Nucleophilic substitution reaction of 1-hydroxytryptophan and 1-hydroxytryptamine derivatives regioselective syntheses of 5-substituted derivatives of tryptophan and tryptamine)

メタデータ	言語: eng
	出版者:
	公開日: 2017-10-03
	キーワード (Ja):
	キーワード (En):
	作成者:
	メールアドレス:
	所属:
URL	http://hdl.handle.net/2297/4330

NUCLEOPHILIC SUBSTITUTION REACTION OF 1-HYDROXYTRYPTOPHAN
AND 1-HYDROXYTRYPTAMINE DERIVATIVES (REGIOSELECTIVE SYN-
THESES OF 5-SUBSTITUTED DERIVATIVES OF TRYPTOPHAN AND
TRYPTAMINE)[1]

Masanori Somei* and Yoshikazu Fukui
Faculty of Pharmaceutical Sciences, Kanazawa University
13-1 Takara-machi, Kanazawa 920, Japan

Abstract————Regioselective nucleophilic substitution at
the 5-position of indole nucleus was observed in the re-
action of 1-hydroxytryptophan and 1-hydroxytryptamine de-
rivatives with acids, suggesting the mechanism of seroto-
nin formation in the central nervous system.

It is generally believed[2] that in the central nervous system L-tryptophan
(1, Scheme 1) is initially converted to L-5-hydroxytryptophan (2) by the
enzyme L-tryptophan hydroxylase, and then decarboxylated to give 5-hydrox-
ytryptamine (serotonin, 3) by the action of 5-hydroxytryptophan decarbox-
ylase. However, the transformation mechanism of 1 to 2 can not be explain-
ed in terms of chemistry. With our "1-hydroxyindole hypotheses"[3] in mind,
we could illustrate the mechanism as follows. Initially, 1 would be oxi-
dized by an oxidase (or with metal and dioxygen, hydrogen peroxide, etc),
to the corresponding 1-hydroxyindole (4), directly or via 2,3-dihydroin-
dole. Then, 4 would generate 2 by the elimination of 1-hydroxy group, fol-
lowed by the nucleophilic attack at the 5 position with water. If the nu-
cleophile was hydrogen peroxide (or superoxide), 4 would generate indole-
quinoneimine (5). 5 might be produced by the direct oxidation of 2. Subse-
quent nucleophilic attack of water on 5 generates neurotoxic 4,5- (6),

5,6- (7), and/or 5,7-dihydroxyindoles, and they cause neurodegenerative Alzheimer's disease.[4] Since 6 and 7 are sensitive to oxidation, formations of highly reactive products such as 4,5- (8) and 5,6-dione derivatives could be predicted. Similar story might be possible in the case of 1-hydroxytryptamine derivatives, resulting in an alternative formation of 3 and melatonin.

Now, we wish to report that 1-hydroxytryptophan derivatives[5] actually undergo regioselective substitution reaction at the 5-position with various nucleophiles under mild acidic conditions.

Scheme 1
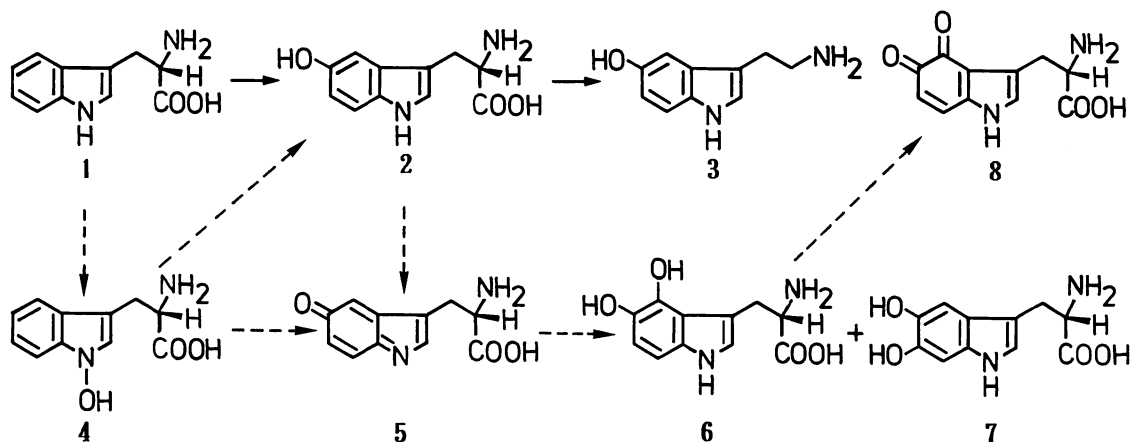
Treatment of (±)-Nb-acetyl-1-hydroxytryptophan methyl ester[6] (9) with 10% sulfuric acid (H_2SO_4) in refluxing methanol (MeOH) for 30 min produced (±)-Nb-acetyl-5-methoxytryptophan methyl ester (10) in 71% yield (Scheme 2). When 3% hydrochloric acid was used instead of H_2SO_4 in the same reaction conditions, the products were 10 and (±)-Nb-acetyl-5-chlorotryptophan methyl ester[6] (11) in the respective yields of 32 and 18%. While, the reaction of 9 with thionyl chloride in anhydrous tetrahydrofuran generated (±)-Nb-acetyl-2-chlorotryptophan methyl ester (13) in 35% yield in addition to 11 and (±)-Nb-acetyltryptophan methyl ester (12) in 9 and 3% yields, respectively. It is interesting to note that when 9 was treated

