The chemistry of 1-hydroxyindole derivatives : nucleophilic substitution reactions on indole nucleus

THE CHEMISTRY OF 1-HYDROXYINDOLE DERIVATIVES: NUCLEOPHILIC SUBSTITUTION REACTIONS ON INDOLE NUCLEUS[1]

Masanori Somei,* Toshiya Kawasaki, Yoshikazu Fukui, Fumio Yamada, Tetsuya Kobayashi, Harumi Aoyama, and Daisuke Shinmyo

Faculty of Pharmaceutical Sciences, Kanazawa University
13-1 Takara-machi, Kanazawa 920, Japan

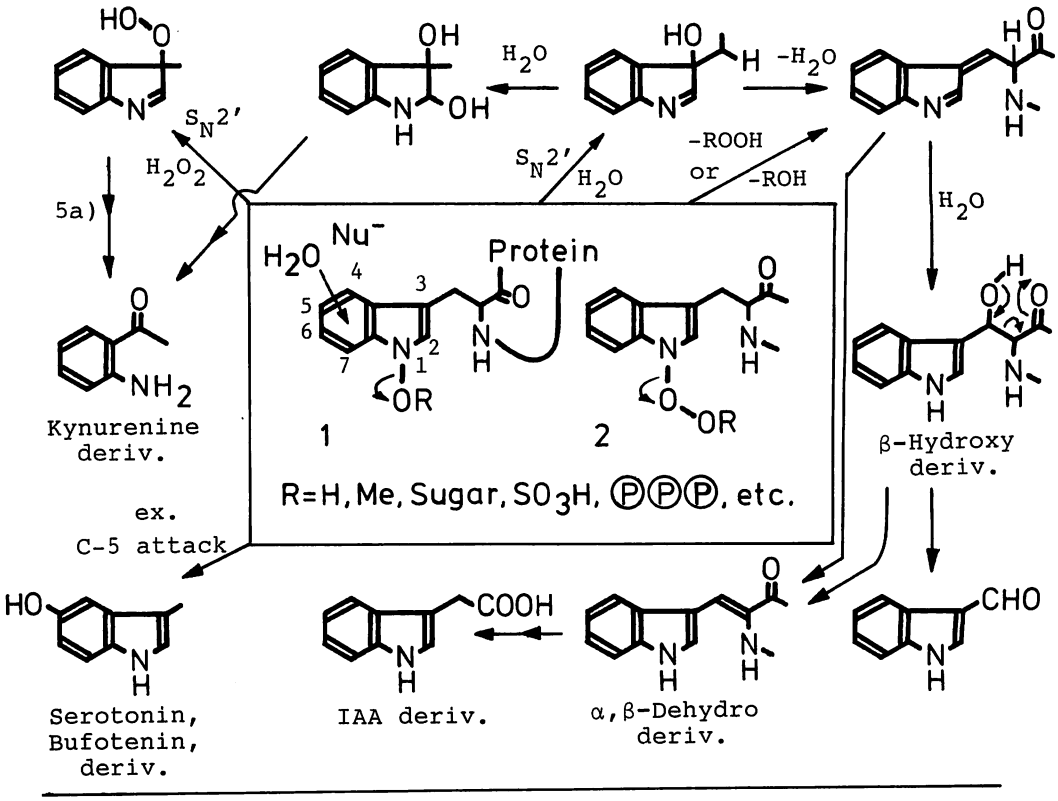
Abstract ——— Nucleophilic substitution reactions were newly found to occur generally in the chemistry of 1-hydroxyindole derivatives. Its application to the synthesis of a phytoalexin, brassicanal A, is reported.

Supposing 1-hydroxy- (**1**) and/or 1-hydroperoxytryptophan (**2**) as a common intermediate of the metabolism of tryptophan,[2] biosyntheses of kynurenine, serotonin, β-hydroxy- and α,β-dehydrotryptophans, indole-3-acetic acid, *etc.* might be explained by the following reaction mechanisms depicted in Scheme 1. Biosyntheses of various indole alkaloids, such as pyrrolo[2,3-*b*]indoles, 4-oxoazetidine-2-spiro-3'-(2'-oxindole) derivatives, 4-substituted indoles including ergot alkaloids, indolactams, and so on, could also be explained as shown in Scheme 2.[2]

