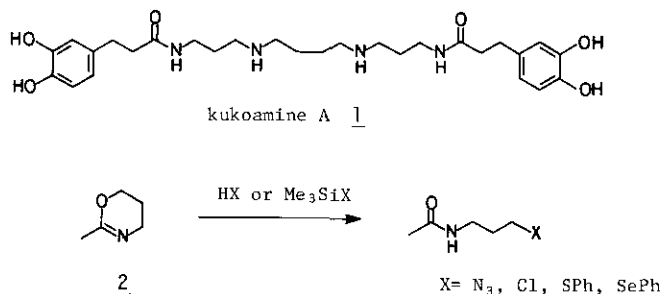


TOTAL SYNTHESIS OF KUKOAMINE A USING 2-METHYL-5,6-DIHYDRO-4H-1,3-OXAZINE
AS A CARBOXAMIDE BUILDING BLOCK

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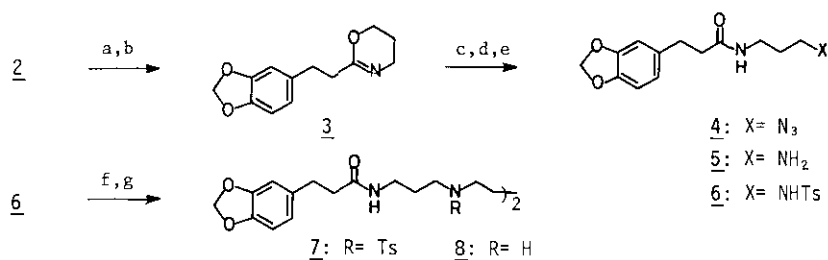
Abstract — Kukoamine A, the active constituent of Oriental medicine "Jikoppi" for hypertension, has been synthesized employing a new methodology for non-spermine-based polyamine construction.

The useful chemical reactivity that lurks in familiar 2-methyl-5,6-dihydro-4H-1,3-oxazine (2) has been revealed recently (Scheme 1).¹ Among the products accessible through this transformation, N-3-azidopropylacetamide seems to serve as a potent building block for polyamines. In order to put such strategy to test in making natural products which belong to a family of spermine and spermidine alkaloids, kukoamine A (1) was taken up as a target. This alkaloid was isolated from root barks of *Lycium chinese* by Hikino and coworkers who have disclosed as well that kukoamine A is responsible for antihypertensive activity,² one of remarkable physiological activities being exhibited by the above Oriental medicine of clinical interest.³



The first total synthesis of kukoamine A has been described by Chantraproma and Ganem,⁴ developing a selective acylating methodology for the terminal amino groups of spermine.⁵ Unlike this approach, we will present here a new approach to the polyamine derivative relying on the above-mentioned strategy which involves essentially three transformations as follows: alkylation of azaenolate of 2, nucleophilic ring opening of the oxazine moiety by hydrogen azide and subsequent reduction of the azide group to amino group, and coupling reaction of thus-obtained aminopropyl-

amide with 1,4-dibromobutane (Scheme 2).



a) LDA (1 eq)/THF/-78 °C, 1 h; b) piperonyl chloride (1 eq)/THF/-78 °C → rt; c) Me₃SiN₃ (1.05 eq)/MeOH (1.06 eq)/DMF/60 °C, 4 h; d) H₂/Pd-CaCO₃/EtOH/rt, 0.5 h; e) TsCl (1 eq)/Et₃N (1.01 eq)/CH₂Cl₂/0 °C, 0.5 h; f) Br(CH₂)₄Br (0.5 mol eq)/K₂CO₃ (5.9 eq)/CH₃CN/reflux 24 h; g) + 4e⁻/MeOH-CH₃CN(9:1)-Me₄NCl-(Pt-Hg)/rt (see reference 15)

Scheme 2.

