THE CHEMISTRY OF 1-HYDROXYINDOLES: SYNTHESES OF METHYL 1-HYDROXYINDOLE-3-ACETATE, Nb-ACETYL-1-HYDROXYTRYPTAMINE, (±)- AND (S)-1-HYDROXYTRYPTOPHAN DERIVATIVES[1)]

Masanori SOMEI,* Toshiya KAWASAKI, Kazuhisa SHIMIZU, Yoshikazu FUKUI, and Toshiharu OHTA
Faculty of Pharmaceutical Sciences, Kanazawa University, 13-1 Takara-machi, Kanazawa 920, Japan

Methyl 1-hydroxyindole-3-acetate, (±)-2-acetoamino-3-(1-hydroxyindol-3-yl)propanol, Nb-acetyl-1-hydroxytryptamine, (±)- and (S)-(+)-Nb-acetyl-1-hydroxytryptophan methyl ester, which are needed for inspecting our hypothesis regarding the metabolism of tryptophan, were prepared for the first time. The structural proof of (±)-Nb-acetyl-1-hydroxytryptophan methyl ester by X-ray crystallographic analysis is also reported.

KEYWORDS methyl 1-hydroxyindole-3-acetate; (±)-2-acetoamino-3-(1-hydroxyindol-3-yl)-propanol; Nb-acetyl-1-hydroxytryptamine; (±)-Nb-acetyl-1-hydroxytryptophan methyl ester; (S)-(+)-Nb-acetyl-1-hydroxytryptophan methyl ester; 1-hydroxyindole; 2,3-dihydroindole; oxidation; X-ray crystallographic analysis; tryptophan

1-Hydroxyindoles are generally believed to be unstable compounds except for cases where electron-withdrawing groups are placed at the proper positions.[2,3,4)] For a representative example, 1-hydroxyindole (2a) can exist only in an inert solvent under protection from light and attempts to isolate it have thus far been unsuccessful.[2,3)] Therefore, it is a quite interesting and challengeable theme to determine whether 1-hydroxytryptophan derivatives can exist or not. Furthermore, it is important to study 1-hydroxytryptophan derivatives as common intermediates for the formation of various indole metabolites *in vivo* in relation to the metabolism of tryptophan.[2)] Based on the hypothesis, we have long been engaged in the chemistry of 1-hydroxy- and 1-methoxyindoles,[2,4)] and developed simple synthesis methods for them.[4)] Here we report the first and simple synthesis of methyl 1-hydroxyindole-3-acetate (2b), (±)-2-acetoamino-3-(1-hydroxyindol-3-yl)propanol (2c), Nb-acetyl-1-hydroxytryptamine (2d), (±)- ((±)- 2e), and (S)-(+)-Nb-acetyl-1-hydroxytryptophan methyl ester ((S)-(+)-2f).

2,3-Dihydroindoles (1b-f) were prepared by reducing the corresponding indoles with sodium cyanoborohydride[5)] in acetic acid. Oxidation of methyl 2,3-dihydroindole-3-acetate (1b) with 30% aqueous hydrogen peroxide (H_2O_2, 10 mol eq.) in the presence of a catalytic amount of sodium tungstate dihydrate ($Na_2WO_4 \cdot 2H_2O$, 0.2 mol eq.) in methanol-water at room temperature for 30 min afforded methyl 1-hydroxyindole-3-acetate[6)] (2b) in 65% yield (Chart 1). The compound (2b) was stable enough for rapid silica gel column chromatography and isolable as a pure colorless oil. However, it gradually decomposed and after standing for one hour at room temperature, it formed unidentified products, though 2b was still the major component. The structure of 2b was determined by converting it to stable methyl 1-methoxyindole-3-acetate (3b)[2b)] by treating it with ethereal diazomethane in 91% yield.

Under similar oxidizing conditions, (±)-2-acetoamino-3-(2,3-dihydroindol-3-yl)propanol ((±)-1c), Nb-acetyl-2,3-dihydrotryptamine (1d), and (±)-Nb-acetyl-2,3-dihydrotryptophan methyl ester ((±)-1e) afforded