with 85% formic acid (HCOOH) at room temperature (26°C) for 45 h, forma-
tions of (±)-*N*b-acetyl-1-formyl-[7] (**14**) and (±)-*N*b-acetyl-5-hydroxytrypto-
phan methyl ester[8] (**15**) were observed in 40 and 34% yields, respectively.
The compound (**10**) was identical with the authentic sample (mixed mp, tlc,
uv, ir, and [1]H-nmr), prepared from commercially available (±)-5-methoxy-

Scheme 2
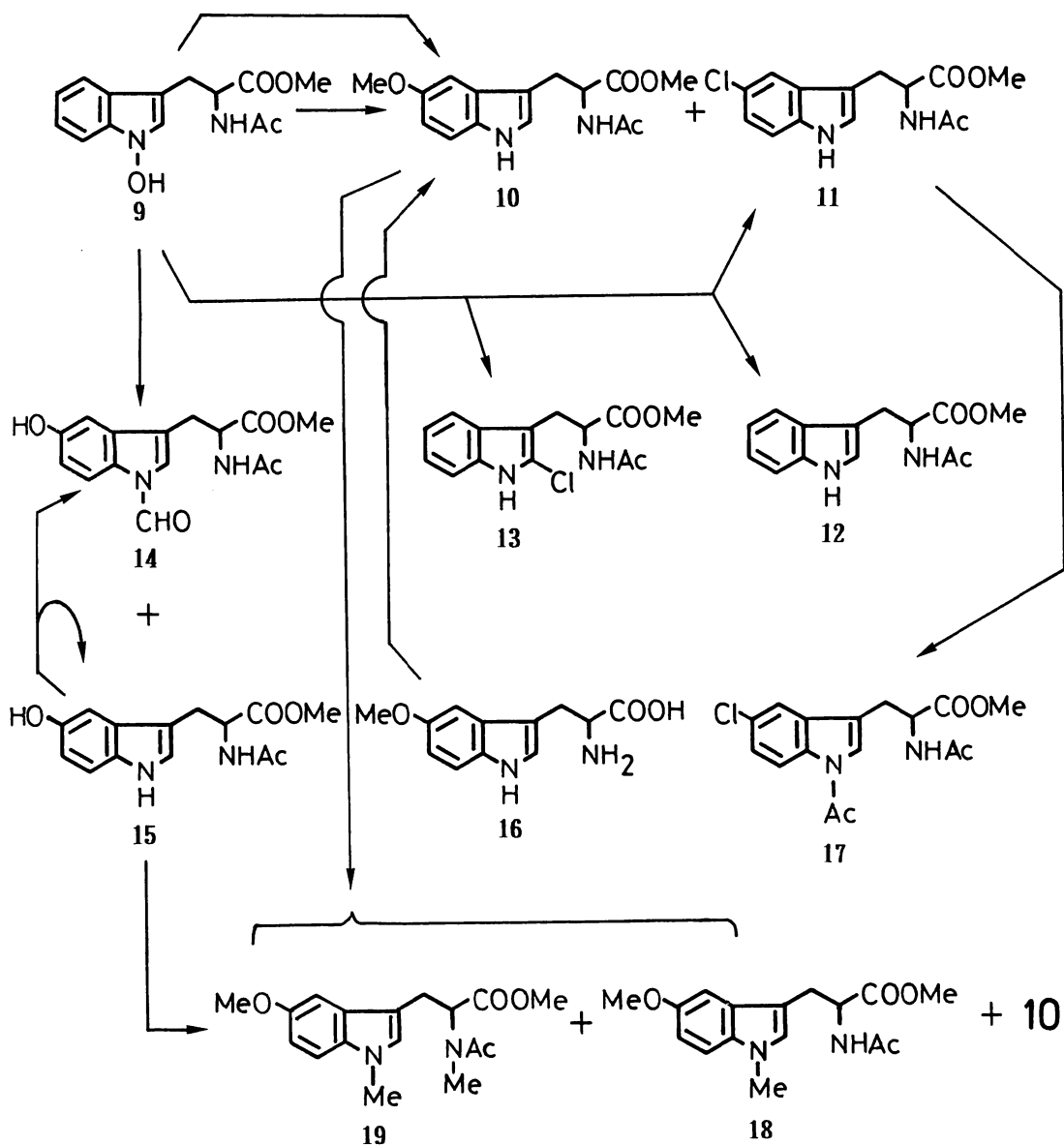
tryptophan (16) by the sequential *Nb*-acetylation and methylation. The structure of 11 was suggested to be either 5- or 6-substituted indole based on the presence of *meta*-coupled proton at δ 7.48 (1H, d, *J*=2 Hz) in its [1]H-nmr spectrum. Finally, it was determined by tranforming 11 to the 1-acetyl derivative (17) in 45% yield by the reaction with sodium hydride (NaH), followed by the treatment with acetyl chloride. Comparison of [1]H-nmr spectrum of 11 with that of 17 clearly showed that the C-7 proton (1H, d, *J*=8 Hz) shifted to lower magnetic field by 1 ppm by the anisotropy effect of 1-acetyl group, proving that 11 was 5-substituted indole. An attempt to convert 15 to 10 with ethereal diazomethane or dimethyl sulfate and potassium carbonate was unsuccessful giving almost quantitative recovery of starting material. However, treatment of 15 with NaH in *N*,*N*-dimethylformamide (DMF) under argon