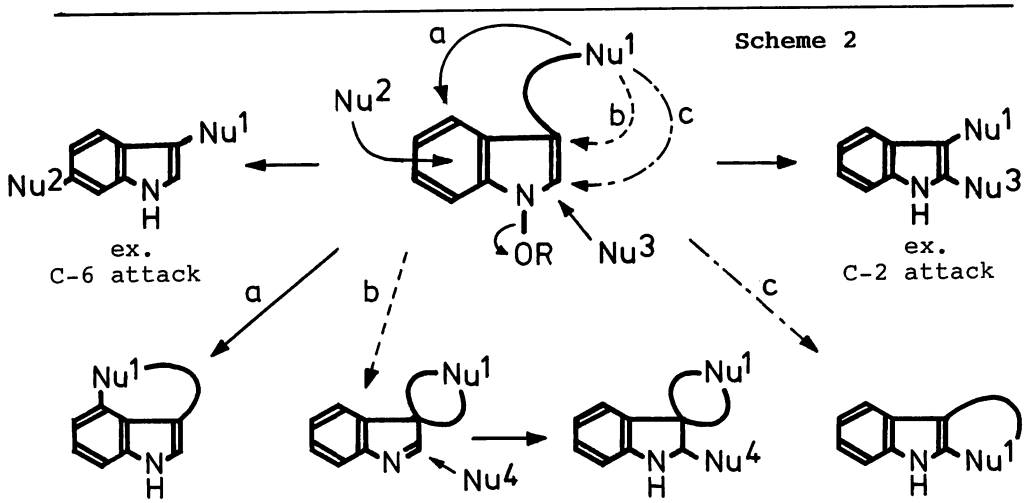
Our hypotheses stated above rely on the unprecedented nucleophilic substitution reactions in the indole chemistry.[3] Now, we wish to report that 1-hydroxyindole and 1-hydroxytryptophan derivatives can actually undergo nucleophilic substitution reactions on the indole nucleus.

The reaction of (±)-*N*b-acetyl-1-hydroxytryptophan methyl ester[4] (**3a**) with mesyl chloride in tetrahydrofuran (THF) and triethylamine (Et_3N) at 0°C

