Communications to the Editor

[Chem. Pharm. Bull. 31(6)2153—2156(1983)]

SYNTHETIC STUDY DIRECTED TOWARD CYCLOPIAZONIC ACID[1)]

Masanori Somei,* Shoichi Tokutake, and Chikara Kaneko
Faculty of Pharmaceutical Sciences, Kanazawa University,
Takara-machi, Kanazawa 920, Japan

The first syntheses of 6,6a,7,8,9,9a-hexahydro- and 6,6a,9,9a-tetrahydro-2H-isoindolo[4,5,6-cd]indoles are described. The preparation of 1,3,4,5-tetrahydrobenz[cd]indole derivatives is also included.

KEYWORDS——cyclopiazonic acid; 6a,9a-cis-6,6a,7,8,9,9a-hexahydro-2H-isoindolo[4,5,6-cd]indole; 6a,9a-cis-6,6a,9,9a-tetrahydro-2H-isoindolo[4,5,6-cd]indole; 6a,9a-trans-6,6a,7,8,9,9a-hexahydro-2H-isoindolo[4,5,6-cd]indole; 1,3,4,5-tetrahydrobenz[cd]indole

Cyclopiazonic acid (1) is a toxic substance isolated from Penicillium cyclopium Westling (strain 1082) by Holzapfel[2)] in 1968. We have been interested in its unique structure and biological activity and planned to synthesize the alkaloid and various related derivatives having substituents especially in the A and/or B regions.

Our synthetic idea is as follows: Functionalization of A and/or B regions can be attained in the course of the synthesis of 1 only by changing the reagents without changing the type of the reactions. Based on the above idea, we have selected and developed the following synthetic route and succeeded for the first time in the preparation of key synthetic intermediates (e.g. 2 and 3), having a novel 6,6a,7,8,9,9a-hexahydro-2H-isoindolo[4,5,6-cd]indole skeleton.

I. Preparation of 1,3,4,5-Tetrahydrobenz[cd]indoles

Aldol condensation reaction of 4-formylindole (4)[3)] with acetone, followed by catalytic hydrogenation over 10% Pd/C, afforded 4-(3-oxobutyl)indole (5)[4a)] in 97% yield. Subsequent treatment of 5 with 1-dimethylamino-2-nitroethylene[5)] in CH_3CN-CF_3COOH (1:1, v/v) afforded 3-(2-nitrovinyl)-4-(3-oxobutyl)indole (6)[4b)] in 84% yield. Similarly, with ethyl α-nitro-β-ethoxyacrylate[6)] in benzene at reflux, a 62% yield of 7[4c)] was formed as a 3:2 mixture of geometric isomers together with a 20% yield of starting material. By the action of t-BuOK in abs. DMSO, intramolecular Michael reaction of 6 was successfully carried out to give 3,4-cis- (8c)[4d)] and 3,4-trans-4-acetyl-3-nitromethyl-1,3,4,5-tetrahydrobenz[cd]indole (8t)[4e)] in 60% and 26% yields, respectively. The major compound (8c) was then subjected to Wittig reaction with methylenetriphenylphosphorane to produce an inseparable 4:1 mixture of 9c and 9t.[4f)] Reduction of the mixture with aq. $TiCl_3$ produced amines, (10c)[4g)] and (10t),[4h)] in 52% and 13% yields, respectively. The mixture of 9c and 9t was allowed to react with HMPT[7)] in the presence of NEt_3 to afford 11c[4i)] and 11t[4j)] in the respective yields of 44% and 15%. Furthermore, reduction of 11c or 11t with $LiAlH_4$ in THF afforded a 88% yield of 10c or a 62% yield of 10t, respectively.

The stereochemistry of these compounds was determined on the basis of the fol-

lowing facts: 1) in the PMR spectra of 11t and 11c, the C-3 proton was clearly discerned and appeared as a doublet at δ4.00 (J=9.2 Hz) and 4.24 (J=4.0 Hz), respectively, proving that 11t had 3,4-trans configuration, whereas 11c had 3,4-cis configuration; 2) in the reduction with aq. $TiCl_3$, the ratio of the products, (10c) and (10t), was identical with that of 9c and 9t, showing that their stereochemistry was retained during the reaction; 3) both compounds, (8c) and (8t), reached equilibrium by the action of t-BuOK in abs. DMSO, where the ratio of 8c and 8t was ca. 3:1, indicating that the major product (9c) in the Wittig reaction had been derived from 8c.

