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

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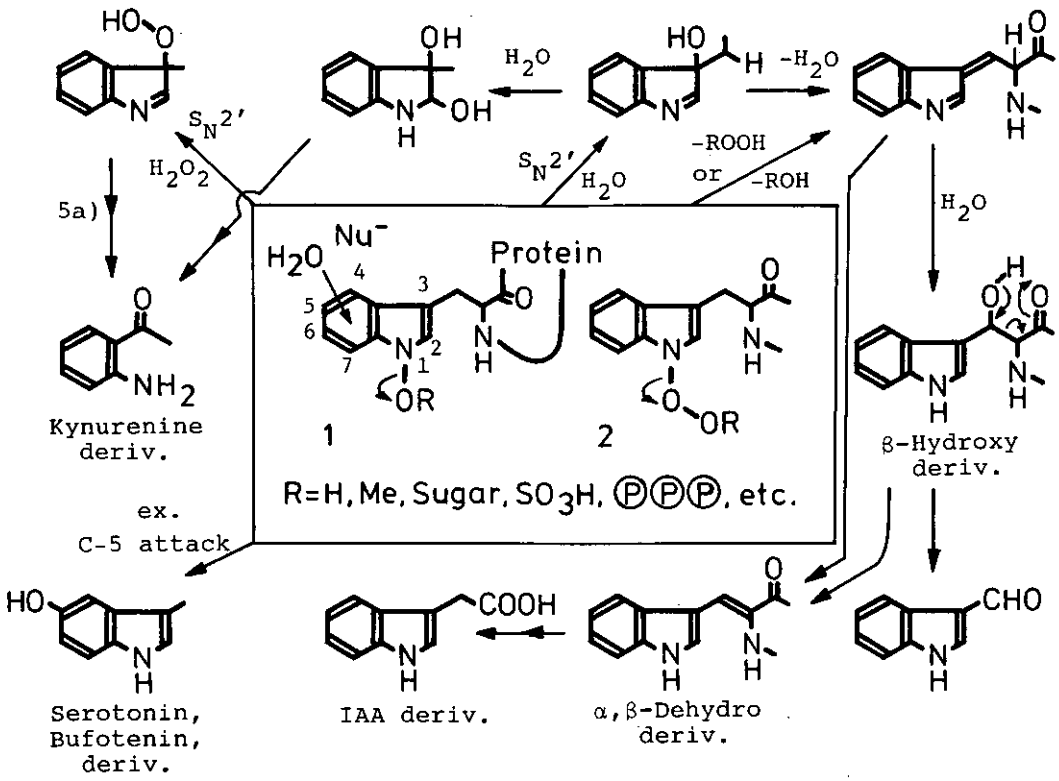
Abstract ——— Nucleophilic substitution reactions were newly found to occur generally in the chemistry of 1-hydroxyindole derivatives. Its application to the synthesis of a phytoalexin, brassicanal A, is reported.

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]

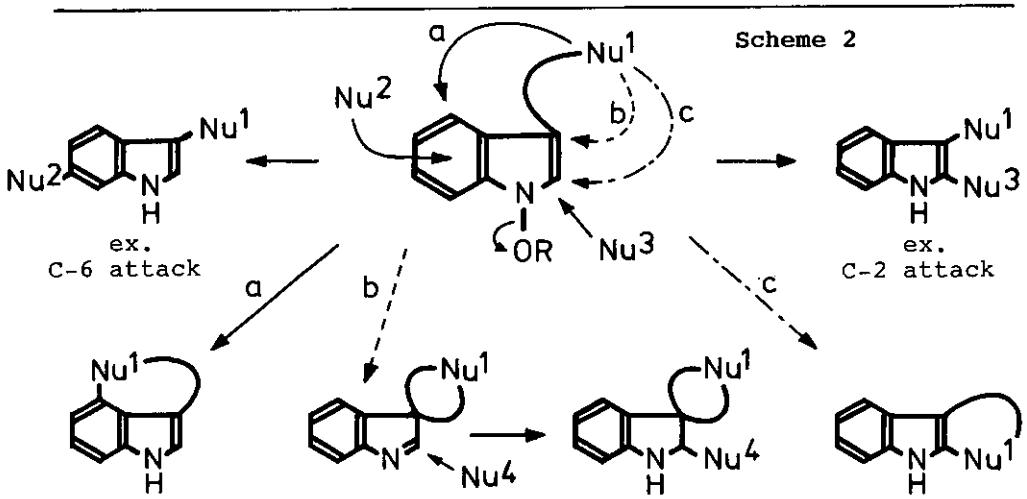
Our hypotheses stated above rely on the unprecedented nucleophilic substitution reactions in the indole chemistry.[3] Now, we wish to report that 1-hydroxyindole and 1-hydroxytryptophan derivatives can actually undergo nucleophilic substitution reactions on the indole nucleus.

