Studies on the syntheses of heterocyclic compounds. Part 782. Another total synthesis of (±)-tubulosine and (±)-deoxytubulosine[1,2]

TETSUJI KAMETANI, YUKIO SUZUKI, AND MASATAKA IHARA
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Received December 13, 1978

TETSUJI KAMETANI, YUKIO SUZUKI, and MASATAKA IHARA. Can. J. Chem. 57, 1679 (1979).

(±)-Tubulosine (**1**) and (±)-deoxytubulosine (**3**) were totally synthesized by the Pictet–Spengler reaction of (±)-4-oxoprotoemetine (**7**) with serotonin (**8**) or tryptamine (**9**) followed by reduction with sodium bis(2-methoxyethoxy)aluminum hydride in pyridine.

TETSUJI KAMETANI, YUKIO SUZUKI et MASATAKA IHARA. Can. J. Chem. 57, 1679 (1979).

On a effectué des synthèses totales de la (±)-tubulosine (**1**) et de la (±)-désoxytubulosine (**3**) par la réaction de Pictet–Spengler de la (±)-oxo-4 protoemétine (**7**) avec la sérotonine (**8**) ou la tryptamine (**9**) suivie par une réduction à l'aide du $Na(CH_3OCH_2CH_2O)_2AlH_2$.

[Traduit par le journal]

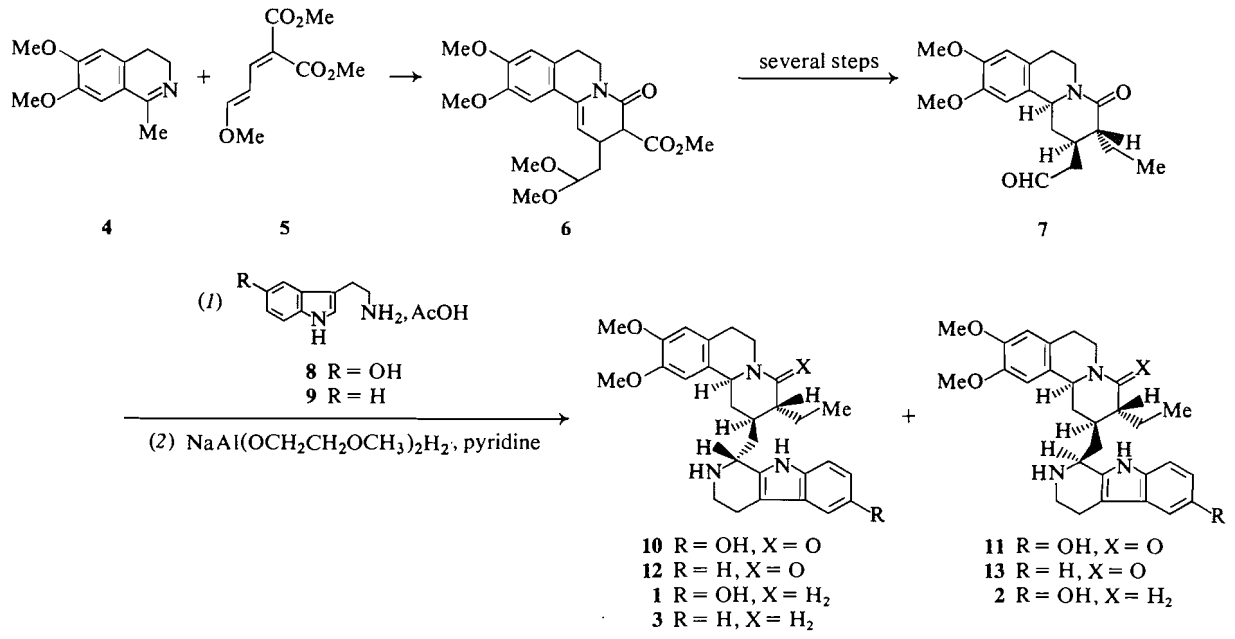
Tubulosine (**1**), isotubulosine (**2**), and deoxytubulosine (**3**) were isolated as levorotatory forms from the same plant, *Alangium lamarckii* (2). Tubulosine derivatives are known to inhibit the protein synthesis and expected to be potential antineoplastic agents (3). Recently we have developed a short synthetic route to emetine through (±)-4-oxoprotoemetine (**7**) which was stereoselectively prepared by the condensation of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (**4**) with dimethyl 3-methoxyallylidenemalonate (**5**) in several steps via the intermediate enamide **6** (Scheme 1). The total yield from **4** was 60% (4). Thus, we have examined the synthesis of tubulosine and related compounds from aldehyde **7**, and we wish to report here the total synthesis of the above alkaloids, during whose reaction a new method of reducing the amide group was also revealed.