In contrast to Michael reaction of 6, the ring closure reaction of 7 was readily effected by weaker bases such as 2N-NaOH and resulted in the formation of two sets of diastereoisomers, showing two spots on TLC. Although a less polar pair of epimers (12)[4k] at the carbon bearing nitro and ethoxycarbonyl groups was formed predominantly (83%), the stereochemistry at the C-3 and C-4 is not determined as yet.

II. Syntheses of 6,6a,7,8,9,9a-Hexahydro-2H-isoindolo[4,5,6-cd]indoles

Treatment of 10c with Ac_2O-pyridine or carbobenzoxy chloride afforded the corresponding acyl derivatives, (13a)[4l] or (13b),[4m] in 98% or 83% yields, respectively. Subsequent protection of the indole nitrogen with methyl chloroformate produced 14a[4n] or 14b[4o] in the respective yields of 78% or 90%. The desired 6a,9a-cis-8-acetyl- (15a)[4p] or 8-benzyloxycarbonyl-7,7-dimethyl-2-methoxycarbonyl-6,6a,7,8,9,9a-hexahydro-2H-isoindolo[4,5,6-cd]indole (15b)[4q] was prepared from 14a or 14b in 50% or 60% yields, respectively, by successive treatment with phenylselenenyl chloride and triphenyltin hydride.[8] In a similar way, a series of the corresponding 3,4-trans or 6a,9a-trans compounds (13c,[4r] 14c,[4s] and 15c[4t]) were successfully prepared starting from 10t. It should be noted that an attempted debenzyloxycarbonylation of 15c produced the desired product (2c)[4u] in 49% yield with a significant amount of the corresponding indoline (16%). In contrast to this result, catalytic hydrogenation of 15b over 10% Pd/C selectively cleaved the N-8 protecting group to afford 2b[4v] in 78% yield.

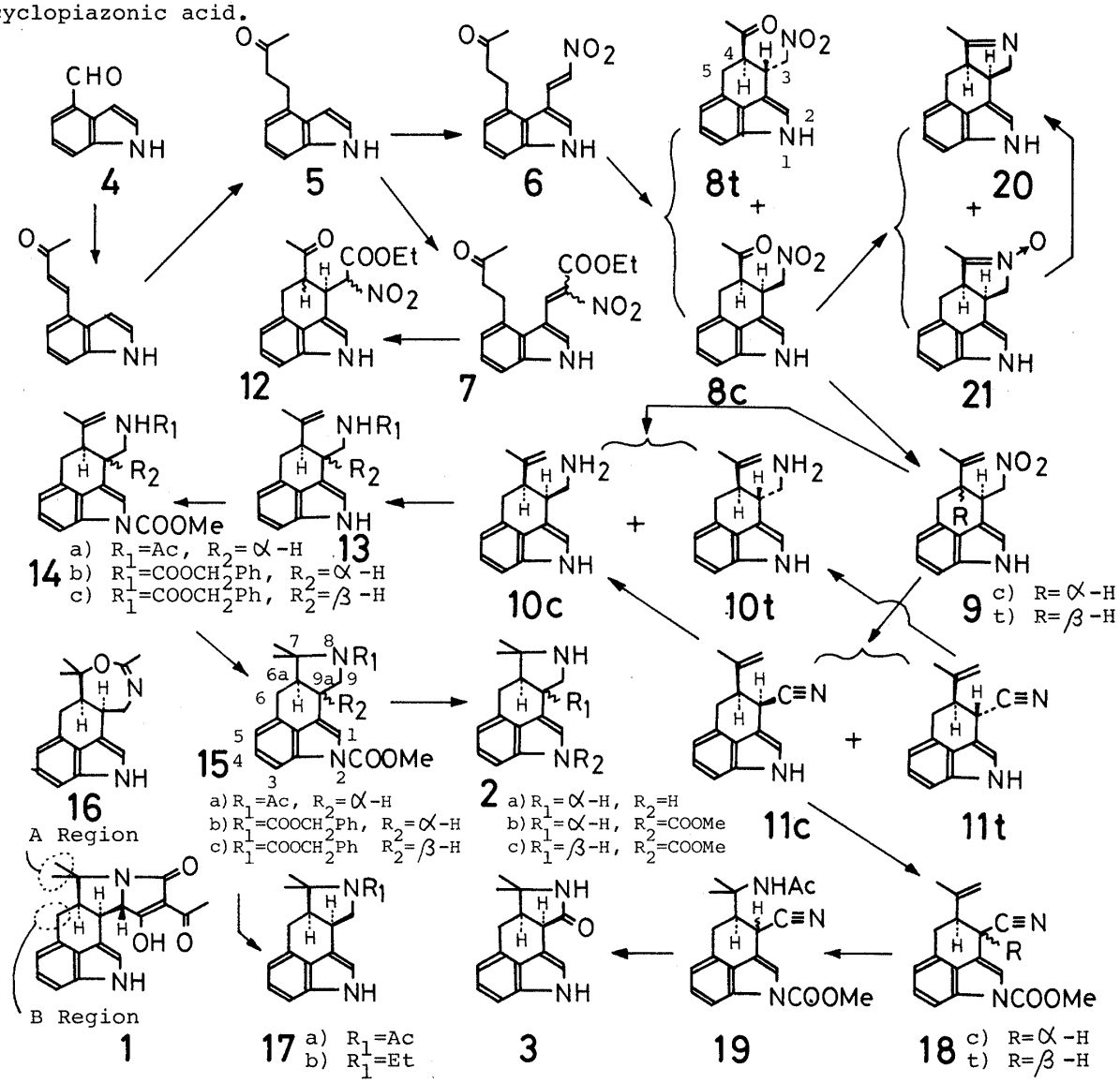
Although another structure such as 16 was possible for 15a, it was excluded by the following series of reactions. Thus, mild alkaline hydrolysis of 15a gave 17a[4w] in 68% yield. Further treatment of 17a with KOH in refluxing ethylene glycol gave 2a[4x] in 52% yield. Acetylation of 2a with Ac_2O-pyridine reproduced 17a in 91% yield. Final confirmation was provided by the reduction of 17a with $LiAlH_4$ in THF affording 64% yield of the N-ethyl compound (17b),[4y] which could not be formed from 16.