Scheme 1



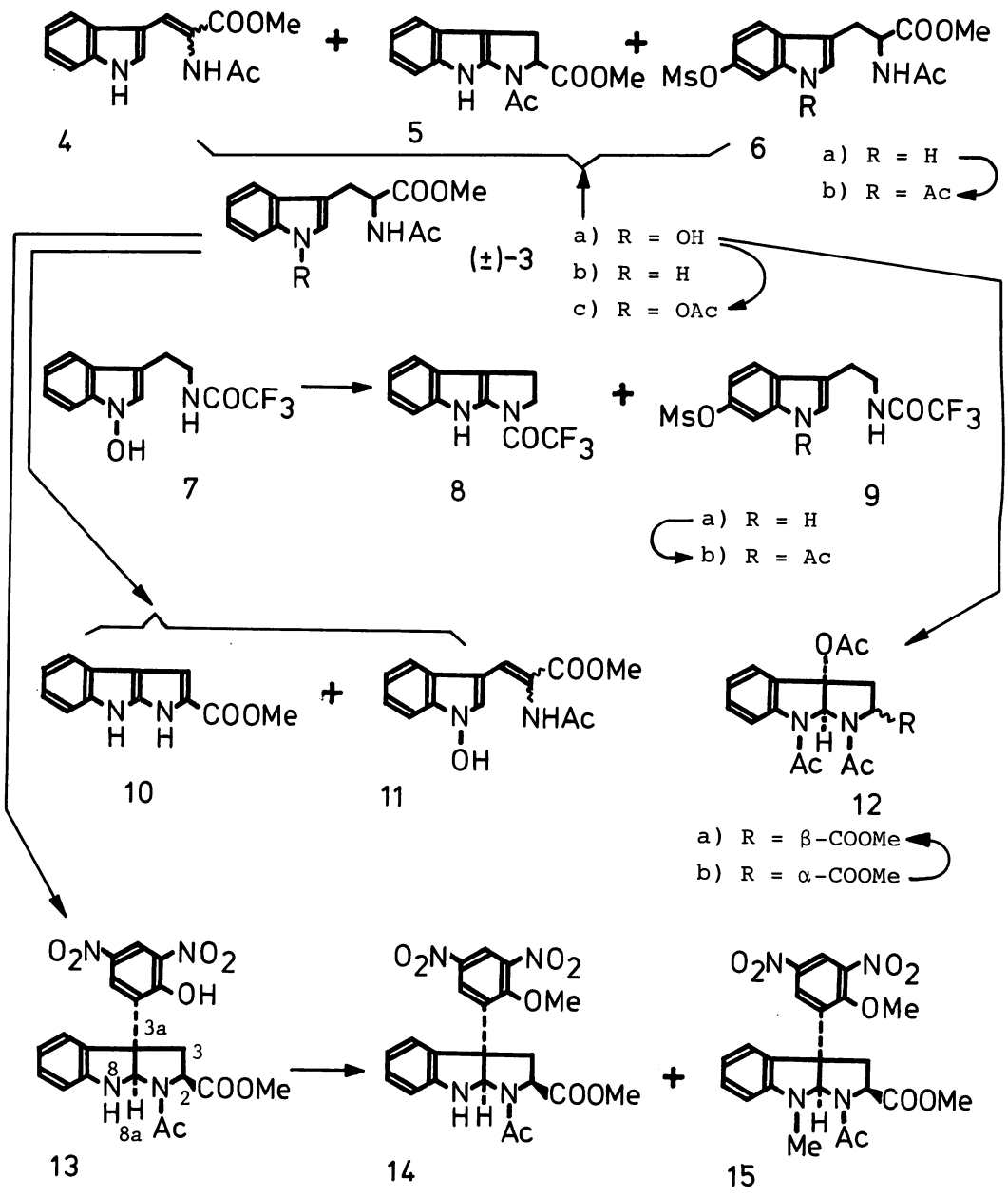
Scheme 2



for 1 h produced the expected α, β-dehydrotryptophan (**4**), 2,3-dihydropyrrolo[2,3-*b*]indole (**5**),[5] and 6-mesyloxytryptophan derivative (**6a**) in 2, 47, and 9% yields, respectively, together with unidentified products (Scheme 3). Under similar reaction conditions, 1-hydroxy-*N*b-trifluoroacetyltryptamine (**7**) produced 1-trifluoroacety -2,3-dihydropyrrolo[2,3-*b*]indole (**8**) and 6-mesyloxy-*N*b-trifluoroacetyltryptamine (**9a**) in 45 and 8% yields, respectively. While, thermolysis of **3a** in *o*-dichlorobenzene at 180 °C for 1 h afforded starting material (**3a**), *N*b-acetyltryptophan methyl ester (**3b**), **4**, pyrrolo[2,3-*b*]indole (**10**), and 1-hydroxy-α, β-dehydrotryptophan derivative (**11**) in 7, 16, 17, 8, and 39% yields, respectively. Structures of **4** and **11** were determined based on the spectral data, and the compound (**4**) was found to be a 3:2 mixture, while **11** was a 2:1 mixture of double bond isomers. Structure of **5** was determined by comparison with an authentic sample prepared from **3b** according to the reported procedure[5d] using *t*-butyl hypochrorite and Et_3N. The structures of **6a** and **9a** were confirmed based on anisotropy effect of 1-acetyl group. Thus, **6a** and **9a** were converted respectively to the corresponding 1-acetyl compounds (**6b**) and (**9b**), in 70 and 25% yields by the reaction with sodium hydride (NaH), followed by treatment with acetyl chloride. Comparisons of their ^{1}H-nmr spectra with those of **6a** and **9a** clearly exhibited that a doublet signal (J=2 Hz, meta coupling) assigned to the 7-proton shifted to low field by 1 ppm, respectively, proving that **6a** and **9a** were 6-substituted indoles.

Treatment of **3a** with acetic anhydride (Ac_2O) at reflux afforded 1-acetoxy derivative (**3c**) in quantitative yield. Similar reaction of **3a** in the presence of sodium acetate (2 mol eq.) afforded 3a-acetoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indoles (**12a**) and (**12b**), in 17 and 21% yields, respectively. Treatment of **12b** with potassium *t*-butoxide in dimethylformamide, followed by the treatment with Ac_2O and pyridine gave **12a** in 50% yield. This fact proved that **12a** and **12b** were stereoisomers at the 2-position bound to the methoxycarbonyl group.

