δ 8.56 (1H, broad s, NH-CO), 7.38-7.17 (5H, m, phenyl), 3.93 (1H, dd, J=5.0, 9.0 Hz, CH-Ph), 3.79-3.62 (1H, m, CH-N-CO), 3.31-3.11 (1H, m, C N-CO), 2.93-2.32 (8H, m, CH_2-CO, CH_2-NH), 2.29-1.98 (2H, broad s, NH), 1.82-1.33 (6H, m, inne CH_2).

14. This ring expansion exemplifies one of the steps observed in the "zip" reaction reported by Schmid et. al. for the sequential incorporation of aminopropyl units in the construction of m crocyclic lactams. U. Kramer, A. Guggisberg, M. Hesse, and H. Schmid, Angew. Chem. Int. Ed. Engl., 16, 861 (1977).

15. Celacinnine: IR ($CDCl_3$) 3450, 3210, 1656 (sh), 1649, 1598, 1548, 1520, 1496 cm^{-1}; NMR ($CDCl_3$ 7.71 (1H, d, J=15.5 Hz, =CH-Ph), 7.51-7.21 (11H, m, phenyl, NH-CO), 6.85 (1H, dd, J=5.0, 15. =CH-CO), 3.97 (1H, m, CH-Ph), 3.85-3.06 (6H, m, CH_2-N-CO), 2.75-2.61 (1H, m, CH-NH), 2.58-2. (3H, m, CH-NH, CH_2-CO), 2.20-1.31 (7H, m, inner CH_2, NH).

16. We thank Dr. D.G. Lynn, University of Virginia and Dr. B. Ganem, Cornell University, for samp of authentic celacinnine.

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