[Chem. Pharm. Bull. 27(12)3183—3185(1979)]

UDC 547.822.3.04 : 547.558.1.04

A Versatile Synthesis of (±)-Solenopsin A

KAORU FUJI, KOHEI ICHIKAWA,[1] and EIICHI FUJITA[1a]

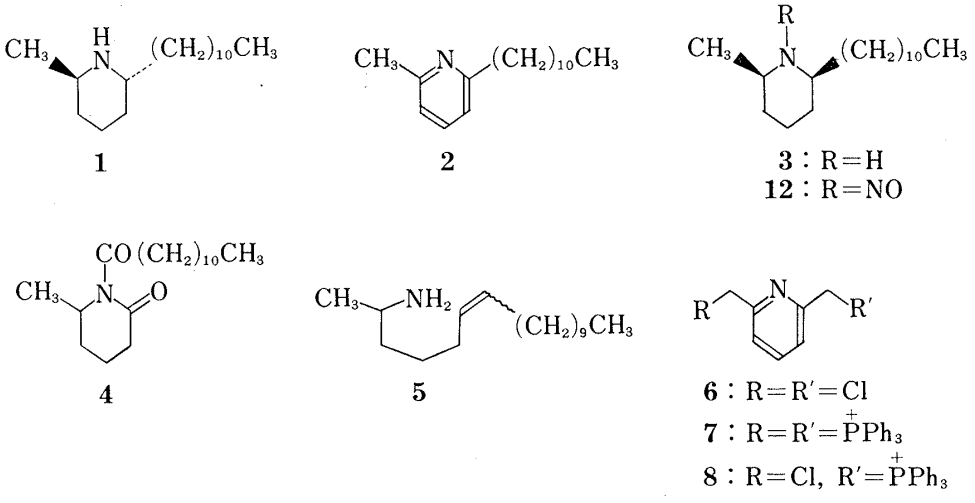
Institute for Chemical Research, Kyoto University[1]

(Received June 8, 1979)

A versatile total synthesis of fire ant venom, solenopsin A (**1**), is described.

Keywords——fire ant venom; *Solenopsis saevissima*; N-nitroso-2,6-disubstituted piperidine; *trans*-2-methyl-6-*n*-undecylpiperidine; *cis*-2-methyl-6-*n*-undecylpiperidine; total synthesis

A fire ant venom, solenopsin A (**1**),[2] isolated from *Solenopsis saevissima* exhibits pronounced hemolytic,[3] insecticidal, and antibiotic[4] activities. The first synthesis of (±)-solenopsin A (**1**) has been achieved by the reduction of the 2,6-disubstituted pyridine derivative **2** with sodium metal in absolute ethanol.[2] However, the yield of solenopsin A (**1**) was only 18% and a 52% yield of the undesired *cis* isomer **3** was obtained. The Mundy rearrangement[5] of the N-acyllactam **4** followed by hydride reduction has given a 1:4 mixture of solenopsin A (**1**) and the *cis* isomer **3** in poor yield.[6] Another interesting synthesis involving the intramolecular aminomercuration of the olefin **5** followed by hydride reduction also afforded

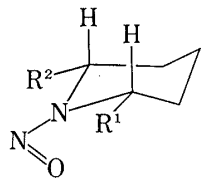


Scheme

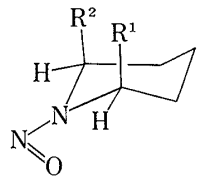
1) Location: *Uji, Kyoto-Fu 611, Japan*; *a*) To whom inquiries should be addressed.
2) J.G. MacConnell, M.S. Blum, and H.M. Fales, *Tetrahedron*, **27**, 1129 (1971). The absolute stereochemistry has not been determined.
3) G.A. Adrouny, V.J. Derbes, and R.C. Jung, *Science*, **130**, 449 (1959).
4) M.S. Blum, J.R. Walker, P.S. Callahan, and A.F. Novak, *Science*, **128**, 306 (1958).
5) B.P. Mundy, K.B. Lipkowitz, M. Lee, and B.R. Larsen, *J. Org. Chem.*, **39**, 1963 (1974), and references cited therein.
6) R.K. Hill and T. Yuri, *Tetrahedron*, **33**, 1569 (1977).

a poor yield (11%) of solenopsin A (**1**) accompanied by a 41% yield of the *cis* isomer **3**.[7] The yields and stereoselectivities of these three syntheses are not satisfactory from the viewpoint of obtaining a large supply of the compound for biological testing. Thus, a direct, stereoselective method is required or, alternatively, an efficient method must be found for converting the *cis* isomer **3** into solenopsin A (**1**). Here we describe a total synthesis of (±)-solenopsin A (**1**) based on the latter approach.