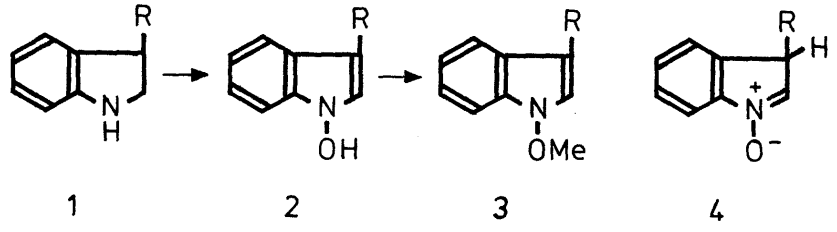

Chart 1

a R= H
b R= $-CH_2COOMe$
c R= (±)-$-CH_2CH(NHAc)CH_2OH$
d R= $-CH_2CH_2NHAc$
e R= (±)-$-CH_2CH(NHAc)COOMe$
f R= (S)-$-CH_2CH(NHAc)COOMe$

the corresponding 1-hydroxyindole derivatives, ((±)-2c), (2d), and ((±)-2e), in 30, 55, and 73% yields, respectively. The compound ((±)-2c)[7] was an unstable oil, but more stable than 2b. To our surprise, the compounds (2d and (±)-2e)[8] were isolated as stable colorless prisms. The structures of (±)-2c, 2d, and (±)-2e were determined by converting them to the corresponding 1-methoxyindoles, ((±)-3c), (3d), and ((±)-3e), in 77, 83, and 83% yields, respectively, by treatment with ethereal diazomethane.

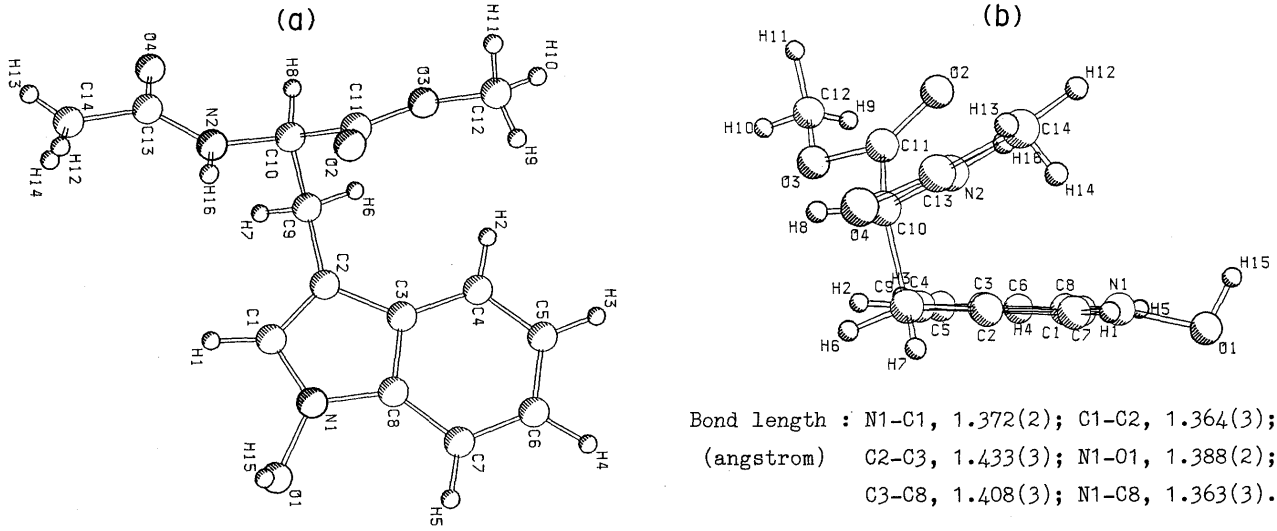

Fig. 1. Perspective View of (±)-Nb-Acetyl-1-hydroxytryptophan Methyl Ester ((±)-2e)

The structure of (±)-2e was unequivocally determined by X-ray single crystallographic analysis[9] as shown in Fig. 1. This is the first example of the X-ray analysis of 1-hydroxyindole itself. The ABX coupling pattern (^{1}H-NMR) of H6, H7, and H8 signals of (±)-2e and bond length between N1 and C1 proved that the contribution of the nitrone structure (4) was negligible in both the solution and solid states. It should be noted that the oxygen atom of the 1-hydroxy group deviates clearly from the plane of the indole nucleus,[3d] as Fig. 1b shows.

Finally, (S)-(+)-Nb-acetyl-1-hydroxytryptophan methyl ester[10] ((S)-(+)-2f) was obtained as stable colorless prisms (mp 116-117°C) in 53% yield from the corresponding 2,3-dihydroindole (1f) by the oxidation with 30% H_2O_2 and $Na_2WO_4 \cdot 2H_2O$. Treating (S)-(+)-2f with ethereal diazomethane afforded a 78% yield of (S)-(+)-Nb-acetyl-1-methoxytryptophan methyl ester[11] ((S)-(+)-3f).