Preparation of 6a,9a-cis-7,7-dimethyl-6,6a,7,8,9,9a-hexahydro-9-oxo-2H-isoindolo[4,5,6-cd]indole (3)[4z] was accomplished in the following way. Protection of the indole nitrogen[9] in 11c was achieved with NaH and methyl chloroformate, but epimerization at C-3 occurred to give 18c[10a] and 18t[10b] in 22% and 52% yields, respectively. Subsequent Ritter reaction of 18c (or 18t) with CH_3CN and H_2SO_4 gave 63% (or 62%) yield of the mixture of stereoisomers (19), which was then subjected to alkaline hydrolysis with KOH in refluxing ethylene glycol to give the desired γ-lactam (3) as a single product in 29% yield. Its stereochemistry was tentatively assigned to be thermodynamically stable 6a,9a-cis-isomer.

On the other hand, reduction of 8c with aq. $TiCl_3$ afforded 6a,9a-cis-7-methyl-6,6a,9,9a-tetrahydro-2H-isoindolo[4,5,6-cd]indole (20)[10c] and its N-oxide (21)[10d] in 62% and 10% yields, respectively. When the reduction was carried out with Zn and NH_4Cl, their yields were changed to 10% and 89%, respectively. The structure of 21

was confirmed by the conversion to 20 in 84% yield by the reduction with excess aq. $TiCl_3$.

Since the introduction of various functional groups into A and/or B regions is possible either by using suitable three carbon reagents in the aldol reaction step or by Michael addition reaction in place of the addition of hydrogen in the second step, our approach seems to provide a useful and convenient method for the preparation of 6,6a,7,8,9,9a-hexahydro-2H-isoindolo[4,5,6-cd]indole derivatives, which would meet our end to develop physiologically active substances. We are currently investigating the conversion of these synthetic intermediates into cyclopiazonic acid.



REFERENCES AND NOTES

1) Presented in part at the 9th Symposium on Progress in Organic Reactions and Syntheses, Hiroshima, November, 1982. This report is part XIX of a series entitled "The Chemistry of Indoles." Part XVIII: M. Somei and T. Shoda, Heterocycles, 17, 417 (1982).