Thus, azaenolate derived from 2⁶ (LDA/THF/-78 °C) was alkylated efficiently with piperonyl chloride⁷ (-78 °C, 0.5 h → rt) to give 2-(3,4-methylenedioxyphenylethyl)-5,6-dihydro-4H-1,3-oxazine (3)⁸, which, without any purification, was dissolved in dry DMF and to this solution were added chlorotrimethylsilane and methanol, successively, at 0 °C. The resulting mixture was heated at 60 °C for 4 h to furnish an expected azidoamide (4) in 75% yield from 2 after recrystallization (ether, -78 °C).⁹ The azido-group was, then, reduced to amino-group by the aid of Lindlar catalyst (H₂/EtOH/rt, 0.5 h)¹⁰, giving rise to N-(3-aminopropyl)amide derivative (5) in 97% yield.¹¹ At this stage 5 was reacted with 1,4-dibromobutane in a two-to-one mole ratio. Although a variety of combinations for both solvent and base were searched, no desired coupling reaction was effected, only giving pyrrolidine derivative in every case. Therefore, 5 was tosylated in a usual manner (TsCl/Et₃N/CH₂Cl₂/0 °C, 0.5 h) to afford tosylamide derivative (6) in 82% yield after purification by recrystallization of chromatographically pure 6 (benzene-ethyl acetate-ether).¹² Obviously 6 seems to allow alkylation of the terminal nitrogen atom with a usual alkyl halide. Thus, coupling reaction of 6 with 1,4-dibromobutane in a two-to-one fashion was successfully performed by the use of weak base (K₂CO₃) suspended in acetonitrile (reflux, 24 h) to give solely the desired product (7) in 97% yield after purification by silicagel chromatography.¹³ A carbon-13 nmr spectrum of this symmetrical molecule exhibited twenty signals reflecting the structure as such. An attempted detosylation from 7 using a conventional recipe (Na/liq NH₃) resulted in the formation of complex mixture. However, an electroreductive protocol gave a satisfactory solution to this problem.¹⁴ Thus, a solution of 7 in CH₃OH-CH₃CN (9 : 1) containing tetramethylammonium chloride as an electrolyte was electrolyzed using Pt-Hg electrodes in a divided cell.¹⁵ Four-faraday

electricity was enough to effect the desired transformation, giving a precursor of kukoamine A (8) in 90% yield. A carbon-13 nmr spectrum of 8 showed fifteen signals whose chemical shifts are fully consistent with those reported.¹⁶

As a conversion of 8 to kukoamine A has been already known,⁴ a formal total synthesis of 1 has been established based on non-condensative, non-spermine-based polyamine construction methodology which features 2 as amide building block. In view of the structural characteristics of the key intermediate 6 present strategy would be applicable to the total synthesis of other alkaloids of this family and make easy access to these possible which is now in progress.

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- 5) Professor Ganem and his coworkers have extended methodology for selectively alkylating spermidine to spermine; see also J. S. McManis and B. Ganem, *J. Org. Chem.*, 1980, 45, 2401, K. Chantraproma, J. S. McManis, and B. Ganem, *Tetrahedron Lett.*, 1980, 21, 2475, and K. Chantraproma and B. Ganem, *Tetrahedron Lett.*, 1980, 21, 2605.
- 6) Prepared as reported: H. Witte and W. Seeliger, *Liebigs Ann. Chem.*, 1974, 996.
- 7) Prepared by the reaction of corresponding alcohol with conc. HCl: *Org. Syn.*, Coll. Vol. IV, 1963, 576.
- 8) 3: ¹H nmr (CDCl₃) 1.79 (2H, quint, J=6 Hz), 2.1-3.0 (4H, m), 3.29 (2H, t, J=6 Hz), 4.06 (2H, t, J=6 Hz), 5.80 (2H, s), and 6.59 (3H, s) ppm; an attempted purification by silicagel chromatography resulted in significant decomposition of the oxazine moiety.
- 9) 4: mp 55-56 °C; ¹H nmr (CDCl₃) 1.72 (2H, quint, J=6.8 Hz), 2.41 (2H, m), 2.89 (2H, m), 3.30 (4H, m), 5.47 (1H, bs), 5.92 (2H, s), and 6.78 (3H, m) ppm; ir (CHCl₃) 3740, 2110, 1675, 1510, 1495, 1450, 1245, 1042, 940, and 815 cm⁻¹.
- 10) E. J. Corey, K. C. Nicolaou, R. D. Balanson, and Y. Machida, *Synthesis*, 1975, 590.
- 11) 5: mp 66-68 °C; ¹H nmr (CDCl₃) 1.56 (4H, m), 2.25-3.01 (6H, m), 3.29 (2H, m), 5.86 (2H, s),

and 6.64 (4H, m) ppm; ir (CHCl₃) 3460, 3340, 1662, 1502, 1490, 1440, 1240, 1035, 930, and 805 cm⁻¹.