Scheme 3

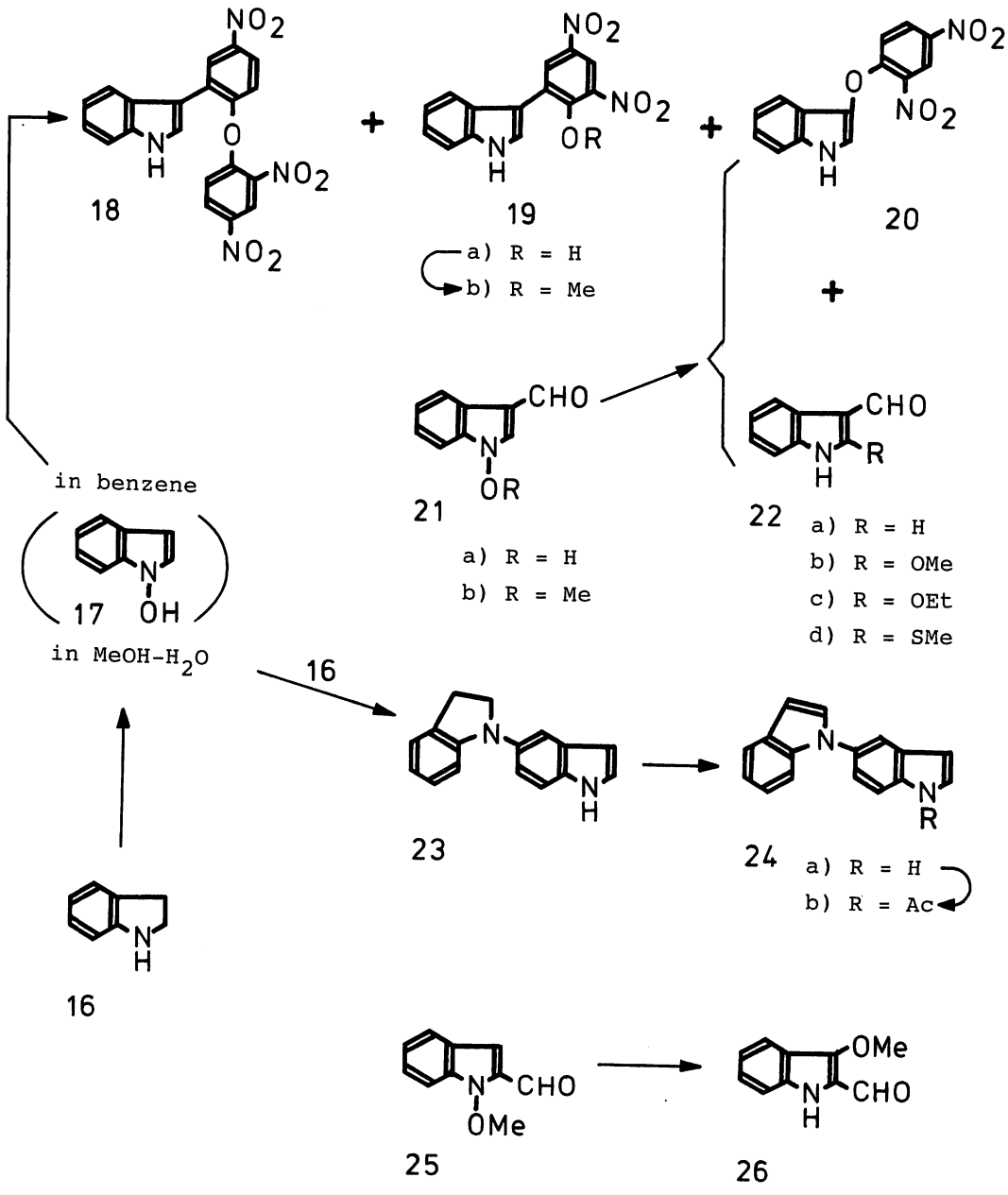

COOMe
NHAc
4
5
6
MsO
a) R = H
b) R = Ac
(±)-3
a) R = OH
b) R = H
c) R = OAc
NCOCF3
7
8
9
10
11
12
OAc
a) R = β-COOMe
b) R = α-COOMe
O2N
NO2
OH
OMe
13
14
15

It is interesting to note that the reaction of **3a** with 2,4-dinitrofluorobenzene (2,4-DNF, 1.2 mol eq.) in THF and Et_3N at room temperature produced 3a-substituted 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole derivative (**13**) and **3b** in 35 and 6% yields, respectively. Subsequent methylation of **13** with diazomethane formed monomethyl (**14**) and dimethyl compounds (**15**) in 32 and 30% yields, respectively. X-Ray crystallographic analysis of **15** verified its structure, and the results shown in Figure 1 exhibited that the two pyrrolidine nuclei were *cis* fused and methoxycarbonyl group at the 2-position was thermodynamically stable *trans* configuration[5] concerning to 3a and 8a hydrogens.

