THE FIRST TOTAL SYNTHESIS OF BUFOBUTANOIC ACID BY TWO ROUTES BASED ON NUCLEOPHILIC SUBSTITUTION REACTION ON INDOLE NUCLEUS

Takashi Kurauchi, Yoshiyuki Nagahama, Masakazu Hasegawa, Koji Yamada, and Masanori Somei*
Faculty of Pharmaceutical Sciences, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-0934, Japan

Abstract — Regioselective nucleophilic substitution reaction of 1-hydroxytryptamines led to establish two novel routes for the first synthesis of bufobutanoic acid. An effective synthesis of 5-benzyloxytryptamine from tryptamine is also reported.

In 1999, Kamano and co-workers isolated bufobutanoic acid (1a, Scheme 1) as a cytotoxic substance against murine P388 lymphocytic leukemia cells from Ch’an Su and determined its structure. From our ongoing project for developing biologically active novel compounds, we have much interested in 1a and intended to establish a methodology applicable for producing its various congeners. To meet our end, we initially needed simple synthesis of 1a. Now, we have succeeded in developing two routes based on 1-hydroxyindole chemistry.

The first route is the one utilizing 1-hydroxy-Nb-methoxycarbonyltryptamine (3a) as an intermediate, a potent inhibitor of platelet aggregation. Thus, 3a, obtained in three steps from tryptamine (2) in 62% overall yield as described before, was converted to 4b in 48% yield by the regioselective hydroxylation at the 5-position upon the reaction with 85% HCOOH at room temperature for 24 h. Interestingly, the corresponding 1-methoxy-Nb-methoxycarbonyltryptamine (3b) provided 4a selectively in 69% yield by the similar treatment with 85% HCOOH at 80°C for 20 min. Subsequent reaction of 4a with 85% HCOOH at room temperature for 2 days provided 4b in 70% yield together with 10% yield of starting material. The reaction of 4b with benzyl bromide in the presence of K₂CO₃ in DMF afforded 4c in 94% yield. Alkaline hydrolysis of 4c with 10% NaOH in refluxing MeOH provided 96% yield of 5-benzyloxytryptamine (5). With an useful building block for preparing various serotonin derivatives in hand, it was converted to 6 in 96% yield by the reaction with succinic anhydride in THF. Catalytic hydrogenation of 6 over 10% Pd/C at room temperature produced 1a in 99% yield. The spectra of 1a are identical with those reported in the literature.

As the second one, six-steps synthesis of 1a in 13% overall yield with 43% originality rate was developed. Tryptamine (2) was initially reacted with succinic anhydride in THF at room temperature, followed by methylation with CH₂N₂ in one pot procedure to give Nb-methoxysuccinyltryptamine (7) in 89% yield. Subsequent reduction of 7 with Et₃SiH in CF₃COOH at 60°C provided the corresponding 2,3-dihydroindole (8) in 99% yield. Our 1-hydroxyindole synthetic method using Na₂WO₄·2H₂O₄ and
Scheme 1

30% H$_2$O$_2$ at room temperature was successfully applied to 8 giving the desired 1-hydroxytryptamine (9a) in 56% yield. Structure of 9a was confirmed by converting it to 1-methoxytryptamine (9b) in 86% yield by the reaction with CH$_2$N$_2$. Then, 9a was treated with 85% HCOOH at 50°C for 50 min to give serotonin derivative (1b) in 38% yield. Finally, ester part of 1b was hydrolyzed with 1M K$_2$CO$_3$ in MeOH at 50°C to provide 1a in 70% yield.

In conclusion, we have disclosed that nucleophilic substitution reaction$^{10}$ of 1-hydroxytryptamines$^{11}$ is a suitable methodology for the preparations of serotonin congeners.

ACKNOWLEDGMENT
This work is supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan, which is gratefully acknowledged.

REFERENCES AND NOTES
gave satisfactory spectral and elemental analysis or high-resolution MS data for crystals or gums, respectively. 1b, gum; 4a, gum; 4b, gum; 4c, gum; 5, mp 97.5—99.5°C; 6, mp 145—147°C; 7, mp 118—120°C; 8, mp 74—75°C; 9a, mp 151.5—153.5°C.


7. Although hydrochloride of 5 is commercially available from Sigma, it is expensive and therefore not suitable as a common starting material for multi-gram scale production of serotonin congeners. Our present method seems to be better to obtain 5 at cheaper cost compared to the conventional one. Another choice is to utilize serotonin hydrochloride as a starting material.


Originality rate is the result of the following calculation:

Originality Rate (%) = 100 x [Number of Newly Developed Steps + 1] ÷ [Total Number of Synthetic Steps + 1]