atmosphere, followed by the reaction with methyl iodide, afforded 10, (±)-*Nb*-acetyl-5-methoxy-1-methyl- (18), and (±)-*Nb*-acetyl-1,*Nb*-dimethyl-5-methoxytryptophan methyl ester (19) in 7, 54, and 18% yields, respectively. Similar methylation of the authentic 10 afforded 18 and 19 in 14 and 73% yields, respectively. Based on these results, the structure of 15 was determined, rigorously. The structure of 14 was proved by the treatment of 15 with 85% HCOOH at 19°C for 72 h, affording a 55% yield of 14 along with a 42% yield of recovered 15.

On the other hand, treatment of *Nb*-acetyl-1-hydroxytryptamine[5] (20, Scheme 3) with 10% H_2SO_4 in MeOH at room temperature (24°C) for 24 h afforded regioselectively *Nb*-acetyl-5-methoxytryptamine (21, melatonin) in 17% yield together with 10% yield of dehydroxylated *Nb*-acetyltryptamine (22). Treatment of 21 with 85% HCOOH for 94 h at 18°C afforded 92% yield of 23, whose [1]H-nmr spectrum supported the proposed structure. Furthermore, the reaction of 20 with 85% HCOOH at room temperature for 19 h afforded *Nb*-acetyl-1-formyl-5-hydroxy-[9] (24) and *Nb*-acetyl-5-hydroxytryptamine[10] (25) in 19 and 17% yields, respectively, together with three minor unknown products. The structure of 21 was proved by the direct comparison with the commer-

cially available melatonin (mixed mp, tlc, uv, ir, and [1]H-nmr).