1-Hydroxyindole[6,7] (**17**) in benzene[3a] reacted with 2,4-DNF (3 mol eq.) in THF and Et_3N at room temperature to produce 1:2 adduct (**18**), 3-arylindole (**19a**), and 3-aryloxyindole (**20**) in the respective overall yields of 6, 17, and 6% from 2,3-dihydroindole (**16**) in addition to many unidentified products. The structure of **18** was established by X-ray crystallographic analysis and the results are shown in Figure 2. The structure of **19a** was confirmed by leading it to monomethyl ether (**19b**) in 89% yield with diazomethane. The compound (**20**) was alternatively obtained in 31% yield together with 48% yield of indole-3-carboxaldehyde (**22a**) by the reaction of 1-hydroxyindole-3-carboxaldehyde[3a] (**21a**) with 2,4-DNF in THF and Et_3N at room temperature.

It should be noted that both 1-hydroxy and 1-methoxy groups are themselves good leaving groups as expected.[2] Thus, when methanol-water solution of 1-hydroxyindole[3a,6] was treated with excess **16**, 5-(2,3-dihydroindol-1-yl)indole (**23**) was produced in 8% yield together with many unidentified products. Treatment of **23** with Ac_2O at reflux afforded 5-(indol-1-yl)indole (**24a**) in 62% yield. Subsequent acetylation of **24a** by the reaction with NaH, followed by treatment with acetyl chloride gave **24b** in 78% yield. Comparison of ^1H-nmr spectrum of **24b** with that of **24a** showed that the proton at the 7 position (doublet, J=8 Hz, *ortho* coupling) shifted to low field by 1

Scheme 4


NO2
O
NO2
NO2
N
H
18
+
NO2
NO2
OR
19
a) R = H
b) R = Me
+
NO2
O
NO2
20
+
CHO
N
OR
21
a) R = H
b) R = Me
CHO
N
R
H
22
a) R = H
b) R = OMe
c) R = OEt
d) R = SMe
in benzene
N
OH
17
in MeOH-H2O
16
16
N
H
23
N
N
R
24
a) R = H
b) R = Ac
CHO
N
OMe
25
OMe
CHO
N
H
26

ppm proving that **24a** and **24b** were 5-substituted indoles.

On the other hand, the reaction of 1-methoxyindole-3-carboxaldehyde[8] (**21b**) and 1-methoxyindole-2-carboxaldehyde[3a] (**25**) with sodium methoxide in methanol at reflux for 2 h produced 2-methoxyindole-3-carboxaldehyde (**22b**) and 3-methoxyindole-2-carboxaldehyde (**26**) in 90 and 75% yields, respectively. Similarly, treatment of **21b** with sodium ethoxide afforded **22c** in 95% yield. Brassicanal A[9a] (**22d**) and **21b**[9b] are phytoalexins isolated from plant family Cruciferae. With our hypotheses in mind, formation of **22d** from **21b** in plant might be predicted. Actually, treatment of **21b** with sodium thiomethoxide afforded 94% yield of **22d** (mp 233-234°C), which was identical with natural product.[9a]