These results show that the stability of 1-hydroxyindoles (2) is governed at least partly by the bulkiness of the 3-substituent. The most important point in the present work is that 1-hydroxytryptophan can exist in peptides and/or enzymes and plays a biologically significant role[2a] in vivo. Preparations of glycosides and phosphate esters and the biological activities of compounds (2 and 3) are currently under investigation.

ACKNOWLEDGMENT The authors express their gratitude to Prof. Y. Tsuda and Mr. S. Hosoi (Kanazawa University) for helpful discussions for X-ray crystallographic analysis. This work is partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan, which is gratefully acknowledged.

REFERENCES AND NOTES

1) This report is part 57 of a series entitled "The Chemistry of Indoles". Part 56: K. Nakagawa and M. Somei, Heterocycles, 32, 873 (1991).
2) a) Leading reference (review): M. Somei, Yuki Gosei Kagaku Kyokai Shi, 49, 205 (1991); b) T. Kawasaki, A. Kodama, T. Nishida, K. Shimizu, and M. Somei, Heterocycles, 32, 221 (1991).
3) a) R.M. Acheson, D.M. Littlewood, and H.E. Rosenberg, J. Chem. Soc., Chem. Commun., 1974, 671 ; b) R.

M. Acheson, P.G. Hunt, D.M. Littlewood, B.A. Murrer, and H.E. Rosenberg, J. Chem. Soc., Perkin Trans. 1, 1978, 1117 ; c) R.M. Acheson, "New Trends in Heterocyclic Chemistry," Elsvier Scientific Pub. Co., New York, pp. 1-33 (1979); d) Acheson and co-workers found that 1-benzoyloxyindole has the pyramidal nitrogen atom (N1) by X-ray crystallographic analysis: R.M. Acheson, M.H. Benn, J. Jacyno, and J.D. Wallis, J. Chem. Soc., Perkin Trans. 2, 1983, 497; e) R.M. Acheson, "Advances in Heterocyclic Chemistry," Vol. 51, Academic Press, Inc., New York, pp. 105-175 (1990).

4) a) M. Somei and T. Shoda, Heterocycles, 16, 1523 (1981); b) M. Somei, H. Ohnishi, and Y. Shoken, Chem. Pharm. Bull., 34, 677 (1986); c) M. Somei and T. Kawasaki, Heterocycles, 29, 1251 (1989).

5) G.W. Gribble, P.D. Lord, J. Skotnicki, S.E. Dietz, J.T. Eaton, and J.L. Johnson, J. Am. Chem. Soc., 96, 7812 (1974).

6) Colorless unstable oil. IR (film) cm^{-1}: 3300, 2960, 1708, 1435, 1330, 1173, 1005, 738. ^{1}H-NMR (CD_3OD) δ : 3.66 (3H, s), 3.70 (2H, s), 6.96 (1H, dt, J=1.2 and 7 Hz), 7.06 (1H, dt, J=1.2 and 7.8 Hz), 7.18 (1H, s), 7.31 (1H, dm, J=7.8 Hz), 7.43 (1H, dm, J=7 Hz). High resolution MS m/z: Calcd for $C_{11}H_{11}NO_3$: 205.0738. Found: 205.0840. UV λ_{max}^{MeOH}nm: 222, 278, 291.

7) Colorless unstable oil. IR (film) cm^{-1}: 3265, 1629, 1547, 738. ^{1}H-NMR (CD_3OD) δ : 1.88 (3H, s), 2.80 (1H, dd, J=14.5 and 7.5 Hz), 3.00 (1H, dd, J=14.5 and 6.5 Hz), 3.53 (2H, d, J=5.1 Hz), 4.14 (1H, m), 6.96 (1H, dd, J=7.6 and 7.1 Hz), 7.10 (1H, s), 7.12 (1H, dd, J=7.6 and 6.8 Hz), 7.32 (1H, d, J=7.1 Hz), 7.57 (1H, d, J=6.8 Hz). High resolution MS m/z: Calcd for $C_{13}H_{16}N_2O_3$: 248.1159. Found: 248.1146. UV λ_{max}^{MeOH}nm: 224, 283, 293.