Scheme 3
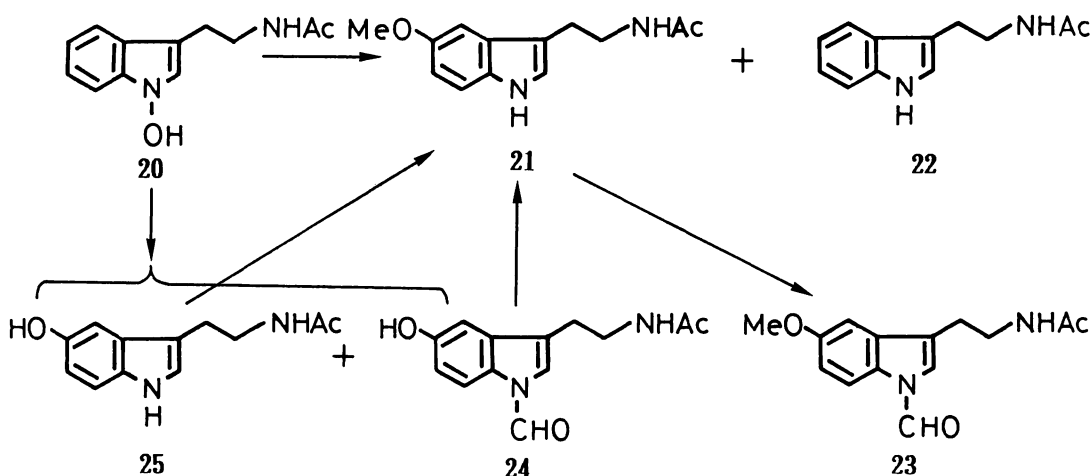
Treatments of both compounds (**24** and **25**) with ethereal diazomethane in MeOH at room temperature afforded the same compound (**21**) in 88 and 94% yields, respectively.

Under basic conditions, **15** was extremely unstable on exposure to air. When the methylation of **15** was carried out, open to air, using NaH and MeI in DMF, (±)-*N*b-acetyl-1-methyltryptophan-4,5-dione (**26**, Scheme 4) was formed in 10% yield together with 13% yield of **10** and tars. However, oxidation of **15** with iodosylbenzene in MeOH[11] for 2 h at 20°C was mild enough to produce (±)-*N*b-acetyltryptophan-4,5-dione methyl ester[12] (**27**) in 39% yield. The spectral data of **27** were superimposable with those of the reported *N*b-ethoxycarbonyltryptamine-4,5-dione (**28**).[13]

Scheme 4
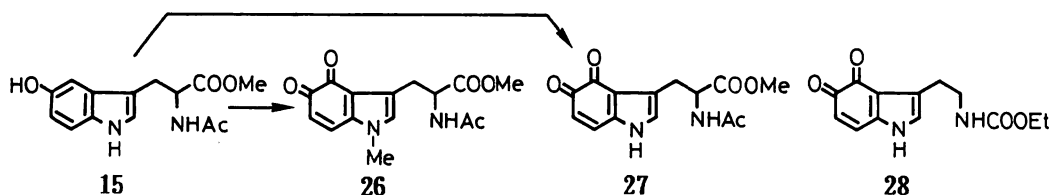
Synaptic vesicles are acidic[14] (pH about 5.5) and function as storation of

chemical transmitter, serotonin (3).[14] However, taking the present results

into consideration, we can speculate the possibility that 3 is formed in

synaptic vesicles *via* the derivatives of 9 and/or 20 by the action of acid.

Abnormal nucleophilic attack of water on 1-hydroxytryptophan or 1-hydroxy-

tryptamine derivatives would generate 4-, 6-, and/or 7-hydroxyindole com-

pounds, and then they would be oxidised to 4,5-, 5,6-,[15] and/or 5,7-dihy-

droxytryptamine[16] analogs, which function as neurotoxin culminating in

neurodegenerative Alzheimer's disease.[4]

In view of synthetic organic chemistry, we could develop a simple and eco-

nomical route to 5-hydroxytryptophan derivatives through the corresponding

1-hydroxyindoles. Synthetic applications and biological evaluations of the

reported compounds in this communication are currently under investigation.

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6. Colorless oil. Ir (film) cm^{-1}: 3317 (br), 1735, 1653, 1434, 1217, 887, 791. ^{1}H-Nmr (500 MHz, CDCl$_3$) δ : 2.00 (3H, s), 3.25 (1H, dd, J=14.8 and 5 Hz), 3.32 (1H, dd, J=14.8 and 5 Hz), 3.72 (3H, s), 4.94 (1H, dt, J=8 and 5 Hz), 6.00 (1H, d, J=8 Hz), 7.00 (1H, d, J=2.4 Hz, collapsed to s after addition of D$_2$O), 7.14 (1H, dd, J=8.6 and 2 Hz), 7.27 (1H, d, J=8.6 Hz), 7.48 (1H, d, J=2 Hz), 8.17 (1H, br s). High resolution ms m/z: Calcd for C$_{14}$H$_{15}$ClN$_2$O$_3$: 296.0740 and 294.0770. Found: 296.0692 and 294.0745.

