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著者	Somei Masanori, Kawasaki Toshiya, Fukui Yoshikazu, Yamada Fumio, Kobayashi Tetsuya, Aoyama Harumi, Shinmyo Daisuke
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THE CHEMISTRY OF 1-HYDROXYINDOLE DERIVATIVES: NUCLEOPHILIC SUBSTITUTION REACTIONS ON INDOLE NUCLEUS¹

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 (+)-*Nb*-acetyl-1-hydroxytryptophan methyl ester⁴ (3a) with mesyl chloride in tetrahydrofuran (THF) and triethylamine (Et₃N) 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-Nb-trifluoroacetyltryptamine (7) produced 1-trifluoroacetyl-2,3-dihydropyrrolo[2,3-*b*]indole (8) and 6-mesyloxy-Nb-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), Nb-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 hypochlorite and Et₃N. 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 ¹H-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 (Ac₂O) 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 Ac₂O 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

It is interesting to note that the reaction of **3a** with 2,4-dinitrofluorobenzene (2,4-DNF, 1.2 mol eq.) in THF and Et₃N 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* configuration⁵ 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 Et₃N 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 Et₃N 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 Ac₂O 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

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

On the other hand, the reaction of 1-methoxyindole-3-carboxaldehyde⁸ (**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.

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