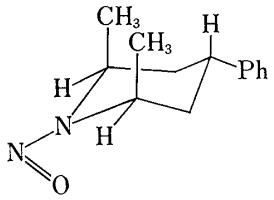
We have reported that the reaction of 2,6-bis(chloromethyl)pyridine (**6**) with triphenylphosphine in refluxing dimethylformamide afforded the diphosphonium salt **7** in 88% yield.[8] On the other hand, the monophosphonium salt **8** was obtained from the same reaction in refluxing benzene. The Wittig reagent **9** prepared from **8** with sodium hydride in dichloromethane was allowed to react with decanal (**10**) to give a *cis*/*trans* mixture **11** in 80% yield. Catalytic reduction of **11** over Raney Ni and PtO_2 under high pressure gave *cis*-2-methyl-6-*n*-undecylpiperidine (**3**), mp 147—148°, in 77% yield. The reaction of **3** with isoamyl nitrite gave rise to the N-nitroso derivative **12** in 94% yield. The observation that the nuclear magnetic resonance (NMR) spectrum of **12** exhibited two methyl doublets at δ 1.10 and 1.44 in a ratio of 3:2 indicated compound **12** to be a mixture of two out of the four stereoisomers **12a—d.**



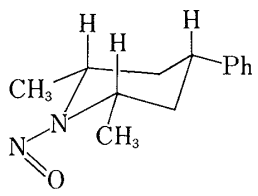
12a : $R^1=CH_3$, $R^2=(CH_2)_{10}CH_3$
12b : $R^1=(CH_2)_{10}CH_3$, $R^2=CH_3$



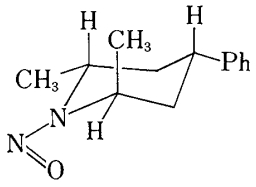
12c : $R^1=CH_3$, $R^2=(CH_2)_{10}CH_3$
12d : $R^1=(CH_2)_{10}CH_3$, $R^2=CH_3$



13



14



15

Equilibrium studies of 2,6-dimethyl derivatives of N-nitroso-4-phenylpiperidine by Fraser *et al.*[9] have shown that the *cis* isomer **13** is at least 1.4 kcal more stable than another *cis* isomer **14**. The structures **12a** and **12b** can therefore be excluded for the mixture **12**. It has been reported that the axial methyl group *syn* to the oxygen atom of the nitroso group in 6-membered N-nitrosamines resonates at higher field than that *anti* to the nitroso oxygen.[10] Thus, it was concluded that the nitrosamine **12** is a mixture of **12c** and **12d** with about 60% of **12c**.

Based on Fraser's observation[9] that the *trans* isomer **15** is 0.8 kcal more stable than the *cis* isomer **13**, the N-nitroso derivative **12** was treated with potassium t-butoxide in dimethyl sulfoxide at 90—100° for 60 hr under nitrogen, then subjected to hydrogenolysis over Raney Ni[11] to give an oil in 94% yield. Gas chromatography with an FFAP column

7) Y. Moriyama, D. Doan-Huynh, C. Monneret, and Q. Khuong-Huu, *Tetrahedron Lett.*, **1977**, 852.
8) K. Fuji, K. Ichikawa, and E. Fujita, *Tetrahedron Lett.*, **1979**, 361.
9) R.T. Fraser, T.B. Grindley, and S. Passannanti, *Can. J. Chem.*, **53**, 2473 (1975).
10) R.K. Harris and R.A. Spragg, *J. Mol. Spectrosc.*, **23**, 158 (1967).
11) D. Enders, T. Hassel, R. Pieter, B. Renger, and D. Seebach, *Synthesis*, **1976**, 548.

gave two peaks of almost equal intensity. The peak having shorter retention time shown to be the *cis* isomer **3** and that having longer retention time was proved to be identical with an authentic sample of (±)-solenopsin A (**1**).[2] Though the proportion of solenopsin A (**1**) is not satisfactory, repetition of the process (nitrosation, equilibration, and denitrosation) finally permits the full conversion of the *cis* isomer **3** into solenopsin A (**1**) in principle. Thus a versatile synthesis of solenopsin A was achieved.