Serotonin (**8**) is commercially available as a complex with creatinine sulfate and was liberated from the complex using Amberlite XAD-4 column chromatography. Condensation of **8** with (±)-4-oxoprotoemetine (**7**) was carried out by stirring an equimolecular mixture in acetic acid at room temperature for 2 days. The Mannich base, *m/e* 489 (M^+), obtained in high yield, consisted of (±)-4-oxotubulosine (**10**) and its C-1′ epimer (**11**) in a 4:1 ratio; the identities of **10** and **11** were verified by tlc and nmr (DMSO-d_6) analysis. The ratio did not change appreciably even when the reaction was carried out under more acidic conditions or at a higher temperature. The product was very insoluble in ordinary solvents and a separation of the diastereoisomeric mixture could not be achieved. Mainly because of its slight solubility, reduction of a mixture of **10** and **11** with lithium aluminum hydride in hot dioxane gave none of the desired product. Eventually the reduction was carried out by treatment of a mixture of **10** and **11** with sodium bis(2-methoxyethoxy)aluminum hydride in pyridine at room temperature for 1 h. The reduction product was purified by column chromatography and recrystallization from methanol to afford (±)-tubulosine (**1**), mp 249–250°C, whose nmr (DMSO-d_6) and mass spectra and chromatographic behavior (tlc and hplc) were identical with those of natural tubulosine donated by Prof. Szántay (4). (±)-Isotubulosine (**2**) was obtained as a minor product but could not be separated from **1** completely. However the structure of **2** was supported by the nmr spectrum (DMSO-d_6), which exhibited one of the methoxyl groups at high field (3.49 ppm) (**6**), and tlc behavior on silica gel, which showed the compound to have a lower R_f value than that of tubulosine (5–7). The preferential formation of tubulosine (**1**) over isotubulosine (**2**) in the Pictet–Spengler reaction using (−)-protoemetine and serotonin (**8**) was also observed by Szántay and Kalaus (5).

Stirring a mixture of aldehyde **7** and tryptamine (**9**) hydrochloride in acetic acid at room temperature for 2 days yielded a mixture of (±)-4-oxodeoxytubulosine (**12**) and its epimer (**13**) in a 4:1 ratio. The former (**12**) was obtained in pure form after preparative thin-layer chromatography and was reduced with sodium bis(2-methoxyethoxy)aluminum hydride in pyridine under the same condition as above to furnish (±)-deoxytubulosine (**3**), mp 156–158°C. The nmr spectrum ($CDCl_3$) of this product was superimposable upon that of an authentic sample of compound **3** given to us by Prof. Battersby. Since lactam **12** was soluble in hot dioxane, reduction with

[1]Dedicated to the memory of R. H. F. Manske.
[2]For Part 781, see ref. 1.

0008-4042/79/131679-03$01.00/0



SCHEME 1[3]

lithium aluminum hydride under reflux was examined but **3** was obtained in very poor yield. Sodium bis(2-methoxyethoxy)aluminum hydride reduced the tertiary amides under mild condition in pyridine and the limit and the scope of this reduction is under investigation.

Experimental

Melting points were determined with a Yanaco micro-melting point apparatus and are uncorrected. Infrared spectra were taken with a Hitachi 215 spectrophotometer. Nuclear magnetic resonance spectra were measured with a JNM-PMX-60 instrument with tetramethylsilane as an internal standard. Mass spectra were taken with Hitachi M-52 spectrometer.

(±)-Tubulosine (1)

A solution of serotonin (**8**) – creatinine sulfate complex (300 mg) in water (50 mL) was subjected to Amberlite XAD-4 (80 mL) column chromatography. After elution with water (100 mL), an eluate of methanol–water (1:1 v/v) gave serotonin (124 mg), which was judged free from creatinine sulfate on the basis of its nmr analysis.

A mixture of serotonin (**8**) (124 mg) and (±)-4-oxoprotoemetine (**7**) (217 mg) in AcOH (30 mL) was stirred for 2 days at room temperature. The solvent was evaporated to give a caramel which was dried under reduced pressure. To a stirred 70% solution of $NaAl(OCH_2CH_2OCH_3)_2H_2$ in toluene (2 mL) was added a solution of the above material in pyridine (2 mL) and the resulting solution was stirred for 1 h at room temperature. The solvents were evaporated and excess reagent was decomposed and neutralized by the addition, under ice-cooling, of a saturated NH_4Cl solution. The resulting mixture was extracted several times with $CHCl_3$. The $CHCl_3$ extract was washed with a saturated NaCl solution, dried (Na_2SO_4), and evaporated to give a reddish viscous material which was purified by column chromatography on silica gel. Elution with $CHCl_3$–MeOH (20:1 v/v), followed by concentration of the solvent, gave a solid, which was recrystallized from MeOH to afford (±)-tubulosine (**1**) (65 mg, 21%) as fine colorless needles, mp 249–250°C, the mass and nmr (DMSO-d_6) spectra and hplc and tlc behavior of which were identical with those of natural tubulosine. *Anal.* calcd. for $C_{29}H_{37}N_3O_3 \cdot 2H_2O$: C 68.08, H 8.08; found: C 67.86, H 7.79.