12) 6: mp 89-90 °C; ¹H nmr (CDCl₃) 1.56 (2H, m), 2.28-2.43 (2H, m), 2.39 (3H, s), 2.71-2.91 (4H, m), 3.15-3.34 (2H, m), 5.82 (1H, TsNH, t, J=6.6 Hz), 5.87 (2H, s), 6.08 (1H, CONH, t, J=5.8 Hz), 6.49-6.71 (3H, m), 7.27 (2H, m), and 7.72 (2H, m) ppm; ir (CHCl₃) 3450, 3400, 3200, 1660, 1505, 1490, 1440, 1328, 1240, 1160, 1092, 1039, 932, and 810 cm⁻¹; ¹³C nmr (CDCl₃) 21.44 (q), 29.34 (t), 31.44 (t), 35.87 (t), 38.36 (t), 39.82 (t), 100.79 (t), 108.15 (d), 108.73 (d), 121.06 (d), 126.96 (d), 129.69 (d), 134.52 (s), 137.10 (s), 143.29 (s), 145.82 (s), 147.58 (s), and 173.21 (s) ppm; before subjecting to the coupling reaction with 1,4-dibromobutane, 6 should be highly purified by recrystallization even after column chromatography because, otherwise, the reaction gave considerable amount of one-to-one type coupling product.

13) 7: mp 130-133 °C; ¹H nmr (CDCl₃) 1.36-1.90 (4H, m), 2.26-2.55 (2H, m), 2.43 (3H, s), 2.75-3.14 (6H, m), 3.14-3.40 (2H, m), 5.88 (2H, s), 6.26 (1H, t, J=6 Hz), 6.57-6.82 (3H, m), 7.30 (2H, m), and 7.62 (2H, m) ppm; ir (CHCl₃) 3450, 1670, 1510, 1495, 1445, 1335, 1248, 1160, 1092, 1042, 938, and 815 cm⁻¹; ¹³C nmr (CDCl₃) 21.44 (q), 25.98 (t), 28.66 (t), 31.48 (t), 36.11 (t), 38.55 (t), 46.40 (t), 48.54 (t), 100.74 (t), 108.15 (d), 108.83 (d), 121.16 (d), 126.96 (d), 129.84 (d), 134.76 (s), 136.03 (s), 143.53 (s), 145.77 (s), 147.53 (s), and 172.29 (s) ppm.

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15) An H-shaped cell divided by a sintered glass filter (5G) was used. In a cathodic part was placed mercury (5 ml) into which a platinum wire was immersed and electrolytic solution [0.116 g of 7 in CH₃OH-CH₃CN (9 : 1) (13 ml) containing Me₄NCl (0.2 g)] was introduced to it. An anodic part was charged with CH₃OH (13 ml) containing the electrolyte (0.2 g) as well. While argon was bubbled into the cathodic room through a ball-like sintered glass, 50 mA of electricity was applied during 17 min. A tic monitoring indicated that no starting 7 remained and a usual workup gave crystalline 8 (0.068 g, 90% yield) as a sole product.

16) 8: mp 119-121 °C; ¹H nmr (CDCl₃) 1.25-1.75 (5H, -NH- and -CH₂-, m), 2.22-2.72 (6H, CH₂-N-CH₂, and COCH₂, m), 2.72-3.00 (2H, Ar-CH₂, m), 3.13-3.44 (2H, CON-CH₂, m), 5.90 (2H, O-CH₂-O, s), and 6.45-6.79 (4H, Ar-H and CONH, m) ppm; ir (CHCl₃) 3480, 3300, 1662, 1525, 1510, 1495, 1365, 1250, 1122, 1100, 1042, 940, and 812 cm⁻¹; ¹³C nmr (CDCl₃) 27.93 (t), 28.90 (t), 31.53 (t), 38.70 (t), 38.75 (t), 48.15 (t), 49.71 (t), 100.74 (t), 108.15 (d), 108.78 (d), 121.11 (d), 134.86 (s), 145.81 (s), 147.58 (s), and 171.95 (s) ppm [¹³C nmr chemical shift reported for 8; 27.50, 28.54, 31.24, 38.15, 38.38, 47.56, 49.27, 100.47, 107.86, 108.47, 120.80, 134.52, 145.48, 147.23, and 171.7 (see reference 4)].

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