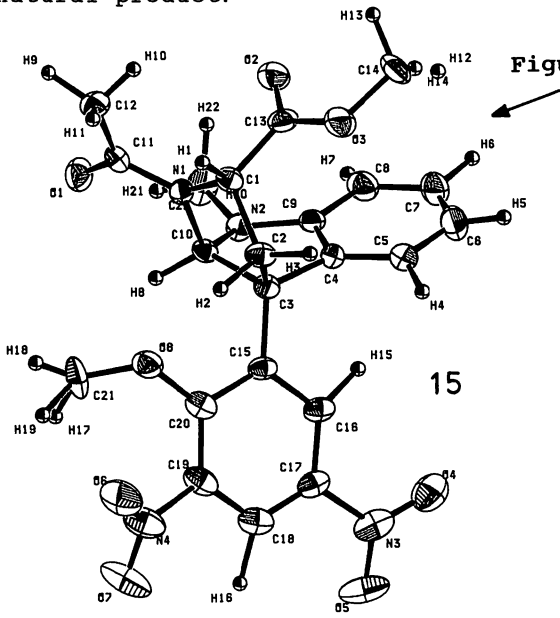


Figure 1 Crystal Structures of **15** and **18**

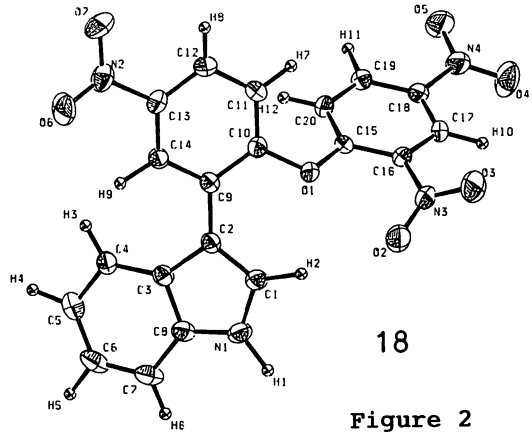


Figure 2

The reactions of 1-hydroxyindoles with other nucleophiles including prenyl thiol, cysteine, active methylene compounds, diketopiperazine derivatives, phenols, and so on, are currently in progress. Electrophilic reactions of 1-hydroxyindoles are also 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. The authors are also indebted to Prof. M. Takasugi (Hokkaido University) for kindly providing us with spectra of brassicanal A.

REFERENCES AND NOTES

1. This report is Part 61 of a series entitled "The Chemistry of Indoles". Part 60: M. Somei and T. Kobayashi, *Heterocycles*, 1992, **34**, 1295.
2. a) Our hypotheses were reported, Book of Abstracts, "The 17th Symposium on Progress in Organic Reactions and Syntheses", Fukuoka, Nov. 1991, p. 206. b) These hypotheses were partly reported, orally at first, Abstracts of Papers, "13th Congress of Heterocyclic Chemistry", Shizuoka, Nov., 1980, p. 33. See also reference 6b.
3. a) T. Kawasaki, A. Kodama, T. Nishida, K. Shimizu, and M. Somei, *Heterocycles*, 1991, **32**, 221. b) T. Nagayoshi, S. Saeki, and M. Hamana, *Chem. Pharm. Bull.*, 1984, **32**, 3678. c) P. G. Gassman, G. A. Campbell, and G. Mehta, *Tetrahedron*, 1972, **28**, 2749. d) Photo rearrangement of 1-methoxyindole: M. Somei and M. Natsume, *Tetrahedron Lett.*, 1973, 2451.
4. M. Somei, T. Kawasaki, K. Shimizu, Y. Fukui, and T. Ohta, *Chem. Pharm. Bull.*, 1991, **39**, 1905.
5. a) M. Nakagawa, S. Kato, S. Kataoka, S. Kodato, H. Watanabe, H. Okajima, T. Hino, and B. Witkop, *Chem. Pharm. Bull.*, 1981, **29**, 1013 and references cited therein. b) M. Taniguchi and T. Hino, *Tetrahedron*, 1981, **37**, 1487. c) M. Nakagawa, H. Watanabe, S. Kodato, H. Okajima, T. Hino, J. L. Flippen, and B. Witkop, *Proc. Natl. Acad. Sci. USA*, 1977, **74**, 4730. d) M. Ohno, T. F. Spande, and B. Witkop, *J. Am. Chem. Soc.*, 1968, **90**, 6521.
6. a) M. Somei and A. Kodama, *Heterocycles*, 1992, **34**, 1285. b) Review: M. Somei, *Yuki Gosei Kagaku Kyokai Shi*, 1991, **49**, 205. c) M. Somei and T. Kawasaki, *Heterocycles*, 1989, **29**, 1251. d) M. Somei and T. Shoda, *Heterocycles*, 1981, **16**, 1523.
7. R. M. Acheson, "Advances in Heterocyclic Chemistry", Vol. 51, Academic Press, Inc., New York, pp. 105-175, 1990 and references cited therein.
8. M. Somei, H. Ohnishi, and Y. Shoken, *Chem. Pharm. Bull.*, 1986, **34**, 677; R. M. Acheson, P. G. Hunt, D. M. Littlewood, B. A. Murrer, and H. E. Rosenberg, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1117.
9. a) K. Monde, N. Katsui, A. Shirata, and M. Takasugi, *Chemistry Lett.*, 1990, 209. b) M. Takasugi, K. Monde, N. Katsui, and A. Shirata, Symposium Papers, The 29th Symposium on the Chemistry of Natural Products, Sapporo, 1987, p. 629.

Received, 23rd June, 1992