Note

Synthesis of *N'*-(3-Hydroxy-12-methyltridecanoyl)nornicotine

Hideyuki KUNO, Makoto SHIBAGAKI,
Toshiaki MATSUZAKI,* Masashi MIYANO,
Norio YASUMATSU,* Hajime MATSUSHITA
and Akira KOIWA

Life Science Research Laboratory,
Japan Tobacco Inc.,

*Tobacco Science Research Laboratory,
Japan Tobacco Inc.,

6-2 Umeoka, Midori-ku, Yokohama,
Midori-ku, Yokohama,
Kanagawa 227, Japan

Received June 28, 1988

The *N'*-acylnornicotine have been isolated from tobacco leaves.^{1~5)} Recently, Zador and Jones described the isolation and biosynthesis of the novel compound, *N'*-(3-hydroxy-12-methyltridecanoyl)nornicotine (**1**), in the trichomes of *Nicotiana stocktonii*.⁶⁾ It is known that **1** was selectively toxic to the larvae of *Manduca sexta*.⁷⁾

In our laboratory, compound **1** was isolated independently from leaf-surface resin of the genus *Nicotiana*, section Repandae, as one of the main components, and the inhibitory effect on tobacco seed germination was examined.⁸⁾

The present paper deals with the synthesis of the acylnornicotine. 8-Methylnonyl bromide (**2**) was prepared by the reaction of 1,6-dibromohexane with 2-methylpropylmagnesium bromide in the presence of dilithium tetrachlorocuprate.⁹⁾ The reaction of the dianion of methyl acetoacetate¹⁰⁾ with **2** gave a ketoester (**3**) in a 12.9% yield based on **2**. The desired acylnornicotine was obtained in a 44.1% yield by the reaction of **3** with nornicotine and subsequent sodium borohydride reduction.

It was elucidated that the synthetic product **1** had two peaks on a gas chromatogram, while the natural product **1** that had been isolated from tobacco leaves had one peak. This shows the existence of two compounds in the synthetic product, and the peak with the longer retention time coincided with that of the natural product. The synthetic product could be assigned as a mixture of diastereomers due to the similarity of their mass spectral data. The configuration of the natural product was presumed to be *S* at the 2'-position, because it is known that the all naturally occurring tobacco nicotinoids have an *S* configuration at 2'-position. The absolute configuration of the natural acylnornicotine (**1**) will be reported later.

Experimental

$^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra were recorded at 500 MHz on a Bruker AM 500 spectrometer in CDCl_3 solution using Me_4Si as an internal standard. EI mass and high mass spectra were recorded on a Hewlett Packard 5996A mass spectrometer and a JEOL JMS-D300 mass spectrometer, respectively. IR spectra were obtained on a JASCO A-3 spectrophotometer, and GLC data were recorded on a Shimadzu GC-9A gas chromatograph.

A THF solution (50 ml) of 2-methylpropylmagnesium bromide (8.01 g) was slowly added to a stirred solution of 1,6-dibromohexane (16.94 g) in THF (50 ml) containing 0.24 g of Li_2CuCl_4 . The mixture was stirred for 1 hr and quenched by water, before being extracted with ethyl ether. The extract was dried over anhydrous magnesium sulfate, and 2-methylnonyl bromide (**2**) was isolated and purified by column chromatography on silica gel with hexane to give 5.23 g (47.3% yield).

Dry THF (50 ml) containing 1.08 g of sodium hydride (a 50% mineral oil) was stirred at 0°C in a nitrogen atmosphere. Then, 2.32 g of methyl acetoacetate was added dropwise and the colorless solution was stirred at 0°C for 10 min. To this solution was added dropwise 15.2 ml of 1.4 *N* *n*-butyllithium in hexane, and the solution was stirred at 0°C for 30 min. To the mixture was then added dropwise 5.00 g of **2** in 5 ml of THF, and the reaction mixture was allowed to slowly warm to room temperature with stirring. Approximately 15 min after adding **2**, the reaction was quenched with 14 ml of aqueous HCl (3.4 *N*). The mixture

was extracted with ethyl ether, and the extract was dried over anhydrous magnesium sulfate. 12-Methyl-3-oxotridecanoate (**3**) was isolated and purified by column chromatography on silica gel with hexane-ethyl acetate (80:20) to give 1.40 g (27.3% yield). $^1\text{H-NMR}$ δ (ppm): 3.73 (s, 3H), 3.44 (s, 2H), 2.52 (t, $J=7.3$ Hz, 2H), 1.65~1.10 (m, 15H), 0.87 (d, $J=6.1$ Hz, 6H).

A solution of 2.10 g of *dl*-nornicotine and 0.70 g of methyl 12-methyl-3-oxotridecanoate (**3**) in 30 ml of xylene was refluxed for 5 hr with 1 g of hydrous zirconium oxide, and then cooled. After the mixture had been filtered, the filtrate was concentrated under reduced pressure, and *N'*-(12-methyl-3-oxotridecanoyl) nornicotine (**4**) was isolated and purified by column chromatography on silica gel with methanol-ethyl acetate (20:80) to give 0.55 g (53.9% yield). $^1\text{H-NMR}$ δ (ppm): 8.60~8.45 (m, 2H), 7.45 (m, 1H), 7.41 (m, 1H), 5.21, 5.08 (dd, $J=3.4$, 4.5 Hz, 1H), 4.27~3.30 (m, 3H), 2.63~1.95 (m, 5H), 1.70~1.15 (m, 17H), 0.95 (d, $J=6.8$ Hz, 6H); IR (neat): 2930, 1720, 1620, 1590 cm^{-1} .

