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THE FIRST TOTAL SYNTHESIS OF BUFOBUTANOIC ACID BY TWO ROUTES BASED ON NUCLEOPHILIC SUBSTITUTION REACTION ON INDOLE NUCLEUS[1]

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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.

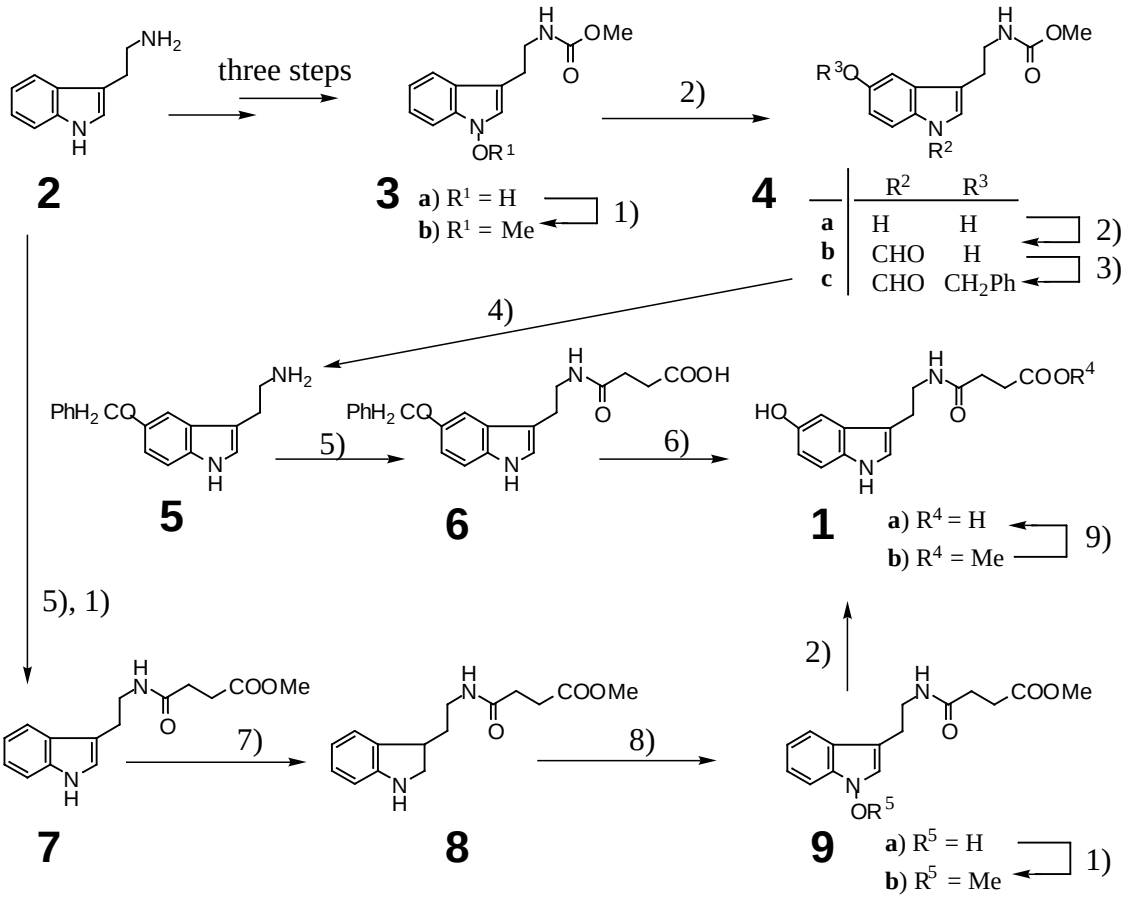
In 1999, Kamano and co-workers[2] isolated bufobutanoic acid (**1a**, Scheme 1) as a cytotoxic substance against murine P388 lymphocytic leukemia cells from Ch'an Su and determined its structure. From our ongoing project for developing biologically active novel compounds,[3] we have much interested in **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.[4]

The first route is the one utilizing 1-hydroxy-*Nb*-methoxycarbonyltryptamine (**3a**) as an intermediate, a potent inhibitor of platelet aggregation.[5] Thus, **3a**, obtained in three steps from tryptamine (**2**) in 62% overall yield as described before,[6] 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[6] (**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 K_2CO_3 in DMF afforded **4c** in 94% yield. Alkaline hydrolysis of **4c** with 10% NaOH in refluxing MeOH provided 96% yield of 5-benzyloxytryptamine (**5**).[7] 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.[2] Thus, the first synthesis of **1a** was achieved in eight steps from **2** in 25% overall yield with 33% originality rate.[8]

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 CH_2N_2 in one pot procedure to give *Nb*-methoxysuccinyltryptamine (**7**) in 89% yield. Subsequent reduction of **7** with Et_3SiH in CF_3COOH[9] at 60°C provided the corresponding 2,3-dihydroindole (**8**) in 99% yield. Our 1-hydroxyindole synthetic method using $Na_2WO_4 \cdot 2H_2O$[4] and

Scheme 1



1) CH_2N_2; 2) 85% HCOOH; 3) $PhCH_2Br$, K_2CO_3, DMF; 4) 10% NaOH, MeOH; 5) succinic anhydride, THF; 6) 10% Pd/C, H_2; 7) Et_3SiH, CF_3COOH; 8) $Na_2WO_4 \cdot 2H_2O$, 30% H_2O_2; 9)1_M K_2CO_3, MeOH.

30% H_2O_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_2N_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 1_M K_2CO_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.

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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.

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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.
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