Communications to the Editor

[Chem. Pharm. Bull. 33(11)5147—5148(1985)]

TOTAL SYNTHESIS OF (±)-PANICULIDINE B[1)]

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The first synthesis of (±)-paniculidine B is achieved from 2-nitrotoluene in seven steps with an overall yield of 16%.

KEYWORDS ——— (±)-paniculidine A; (±)-paniculidine B; 1-methoxyindole; 3-iodo-1-methoxyindole; 4-(1-methoxyindol-3-yl)-2-butanone

Kinoshita and co-workers[2)] isolated paniculidine B from Murraya paniculata (Linn.) Jack. and established its structure as 2-methyl-4-(1-methoxyindol-3-yl)-1-butanol. As part of our project for synthesizing 1-methoxyindole alkaloids,[3)] we are greatly interested in this alkaloid. In this report, we describe the first total synthesis of (±)-paniculidine B (1).

1-Methoxy-3-indolecarbaldehyde (4) is readily available in two steps in 63% overall yield from 2-nitrotoluene (2) according to our synthesis method.[4)] The aldol condensation reaction of 4 with acetone in the presence of 2N-NaOH afforded 4-(1-methoxyindol-3-yl)-3-buten-2-one (5)[5a)] in 96% yield. Subsequent selective hydrogenation of the conjugated double bond in 5 was the most difficult step. Various reduction methods with such reagents as pyridine/$NaBH_4$,[6)] CuI/$LiAlH_4$,[7)] $PdCl_2$/$NaBH_4$,[8)] Zn(Hg)/HCl,[9)] etc., were examined but they were found to be unsuccessful due to the intrinsicly unstable nature of 1-methoxyindole to reduction, culminating in the formation of demethoxylated products. Among them, catalytic hydrogenation over 10% Pd/C in $CHCl_3$ afforded the best result[10)] and the desired 4-(1-methoxyindol-3-yl)-2-butanone (6a)[5b)] and the corresponding demethoxy compound (6b) were obtained in 36% and 16% yields, respectively, though the yield of 6a is still not satisfactory.

The compound (6a) was also produced by the other route. Thus, 3-iodo-1-methoxyindole (7)[5c)] was prepared in 27% yield by the treatment of 1-methoxyindole (2) with I_2/morpholine.[11)] The improved Heck reaction[12)] of 7 with 3-buten-2-ol in the presence of tetra-n-butylammonium bromide gave 6a in 36% yield.

Next, the reaction of 6a with TosMIC[13)] proceeded successfully to give 4-(1-methoxyindol-3-yl)-2-methylbutanenitrile (8)[5d)] in 84% yield. Treatment of 8 with DIBAL produced the desired 4-(1-methoxyindol-3-yl)-2-methylbutyraldehyde (9)[5e)] in 88% yield. Subsequent reduction of 9 with $NaBH_4$ in MeOH afforded paniculidine B (1) in 98% yield.

It should be noted that alkaline hydrolysis of 8 produced a 49% yield of demethoxy compound (10b), while the desired carboxylic acid (10a)[5f)] was produced in only 22% yield. Both of these carboxylic acids (10a and 10b) were methylated quantitatively with ethereal diazomethane to yield methyl 4-(1-methoxyindol-3-yl)-2-methylbutyrate (11a)[5g)] or paniculidine A (11b), respectively. Reduction of 11a with $LiAlH_4$ also afforded paniculidine B (1) in 94% yield.

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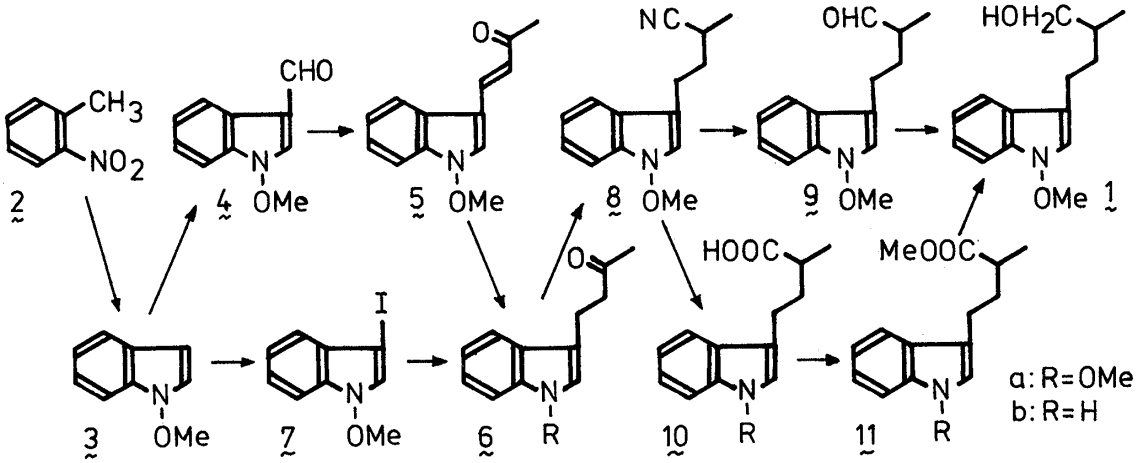
The UV, MS, and ^{1}H-NMR (400 MHz) spectra of the synthetic paniculidine A and B were identical to those of natural products.