Experimental

Melting points were determined on a micro hot-stage and are uncorrected. Infrared (IR) spectra were recorded with a Hitachi EPS-3 spectrophotometer, and NMR spectra with a JEOL JNM-FX 100 spectrometer at 100 MHz. Analytical gas chromatography (GLC) was performed on a Shimadzu GC-4CM gas chromatograph equipped with a flame ionization detector. Preparative separation was carried out with a Varian Aerograph model 920 gas chromatograph with a thermal conductivity detector.

Synthesis of 8——A solution of 2,6-bis(chloromethyl)pyridine (**6**) (1.76 g) and triphenylphosphine (5.24 g) in benzene (100 ml) was heated under reflux for 6 hr and then cooled in ice-water to give a crude crystalline material. Recrystallization from benzene–$CHCl_3$ afforded **8** (3.2 g, 74%), mp 280—285° (dec.). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1591, 1488, 1441. NMR ($CDCl_3$) δ: 4.25 (2H, s), 5.82 (2H, d, J=15 Hz), 7.00—8.46 (18H, m). *Anal.* Calcd. for $C_{25}H_{22}NPCl_2$: C, 68.50; H, 5.06; N, 3.20. Found: C, 68.77; H, 5.12; N, 3.16.

Synthesis of *cis*-2-Methyl-6-*n*-undecylpiperidine (**3**)——A solution of **8** (876 mg) in CH_2Cl_2 (20 ml) was treated with sodium hydride (47% dispersion in mineral oil, 102 mg). After stirring for 30 min at room temperature, decanal (**10**) (312 mg) was added. The mixture was heated under reflux for 3 hr, filtered, and evaporated down to give a crude oil which was chromatographed on silica gel. Elution with hexane gave a mixture **11** (445 mg, 80%).

The mixture **11** (445 mg) in MeOH (50 ml) was hydrogenated overnight over Pd-C (500 mg) and Raney Ni (W-2) at a preseure of 50 atm at 60°. The catalyst was removed by filtration and the filtrate was concentrated. The residue was chromatographed on silica gel. Elution with MeOH gave *cis*-2-methyl-6-*n*-undecylpiperidine (**3**) (311 mg, 77%), mp 147—148°, which was identical with an authentic sample (NMR spectrum, thin layer chromatogram, and gas-liquid phase chromatography).

Nitrosation of *cis*-2-Methyl-6-*n*-undecylpiperidine (**3**)——A mixture of *cis*-2-methyl-6-*n*-undecylpiperidine (**3**) (50 mg) and isoamyl nitrite (0.5 ml) in CH_2Cl_2 (1.5 ml) was stirred for 2 hr, then evaporated down to leave a crude oil. Chromatography over alumina with CH_2Cl_2 gave an oil **12** (52 mg, 94%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1622, 1460. NMR ($CDCl_3$) δ: 0.87 (3H, t, J=4.4 Hz), 1.10 and 1.44 (in a ratio of 3: 2, total 3H, each d, J= 7.0 Hz), 1.15—1.80 (20H, m), 1.87 (6H, m), 5.00 (2H, m). *Anal.* Calcd. for $C_{17}H_{34}N_2O$: C, 72.28; H, 12.13; N, 9.92. Found: C, 72.36; H, 12.18; N, 9.93.

Solenopsin A (**1**)——The N-nitroso derivative **12** (765 mg) was heated to 90—100° with *t*-BuOK (1.2 g) in dimethyl sulfoxide (7 ml) for 60 hr under nitrogen. An oil obtained by extractive workup with ether was hydrogenolyzed overnight in 50 ml of methanol over Raney Ni (W-2) at 60° under 30 atm of hydrogen. Filtration and removal of the solvent gave an oil which was chromatographed over alumina. Elution with dichloromethane-methanol afforded an oil (632 mg, 94%). Analysis of the oil by GLC (FFAP, 180°) showed that it was a mixture of solenopsin A (**1**) (retention time (t_R) 11.7 min) and the *cis* isomer **3** (t_R 8.5 min). Solenopsin A (**1**) was isolated from the mixture by preparative GLC; it was identical with authentic solenopsin A (NMR and IR spectra).

Acknowledgement We are grateful to Dr. Ito, Toagosei Chemical Industry Co. Ltd., for a gift of 2,6-bis(chloromethyl)pyridine, and to Dr. H.M. Fales, National Heart Institute, U.S.A., for providing an authentic sample of solenopsin A.