Further elution with the same solvent gave a fraction which mainly consisted of (±)-isotubulosine (**2**) and a small amount of (±)-tubulosine which were not separable by recrystallization.

(±)-4-Oxodeoxytubulosine (12)

A mixture of (±)-4-oxoprotoemetine (**7**) (150 mg) and tryptamine (**9**) hydrochloride (90 mg) in AcOH (5 mL) was stirred for 2 days at room temperature. After evaporation of the solvent, the residue was basified with a saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with a saturated NaCl solution, dried (Na_2SO_4), and evaporated to give a syrup, which was purified by ptlc on silica gel to afford (±)-4-oxodeoxytubulosine (**12**) (128 mg, 59.8%) as a syrup; ir ν_{max} ($CHCl_3$): 1620 cm^{-1} (C=O); nmr ($CDCl_3$) δ: 1.00 (3H, m, CH_2CH_3), 3.93 (6H, s, 2 × OMe), 6.67 and 6.87 (2H, each s, 2 × ArH); ms *m/e* 473 (M^+).

(±)-Deoxytubulosine (3)

To a stirred 70% solution of $NaAl(OCH_2CH_2OCH_3)_2H_2$ in toluene (2 mL) was added (±)-4-oxodeoxytubulosine (**12**) (128 mg) in pyridine (2 mL) and the solution was stirred for 1 h at room temperature. The solvents were removed and excess reagent was decomposed and neutralized by the addition, with ice cooling, of a saturated NH_4Cl solution. The resulting mixture was extracted with $CHCl_3$. The extract was washed with a saturated NaCl solution, dried (Na_2SO_4), and evaporated to give a reddish viscous material which was dissolved in 2% HCl (5 mL). The resulting solution was washed with Et_2O. The aqueous layer was basified with solid $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with a

[3]All compounds having chiral centers are racemates.

saturated NaCl solution, dried (Na_2SO_4), and evaporated to give a reddish solid. Recrystallization from $CHCl_3$–MeOH gave (±)-deoxytubulosine (**3**) (51 mg, 41%) as colorless needles, mp 156–158°C; the nmr spectrum ($CDCl_3$) was identical with that of the authentic sample (**3**); ms *m/e* 459 (M^+). *Anal.* calcd. for $C_{29}H_{37}N_3O_2 \cdot H_2O$: C 72.86, H 8.23, N 8.80; found: C 72.65, H 8.18, N 8.75.

Acknowledgments

We thank Prof. C. Szántay and Prof. A. R. Battersby for their kind gifts of (−)-tubulosine and of an nmr spectrum of deoxytubulosine, respectively. We also thank Mr. K. Kawamura, Mrs. C. Koyanagi, Miss K. Mushiake, Mrs. R. Kobayashi, Miss M. Tanno, Miss K. Katsuma, Miss K. Kikuchi, Miss. Y. Katoh, and Miss J. Okazaki for microanalyses and spectral measurements and for the preparation of this manuscript.

1. T. Kametani, Y. Kigawa, H. Nemoto, M. Ihara, and K. Fukumoto. Heterocycles, **12**, 685 (1979).
2. T. Kametani. The chemistry of the isoquinoline alkaloids. Vol. I. Elsevier Publishing Co., New York. 1969. p. 163; Vol. II. Kinkodo Publishing Co., Sendai, Japan. 1974. pp. 266–267.
3. R. S. Gupta and L. Siminovitch. Biochemistry, **16**, 3209 (1977); C. Pareyre and G. Deysson. Cell Tissue Kinet. **8**, 67 (1975); C. Pareyre. Bull. Soc. Bot. Fr. **121**, 3 (1974); R. K. Johnson and W. R. Washington. Biochem. J. **140**, 87 (1974); C. Pareyre and G. Deysson. C. R. Acad. Sci. Ser. D. **277**, 2689 (1973).
4. T. Kametani, Y. Suzuki, H. Terasawa, M. Ihara, and K. Fukumoto. Heterocycles, **8**, 119 (1977); T. Kametani, Y. Suzuki, H. Terasawa, and M. Ihara. J. Chem. Soc. Perkin Trans. I. In press.
5. C. Szántay and G. Kalaus. Chem. Ber. **102**, 2270 (1969).
6. A. Popelak, E. Haack, and H. Spingler. Tetrahedron Lett. 5077 (1969).
7. H. T. Openshaw and N. Whittaker. J. Chem. Soc. C, 91 (1969).
8. A. R. Battersby, J. R. Merchant, E. A. Ruveda, and S. S. Salgar. Chem. Commun. 315 (1965); A. R. Battersby, R. S. Kapil, D. S. Bhakuni, S. P. Popli, J. R. Merchant, and S. S. Salgar. Tetrahedron Lett. 4965 (1966).