ACKNOWLEDGEMENTS We express our thanks to Dr. Kinoshita for providing us with the spectral data of paniculidine A and B. This work is supported by a Grant-in-Aid for Scientific Research (Grant No. 60570983) from the Ministry of Education, Science and Culture of Japan, which is greatfully acknowledged.

REFERENCES AND NOTES

1) This report is part XXIX of a series entitled "The Chemistry of Indoles." Part XXVIII: M. Somei and Y. Saida, Heterocycles, in press.
2) T. Kinoshita, S. Tatara, and U. Sankawa, Chem. Pharm. Bull., 33, 1770 (1985).
3) M. Somei, H. Sato, N. Komura, and C. Kaneko, Heterocycles, 23, 1101 (1985); M. Somei, H. Sato, and C. Kaneko, ibid., 20, 1797 (1983).
4) M. Somei, K. Kizu, M. Kunimoto, and F. Yamada, Chem. Pharm. Bull., 33, 3696 (1985); M. Somei and T. Shoda, Heterocycles, 16, 1523 (1981).
5) All melting points are uncorrected. ^{1}H-NMR (NMR) spectra were taken in deuterated chloroform (d-C) or carbon tetrachloride (C-T). Chemical shifts are reported in ppm (δ) from TMS. All oily compounds gave satisfactory high MS data and crystalline compounds afforded acceptable combustion data. IR absorption bands are shown in cm^{-1}. a) mp 79-81°C. IR (KBr): 1656, 1617. NMR (C-T): 2.18 (3H, s), 3.99 (3H, s), 6.46 (1H, d, J=16 Hz), 6.78-7.26 (3H, m), 7.38 (1H, s), 7.41 (1H, d, J=16 Hz), 7.52-7.80 (1H, m); b) colourless oil. IR (film): 2940, 1708, 1452, 1160. NMR (d-C): 2.08 (3H, s), 2.58-3.08 (4H, m, A_2B_2), 3.93 (3H, s), 6.81-7.51 (5H, m); c) mp 45-46°C (unstable colourless prisms). IR (film): 3120, 1570, 1438, 1322. NMR (C-T): 3.96 (3H, s), 6.69-7.34 (5H, m); d) colourless oil. IR (film): 2240, 1450, 1098. NMR (d-C): 1.33 (3H, d, J=7 Hz), 1.79-2.11 (2H, m), 2.60 (1H, sext, J=7 Hz), 2.80-3.04 (2H, m), 4.05 (3H, s), 6.95-7.61 (5H, m); e) colourless oil. IR (film): 2725, 1722, 1453. NMR (C-T): 1.07 (3H, d, J=6.5 Hz), 1.40-2.49 (3H, m), 2.67 (2H, t, J=7 Hz), 3.91 (3H, s), 6.79 (1H, br s), 6.69-7.42 (4H, m), 9.30 (1H, d, J=1.5 Hz); f) colourless oil. IR (film): 3500-2300, 1702, 1450, 1232. NMR (C-T): 1.21 (3H, d, J=7 Hz), 1.44-2.52 (3H, m), 2.69 (2H, t, J=7 Hz), 3.91 (3H, s), 6.61-7.42 (5H, m), 10.49 (1H, br s); g) colourless oil. IR (film): 2940, 1738, 1452, 1204. NMR (C-T): 1.10 (3H, d, J=7 Hz), 1.38-2.44 (3H, m), 2.61 (2H, t, J=7 Hz), 3.53 (3H, s), 3.92 (3H, s), 6.78 (1H, br s), 6.68-7.44 (4H, m).
6) K. Igbal and W.R. Jackson, J. Chem. Soc., C , 1968, 616.
7) E.C. Ashby and J.J. Lin, Tetrahedron Lett., 1975, 4453.
8) T.W. Russel, D.M. Duncan, and S.C. Hansen, J. Org. Chem., 42, 551 (1977).
9) B.R. Davis and P.D. Woodgate, J. Chem. Soc., 1966, 2006.
10) Catalytic hydrogenation over 10% Pd/C produced 6a, 6b, and the corresponding alcohols. Their product ratios varied with the examined solvents such as MeOH, MeOH/HCl, MeOH/NaOH, AcOEt, EtOH, t-BuOH, acetone, acetic acid, and $CHCl_3$.
11) P. Chabrier, J. Seyden-Penne, and A. Fouace, C. R. Acad. Sci., 245, 174 (1957); C.A. Giza and R.L. Hinman, J. Org. Chem., 29, 1453 (1964).
12) T. Jeffery, J. Chem. Soc., Chem. Commun., 1984, 1287; M. Somei, T. Hasegawa, T. Suzuki, and M. Wakita, Abstracts of Papers, 105th Annual Meeting of Pharmaceutical Society of Japan, Kanazawa, April, 1985, p. 679.
13) O.H. Oldenziel and A.M. Van Leusen, Tetrahedron Lett., 1973, 1357.

(Received September 19, 1985)

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