Tetrahedron Letters Vol. 22, pp 23 - 24 0040-4039/81/0101-0023$02.00/0

TOTAL SYNTHESIS OF KUKOAMINE A, AN ANTIHYPERTENSIVE CONSTITUENT OF LYCIUM CHINENSE[1]

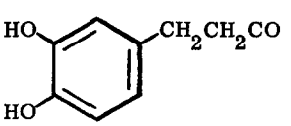
Kan Chantrapromma and Bruce Ganem[2*]

Department of Chemistry
Baker Laboratory
Cornell University
Ithaca, New York 14853

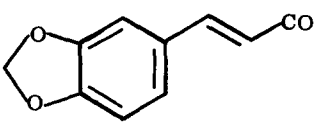
Summary: The active constituent of "jikoppi," a clinically effective Oriental medicine for hypertension, has been synthesized from spermine using new methodology for polyamine alkylation.

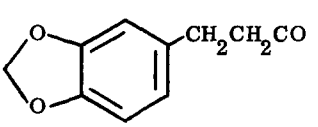
Among the many herbal extracts and plant preparations used for centuries by medical practitioners in Asia and the Orient, the crude drug "jikoppi" from root barks of Lycium chinense is of special interest to modern medicine. Besides being clinically effective against high blood pressure, this extract has been reported to exhibit hypoglycemic, fever-lowering and anti-stress-ulcer activity in experimental animals.[3] Earlier this year, Hikino and coworkers isolated polyamine derivative 1 from "jikoppi" and confirmed its antihypertensive activity.[3] Here we disclose a practical synthesis of 1 in which methodology we developed for selectively alkylating spermidine[1,4,5] has now been extended to the tetraamine 2, spermine.

$$RNH(CH_2)_3NH(CH_2)_4NH(CH_2)_3NHR$$

1 R = 

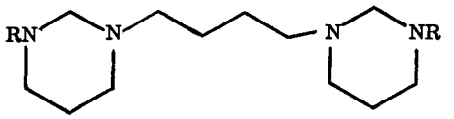
2 R = H

5 R = 

6 R = 

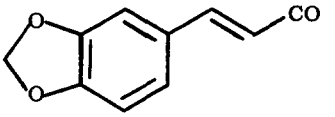
Direct acylation of 2 occurs randomly and affords a mixture of products. As with spermidine, this difficulty could be surmounted by tandem protection of spermine's two 1,3-diaminopropyl groups. Thus, 2 formed crystalline bis-hexahydropyrimidine 3, mp 82-83°C, in 95% yield upon treatment with aqueous formalin solution (1.8 eq, 0°, 50 min). Acylation of 3 with 3,4-methylenedioxycinnamoyl chloride (2 equiv, Et_3N, DMAP, 12h) furnished pure 4 (83%) as an amorphous solid [mp 160-161°; IR λ_{max} ($CHCl_3$) 6.08 mμ; m/e (CI) 574 (M+)].[6] Their purpose served, the gem-

diamine heterocycles in 4 were removed by a Knoevenagel reaction (Et, H-malonate, C_5H_5N, EtOH, heat, 2h, 83%) and the resulting caffeoylspermine derivative 5 (mp 124-28°) reduced with PtO_2-H_2-HOAc to bis-amide 6 in quantitative yield. Like kukoamine A, 4,5 and 6 were symmetrical by ^{13}C-NMR spectroscopy.[6,7]



3 R = H

4 R =



Cleavage of the methylenedioxy rings in 6 using excess BCl_3 (CH_2Cl_2, 0° → rt, 18h) gave synthetic 1 which could be purified by gel filtration (Sephadex LH-20) of its bis-hydrochloride salt (95% yield). Spectra and physical properties of (±) kukoamine A were fully in accord with the natural product.

Further biological studies should be aided by this ready synthesis of 1 in five steps and 62% overall yield.

Acknowledgment: We are grateful to the National Institutes of Health (AM 26754) for generous financial support.

REFERENCES AND FOOTNOTES

1. Part 4 of "The Chemistry of Naturally-Occurring Polyamines." For Part 3 see K. Chantrapromma and B. Ganem, Tetrahedron Lett., 21, 2605 (1980).

2. Fellow of the A. P. Sloan Foundation, 1978-82; Recipient of a Camille and Henry Dreyfus Teacher-Scholar Grant, 1978-83.

3. S. Funayama, K. Yoshida, C. Konno and H. Hikino, Tetrahedron Lett., 21, 1355 (1980) and references (2) and (3) therein.

4. J. S. McManis and B. Ganem, J. Org. Chem., 45, 2401 (1980).

5. K. Chantrapromma, J. S. McManis and B. Ganem, Tetrahedron Lett., 21, 2475 (1980).

6. Satisfactory IR, PNMR, MS and elemental analysis data were obtained for a chromatographically pure sample of this substance.

7. For 6: δ ($CDCl_3$) 171.7 (C=O), 147.23, 145.48 (aryl C-O), 134.52 (aryl C-), 120.80, 108.47, 107.86 (aryl C-H), 100.47 (O-C-O), 49.27, 47.56, 38.38 (C-CH_2-N), 38.15, 31.24 (aryl-C-C), 28.54, 27.50 (C-CH_2-C).

(Received in USA 8 August 1980)