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



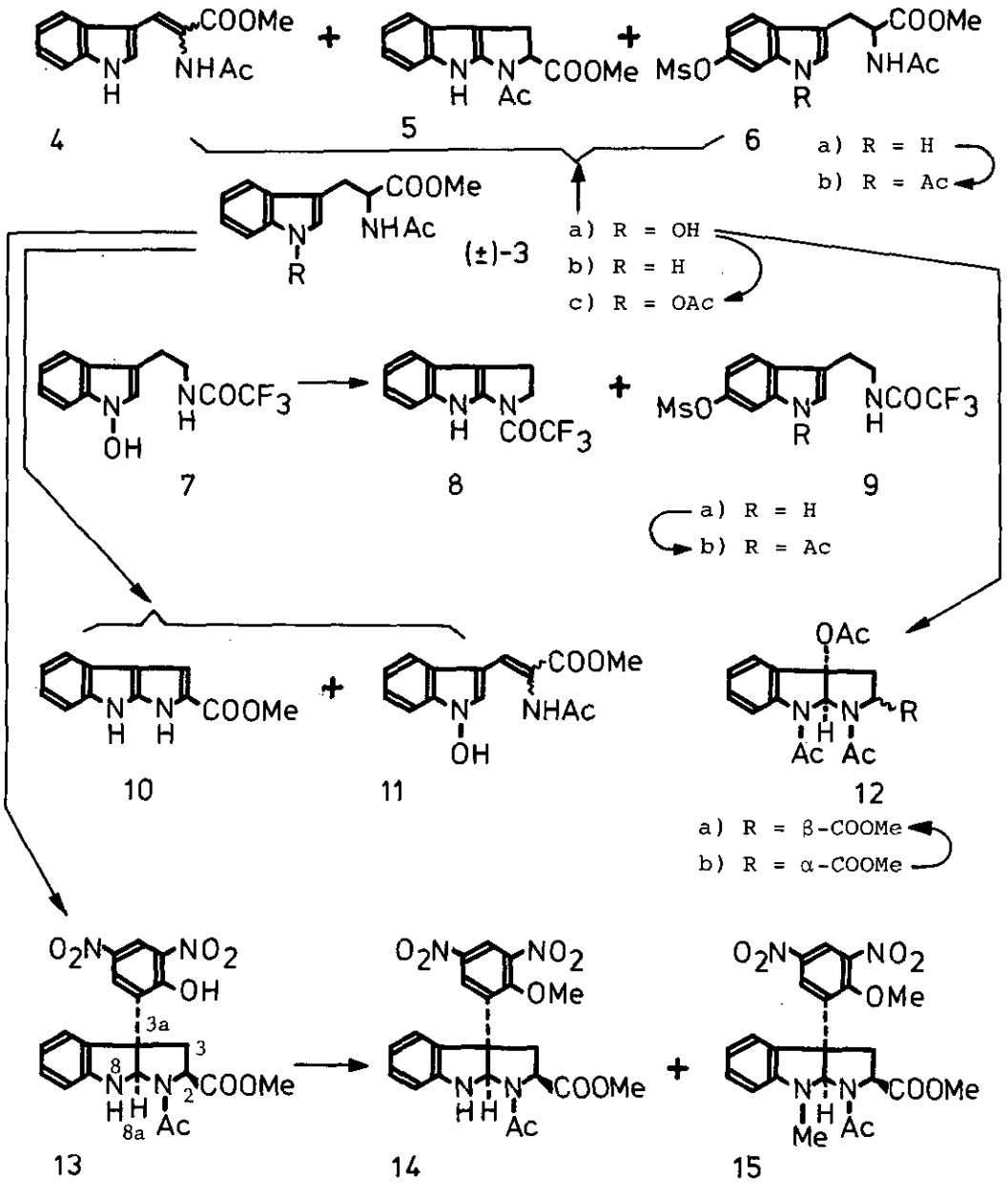
Scheme 2



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-trifluoroacetyl-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