To a solution of 0.55 g of **4** in 20 ml of 2-propanol was added dropwise 28.0 mg of sodium borohydride. The mixture was stirred for 1 hr at room temperature. After removing the solvent, 20 ml of ethyl ether and 20 ml of water were added. The ethyl ether extract was dried over anhydrous magnesium sulfate and filtered, the product (0.45 g) being obtained by removing the solvents from the filtrate (81.8% yield).

The synthetic and natural products (**1**) were analyzed by gas chromatography. The column employed was 25 m of a fused silica capillary, and the column temperature was programmed from 100 to 280°C at a rate of 5°C/min. The retention times of the peaks (min) were 47.59, 47.71 (synthetic **1**) and 47.71 (natural **1**). The mass and IR spectra of the synthetic **1** coincided with those of the natural **1**. MS (trimethylsilylated deriv. of **1**) m/z (rel. intensity): 446 (M^+ , 11), 432 (43), 357 (13), 306 (20), 292 (73), 190 (20), 175 (82), 147 (100), 106 (27), 73 (77), 43 (61). Found: m/z 374.2963. Calcd. for $\text{C}_{23}\text{H}_{38}\text{O}_2\text{N}_2$: M^+ , 374.2934. IR (neat): 3400, 2930, 1620, 1590 cm^{-1} .

The $^1\text{H-NMR}$ data show that the synthetic **1** was a mixture of diastereomers, and contains every signal corresponding to that of the natural **1**. $^1\text{H-NMR}$ of synthetic **1** δ (ppm): 8.60~8.45 (m, 2H), 7.47 (m, 1H), 7.28 (m, 1H),

5.23, 5.20, 5.02, 4.96 (dd, $J=3.4$, 4.5 Hz, 1H), 4.18~3.57 (m, 3H), 2.61~2.30 (m, 3H), 2.10~1.81 (m, 4H), 1.65~1.07 (m, 17H), 0.86 (d, $J=6.8$ Hz, 6H). $^1\text{H-NMR}$ of natural **1** δ (ppm): 8.60~8.45 (m, 2H), 7.47 (m, 1H), 7.28 (m, 1H), 5.23, 4.96 (dd, $J=3.4$, 4.5 Hz, 1H), 4.18~3.57 (m, 3H), 2.61~2.30 (m, 3H), 2.10~1.81 (m, 4H), 1.65~1.07 (m, 17H), 0.86 (d, $J=6.8$ Hz, 6H). $^{13}\text{C-NMR}$ of synthetic **1** δ (ppm): 172.62, 171.96, 171.88, 149.23, 149.22, 148.47, 148.43, 147.64, 147.58, 147.43, 138.45, 133.47, 133.27, 133.06, 132.99, 123.96, 123.88, 123.55, 68.29, 68.17, 68.15, 68.00, 59.60, 59.49, 58.75, 58.62, 47.79, 47.02, 47.00, 41.18, 41.09, 40.99, 40.69, 39.20, 36.70, 36.63, 36.54, 36.51, 36.28, 36.13, 33.96, 33.91, 30.78, 30.05, 29.81, 29.79, 28.13, 28.11, 27.56, 27.55, 25.75, 25.73, 23.93, 22.83, 21.73. $^{13}\text{C-NMR}$ of natural **1** δ (ppm): 172.62, 171.98, 149.26, 148.46, 147.67, 147.49, 138.34, 133.50, 132.99, 123.96, 123.52, 68.18, 68.06, 59.62, 58.76, 47.79, 47.02, 41.23, 40.72, 39.23, 36.66, 36.55, 36.32, 33.98, 29.80, 28.15, 27.58, 25.73, 23.99, 22.84, 21.76.

References

- 1) M. Miyano, N. Yasumatsu, H. Matsushita and K. Nishida, *Agric. Biol. Chem.*, **45**, 1029 (1981).
- 2) H. Matsushita, Y. Tsujino, D. Yoshida, A. Saito, T. Kisaki, K. Kato and M. Noguchi, *Agric. Biol. Chem.*, **43**, 193 (1979).
- 3) A. J. N. Bolt, *Phytochemistry*, **11**, 2341 (1972).
- 4) S. Matsushima, T. Ohsumi and S. Sugawara, *Agric. Biol. Chem.*, **47**, 507 (1983).
- 5) M. Miyano, H. Matsushita, N. Yasumatsu and K. Nishida, *Agric. Biol. Chem.*, **43**, 2205 (1979).
- 6) E. Zador and D. Jones, *Plant Physiol.*, **82**, 479 (1986).
- 7) D. Jones, G. Jones, T. Hagen and E. Creech, *Entomol. Exp. Appl.*, **38**, 157 (1985).
- 8) T. Matsuzaki, M. Miyano, N. Yasumatsu, H. Matsushita and A. Koiwai, *Agric. Biol. Chem.*, **52**, 1899 (1988).
- 9) L. Friedman and A. Shani, *J. Am. Chem. Soc.*, **98**, 7101 (1974).
- 10) S. N. Huckin and L. Weiler, *J. Am. Chem. Soc.*, **96**, 1082 (1973).