8) 2d: mp 138-139°C (recrystallized from AcOEt). IR (KBr) cm^{-1}: 3250, 3105, 1619, 1602, 1580, 743. ^{1}H-NMR (CD_3OD) δ: 1.89 (3H, s), 2.89 (2H, t, J=7.3 Hz), 3.43 (2H, t, J=7.3 Hz), 6.99 (1H, t, J=8.3 Hz), 7.10 (1H, s), 7.12 (1H, t, J=8.3 Hz), 7.34 (1H, d, J=8.3 Hz), 7.52 (1H, d, J=8.3 Hz). MS m/z: 218 (M^+), 202. Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.02; H, 6.53; N, 12.77. UV λ_{max}^{MeOH}nm (log ε): 225 (4.52), 281 (3.62), 295 (3.66).
(±)-2e: mp 153-154°C (dec., recrystallized from MeOH). IR (KBr) cm^{-1}: 3259, 3125, 1739, 1640, 1547, 727. ^{1}H-NMR (CD_3OD) δ: 1.92 (3H, s), 3.06 (1H, dd, J=13.9 and 7.6 Hz), 3.28 (1H, dd, J=13.9 and 5.9 Hz), 3.65 (3H, s), 4.66 (1H, dd, J=7.6 and 5.9 Hz), 6.97 (1H, ddd, J=7.1, 6.8, and 1.5 Hz), 7.09 (1H, s), 7.12 (1H, ddd, J=7.6, 6.8, and 1.5 Hz), 7.32 (1H, dm, J=7.1 Hz), 7.47 (1H, dm, J=7.6 Hz). MS m/z: 276 (M^+), 260. Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.78; H, 5.92; N, 10.09. UV λ_{max}^{MeOH}nm (log ε): 224 (4.55), 282 (3.65), 294 (3.68).

9) Crystal data for (±)-2e: $C_{14}H_{16}N_2O_4$, M=276.29, triclinic, space group $P\bar{1}$, with unit cell dimensions a=8.1707(8), b=12.105(1), c=8.019(1) Å, α=107.94(1)°, β=109.54(1)°, γ=73.156(8)°, V=695.6(1)Å^3, Z=2, and Dc=1.319 g/cm^3. The reflection data were collected on a Rigaku AFC-5 diffractometer for 3°< 2θ <55° using Mo Kα radiation (λ=0.71069A) and the ω-2θ scan method at a 2θ scan speed of 6°/min. The structure was solved by the direct method using the MITHRIL program and refined by full-matrix least squares. The final R value was 0.043 for 2210 independent reflections [I>3σ(I)].

10) (S)-(+)-2f: mp 116-117°C (recrystallized from MeOH-H_2O). $[\alpha]_D^{24}$ +11.8° (MeOH, c=0.102). IR (KBr) cm^{-1}: 3370, 3240, 1733, 1655, 1534, 745. ^{1}H-NMR (5% CD_3OD in $CDCl_3$) δ: 1.90 (3H, s), 3.19 (1H, dd, J= 15 and 5.8 Hz), 3.27 (1H, dd, J=15 and 5.2 Hz), 3.71 (3H, s), 4.86 (1H, dd, J=5.8 and 5.2 Hz), 7.01 (1H, s), 7.06 (1H, t, J=8.3 Hz), 7.19 (1H, t, J=8.3 Hz), 7.42 (1H, d, J=8.3 Hz), 7.45 (1H, d, J=8.3 Hz). MS m/z: 276 (M^+), 260. Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.85; H, 5.88; N, 10.14. UV λ_{max}^{MeOH}nm (log ε): 224 (4.53), 282 (3.64), 293 (3.66).

11) (S)-(+)-3f: Colorless oil. $[\alpha]_D^{20}$ +16.8° (MeOH, c=0.107). IR (film) cm^{-1}: 3270, 1741, 1658, 1540, 736. ^{1}H-NMR ($CDCl_3$) δ: 1.97 (3H, s), 3.25 (1H, dd, J=14.6 and 4.9 Hz), 3.31 (1H, dd, J=14.6 and 5.4 Hz), 3.70 (3H, s), 4.05 (3H, s), 4.93 (1H, ddd, J=7.8, 5.4, and 4.9 Hz), 6.03 (1H, d, J=7.8 Hz), 7.04 (1H, s), 7.11 (1H, dd, J=8.3 and 7.8 Hz), 7.24 (1H, t, J=8.3 Hz), 7.40 (1H, d, J=8.3 Hz), 7.49 (1H, d, J=7.8 Hz). High resolution MS m/z: Calcd for $C_{15}H_{18}N_2O_4$: 290.1266. Found: 290.1296. UV λ_{max}^{MeOH}nm (log ε): 223 (4.47), 276 (3.66), 289 (3.68).

(Received May 24, 1991)