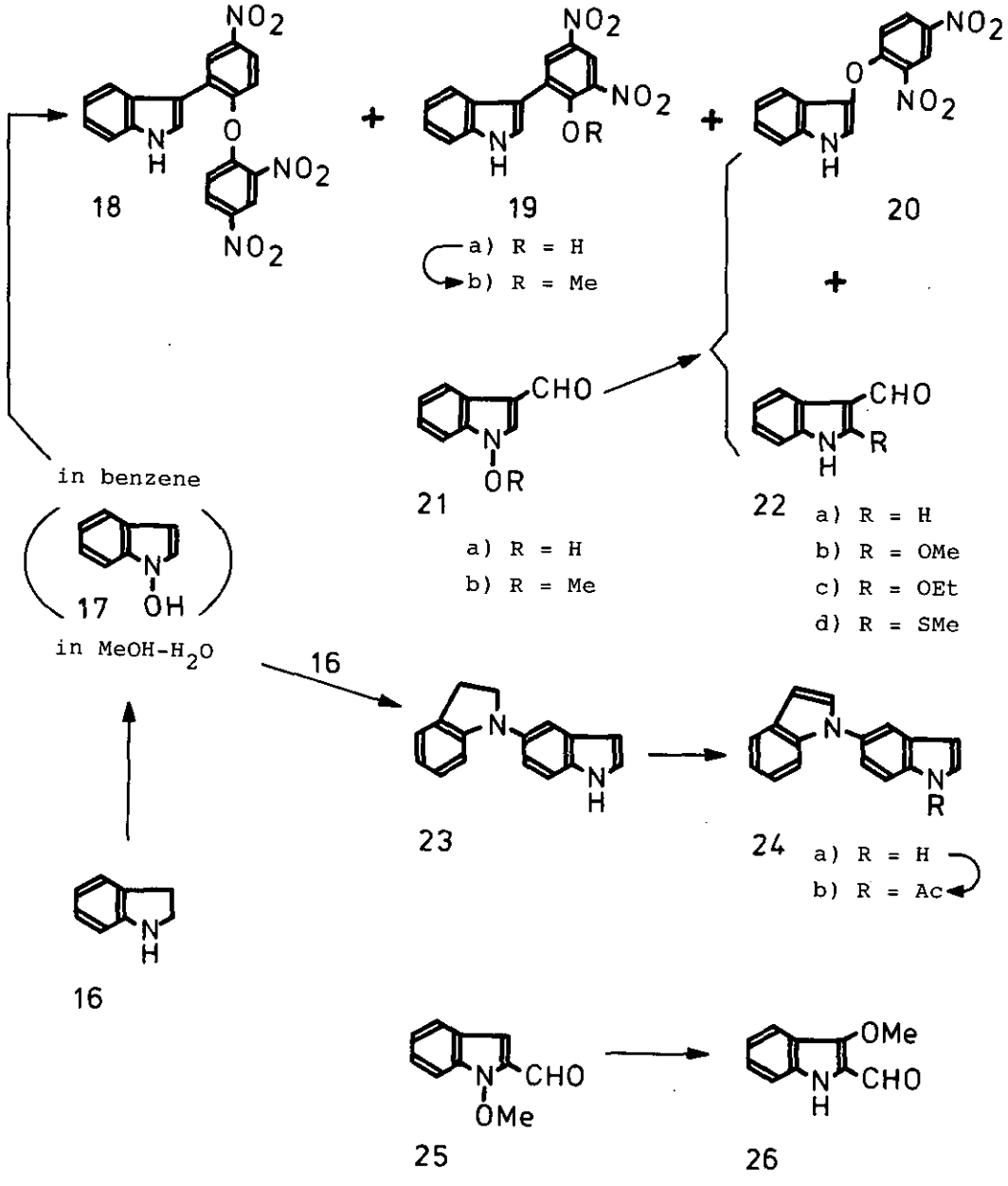

COOMe
NHAc
4
5
6
MsO
a) R = H
b) R = Ac
a) R = OH
b) R = H
c) R = OAc
(±)-3
NCOCF3
OH
7
8
9
10
11
OAc
Ac Ac
12
a) R = β-COOMe
b) R = α-COOMe
O2N
NO2
OH
OMe
3a
8a
13
14
15
Me

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
N
H
19
a) R = H
b) R = Me
+
NO2
O
NO2
N
H
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
N
H
23
N
N
R
24
a) R = H
b) R = Ac
N
H
16
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]

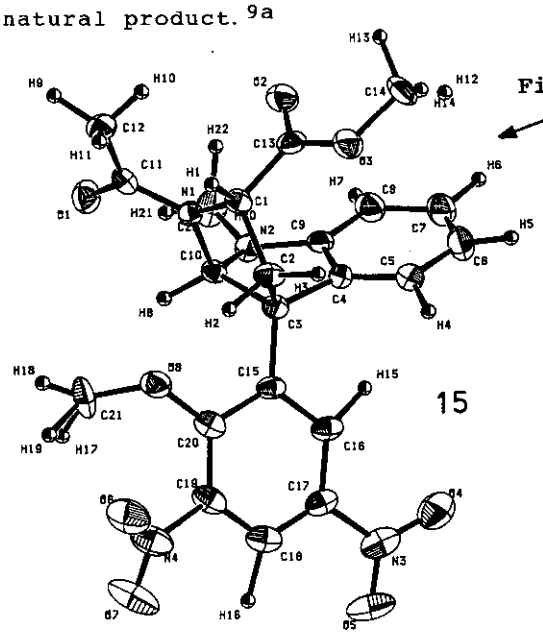


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Figure 1 Crystal Structures of **15** and **18**

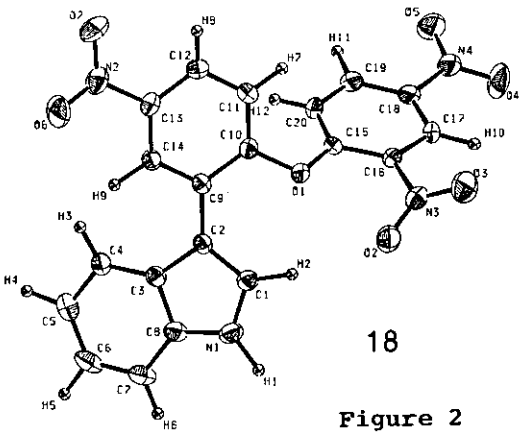

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Figure 2

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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