7. mp 163-164°C (colorless prisms from MeOH). Ir (KBr) cm^{-1}: 3324, 3178, 1735, 1686, 1639, 1605, 1551, 1467, 1400. ^{1}H-Nmr (DMSO-d$_6$, recorded at 120°C) δ : 1.83 (3H, s), 2.98 (1H, ddd, J=14.8, 7.8, and 0.8 Hz), 3.08 (1H, ddd, J=14.8, 6, and 0.8 Hz), 3.62 (3H, s), 4.61 (1H, dt, J=7.8 and 6 Hz), 6.80 (1H, dd, J=8.8 and 2.4 Hz), 6.92 (1H, d, J=2.4 Hz), 7.46 (1H, s), 7.85 (1H, br s), 7.92 (1H, d, J=8.8 Hz), 8.86 (1H, s), 9.19 (1H, s). Ms m/z: 304 (M$^+$). *Anal.* Calcd for C$_{15}$H$_{16}$N$_2$O$_5$: C, 59.20; H, 5.30; N, 9.21. Found: C, 58.96; H, 5.22; N, 9.17.

8. Colorless oil. Ir (film) cm^{-1}: 3368, 1732, 1643, 1438, 1372, 1207. ^{1}H-Nmr (CD$_3$OD) δ : 1.92 (3H, s), 3.08 (1H, ddd, J=14.7, 7.7, and 0.8 Hz), 3.20 (1H, ddd, J=14.7, 6, and 0.8 Hz), 3.53 (3H, s), 4.69 (1H, dd, J=7.7 and 6 Hz), 6.66 (1H, dd, J=8.6 and 2.4 Hz), 6.88 (1H, dd, J=2.4 and 0.7 Hz), 7.00 (1H, s), 7.15 (1H, dd, J=8.6 and 0.7 Hz). High resolution ms m/z: Calcd for C$_{14}$H$_{16}$N$_2$O$_4$: 276.1109. Found: 276.1111.

9. mp 209-210°C (colorless prisms from MeOH-H$_2$O). Ir (KBr) cm^{-1}: 3251, 1670. 1628, 1606, 1460, 1400, 1300, 1246, 1197, 779. ^{1}H-Nmr (DMSO-d$_6$, recorded at 120°C) δ : 1.80 (3H, s), 2.75 (2H, t, J=7.2 Hz), 3.36 (2H, dt, J=6.2 and 7.2 Hz), 6.80 (1H, dd, J=9 and 2 Hz), 6.94 (1H, d, J=2 Hz), 7.46 (1H, s), 7.49 (NH or OH, br s), 7.92 (1H, d, J=9 Hz), 8.84

(NH or OH, br s), 9.17 (1H, s). Ms m/z: 246 (M^+). *Anal.* Calcd for
$C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.40; H, 5.80; N,
11.32.

10. Colorless oil. Ir (film) cm^{-1}: 3359, 2906, 1623, 1364, 1184, 1090, 932,
792. ^{1}H-Nmr (CD_3OD) δ: 1.91 (3H, s), 2.85 (2H, dt, J=1 and 7.3 Hz),
3.43 (2H, t, J=7.3 Hz), 6.65 (1H, dd, J=8.6 and 2.4 Hz), 6.92 (1H, dd,
J=2.4 and 0.6 Hz), 7.00 (1H, s), 7.15 (1H, dd, J=8.6 and 0.6 Hz). High
resolution ms m/z: Calcd for $C_{12}H_{14}N_2O_2$: 218.1054. Found: 218.1046.

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12. mp 196°C (decomp., purple powder from MeOH). Ir (KBr) cm^{-1}: 3176, 1740,
1633, 1503, 1452, 1209, 776. ^{1}H-Nmr (CD_3OD) δ: 1.90 (3H, s), 3.00 (1H,
dd, J=14.5 and 9 Hz), 3.24 (1H, dd, J=14.5 and 5.3 Hz), 3.70 (3H, s),
4.71 (1H, dd, J=9 and 5.3 Hz), 5.94 (1H, d, J=9.9 Hz), 6.71 (1H, s), 7.
25 (1H, d, J=9.9 Hz). Uv λ_{max}^{MeOH} nm (log ε): 234 (4.35), 349 (3.45),
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