2) C.W. Holzapfel, Tetrahedron, 24, 2101 (1968); C.W. Holzapfel, R.D. Hutchison, and D.C. Wilkins, ibid., 26, 5239 (1970); R.M. McGrath and P.S. Steyn, J. Chem. Soc., Chem. Commun., 1973, 812; A.A. Chalmers, C.P. Gorst-Allman, and P.S. Steyn, ibid., 1982, 1367.

3) M. Somei, Y. Karasawa, and C. Kaneko, Chemistry Letters, 1980, 813; M. Somei, F. Yamada, Y. Karasawa, and C. Kaneko, ibid., 1981, 615.
4) All melting points are uncorrected. All oily compounds gave satisfactory high mass data and crystalline compounds afforded acceptable combustion data. IR spectra of crystalline compounds were recorded in KBr pellets and oily compounds for films. Absorption bands are shown in cm^{-1}. PMR spectra were taken in deuterochloroform unless otherwise stated. Chemical shifts of major signals are reported in ppm (δ) from TMS.
a) mp 60.5-62°C. IR: 1698. PMR: 2.14 (3H, s), 2.97 (4H, A_2B_2, m), 6.43 (1H, dd, J=3 and 2 Hz); b) mp 165-166°C. IR: 1712, 1508, 1308. PMR (CD_3OD): 2.15 (3H, s), 7.64 and 8.46 (each 1H, d, J=12.2 Hz), 7.92 (1H, s); c) mp 132-133°C (3:2 mixture of geometric isomers). IR: 1686, 1616, 1534, 1510. PMR: 1.35 (3H, t, J=7 Hz), 2.17 (3H, s), 4.31 and 4.37 (3:2, total 2H, each q, J=7 Hz), 7.59 and 7.85 3:2, total 1H, each d, J=3 Hz), 8.02 and 8.60 (3:2, total 1H, each s); d) mp 149-150°C. IR: 1702, 1544, 1376. PMR: 2.23 (3H, s), 2.93-3.46 (3H, m), 3.99-4.37 (1H, m), 4.46-4.79 (2H, m); e) mp 104-105°C. IR: 1708, 1520, 1384. PMR: 2.27 (3H, s), 2.91-3.48 (3H, m), 4.16-4.96 (3H, m); f) oil, IR: 1642, 1540, 1378. PMR: 1.94 and 1.81 (4:1, total 3H, each s); g) oil. IR: 3400, 3150, 1640, 1440. PMR: 1.66 (2H, br s, NH_2), 1.83 (3H, s), 4.83 (2H, br s); h) mp 148.0-149.5°C. IR: 3380, 3060, 1640, 1442. PMR: 1.53 (2H, br s, NH_2), 1.78 (3H, s), 4.75 (2H, br s); i) oil. IR: 2230, 1642. PMR: 1.88 (3H, s), 4.24 (1H, d, J=4 Hz), 5.02 (2H, br s); j) mp 131.0-131.5°C. IR: 2220, 1638. PMR: 1.86 (3H, s), 4.00 (1H, br d, J=9.2 Hz), 4.88 and 4.94 (each 1H, br s); k) oil. IR: 1742, 1706, 1560, 1348. PMR: 1.15 and 1.33 (1:1, total 3H, each t, J=7 Hz), 2.14 (3H, s), 4.10 and 4.29 (1:1, total 2H, each q, J=7 Hz); l) oil. IR: 3290, 1638, 1538. PMR: 1.87 (3H, s), 1.89 (3H, s), 2.26-4.10 (6H, m), 4.89 (2H, br s); m) oil. IR: 3435, 1696, 1644. PMR: 1.82 (3H, s), 4.83 (2H, br s), 4.99 (2H, s), 7.13 (5H, s); n) oil. IR: 3260, 1732, 1630. PMR: 1.93 (3H, s), 1.98 (3H, s), 3.97 (3H, s), 4.87 and 4.95 (each 1 H, br s), 7.68 (1H, d, J=8 Hz); o) oil. IR: 3390, 1720, 1640. PMR: 1.84 (3H, s), 2.28-3.68 (6H, m), 3.91 (3H, s), 4.85 and 4.92 (each 1H, br s), 5.01 (2H, s), 7.18 (5H, s), 7.67 (1H, d, J=8 Hz); p) oil. IR: 1728, 1628. PMR: 1.43 (3H, s), 1.55 (3H, s), 2.00 (3H, s), 3.96 (3H, s), 7.68 (1H, d, J=8 Hz); q) oil. IR: 1738, 1696. PMR showed the presence of rotational isomers. PMR at 80°C (pyridine-d_5): 1.32 and 1.52 (each 3H, s), 3.90 (3H, s), 5.24 (2H, s), 6.96-7.58 (8H, m), 7.94 (1H, d, J=8 Hz); r) oil. IR: 3380, 1696. PMR: 1.76 (3H, s), 4.72 (2H, br s), 4.99 (2H, s), 7.16 (5H, s); s) oil. IR: 3360, 1724. PMR: 1.76 (3H, s), 3.92 (3H, s), 4.76 (2H, br s), 5.01 (2H, s), 7.18 (5H, s), 7.66 (1H, d, J=8 Hz); t) oil. IR: 1732, 1688. PMR showed the presence of rotational isomers: 1.27 and 1.34 (total 3H, each s), 1.45 and 1.57 (total 3H, each s), 3.91 (3H, s), 5.04-5.20 (total 2H, m), 7.21 (5H, s), 7.69 (1H, d, J=8 Hz); u) oil. IR: 3350, 1726. PMR: 1.16 (3H, s), 1.32 (3H, s), 3.93 (3H, s), 7.65 (1H, d, J=8 Hz); v) oil. IR: 3350, 1730. PMR (pyridine-d_5): 0.93 and 1.25 (each 3H, s), 3.82 (3H, s), 7.87 (1H, d, J=8 Hz); w) oil. IR: 3260, 1628. PMR: 1.49 (3H, s), 1.55 (3H, s), 2.00 (3H, s); x) oil. IR: 3210, 1604. PMR (10% CD_3OD in $CDCl_3$): 0.86 (3H, s), 1.24 (3H, s); y) oil. IR: 3100, 1619. PMR (10% CD_3OD in $CDCl_3$): 0.47 and 1.19 (each 3H, s), 1.12 (3H, t, J=7 Hz), 2.19 and 2.30 (total 2H, each q, J=7 Hz, showing the presence of conformational isomers); z) mp 248.5-249.5°C. IR: 3280, 1686. PMR (10% CD_3OD in $CDCl_3$): 0.80 (3H, s), 1.36 (3H, s), 2.32-4.09 (5H, m), 6.61-7.22 (4H, m).
5) G. Büchi and C-P. Mak, J. Org. Chem., 42, 1784 (1977).
6) U. Hengartner, D. Valentine, JR., K.K. Johnson, M.E. Larscheid, F. Pigott, F. Scheidl, J.W. Scott, R.C. Sun, J.M. Townsend, and T.H. Williams, J. Org. Chem., 44, 3741 (1979).
7) G.A. Olah, Y.D. Bankar, and B.G.B. Gupta, Synthesis, 1979, 36.
8) D.L.J. Clive, V. Farina, A. Singh, C.W. Wong, W.A. Kiel, and S.M. Menchen, J. Org. Chem., 45, 2120 (1980).
9) Attempts to protect indole nitrogen with other acylating agents in the presence of 4-N,N-dimethylaminopyridine were unsuccessful: K. Nikisch, W. Klose, and F. Bohlmann, Chem. Ber., 113, 2036 (1980).
10) a) oil. IR: 2240, 1740. PMR: 1.87 (3H, s), 3.95 (3H, s), 4.17 (1H, d, J=4 Hz), 4.99 (2H, br s); b) mp 109-110°C. IR: 2250, 1738, 1642. PMR: 1.87 (3H, s), 2.67-3.13 (3H, m), 3.90 (1H, br d, J=9 Hz), 3.97 (3H, s), 4.91 and 4.99 (each 1H, br s); c) mp 158-159°C. IR: 1620, 1592, 1432. PMR: 1.97 (3H, s), 2.73-3.42 (3H, m), 3.44-4.33 (3H, m), 6.60-7.16 (4H, m), 8.30 (1H, br s); d) mp 207-209°C. IR: 1596, 1438, 1208, 1186. PMR (10% CD_3OD in $CDCl_3$): 2.12 (3H, br s), 2.41-4.32 (6H, m), 6.64-7.22 (4H, m).

(Received May 6, 1983)