

SYNTHESIS OF 1,3-BIS(HYDROXYMETHYL)- β -CARBOLINE DERIVATIVES

Fumiko Hamauchi* and Sadao Ohki

Tokyo College of Pharmacy, Hachioji, Tokyo 192-03, Japan

1,3-Bis(hydroxymethyl)- β -carboline derivatives were synthesized by Pictet-Spengler or Bischler-Napieralski reactions, followed by LAH reductions. Among them, 1,3-bis(hydroxymethyl)-2-benzyl-1,2,3,4-tetrahydro- β -carboline (2) hydrochloride was proved to be comparatively effective as an antiinflammatory agent.

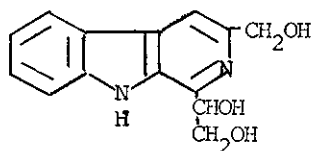
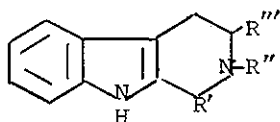
Several biologically active hydroxymethyl- β -carbolines were found in the natural world.¹ One of them, pyridindolol^{1a} (9) which was recently isolated from Actinomycetes, is a β -galactosidase inhibitor.

We synthesized 1,3-bis(hydroxymethyl)- β -carboline derivatives and examined their pharmacological activity.

The reduction with LiAlH_4 (LAH reduction) of cis-1,3-dialkoxycarbonyl-2-benzoyl-1,2,3,4-tetrahydro- β -carboline² (1) afforded cis-1,3-bis(hydroxymethyl)-2-benzyl-1,2,3,4-tetrahydro- β -carboline (2) (hydrochloride; mp 222°C) and 3-hydroxymethyl-2-benzyl-1,2,3,4-tetrahydro- β -carboline (3) (monohydrate; mp 142-143°C), the later of which was dehydroxymethylated compound of 2.

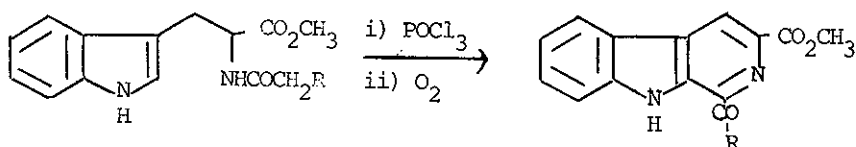
1-(1,2-Dihydroxyethyl)-3-hydroxymethyl-1,2,3,4-tetrahydro- β -carboline (4) (mp 188°C) was prepared by condensation of tryptophanol and glyceraldehyde.

Dehydrogenation of 4 with Pd-C did not afford 9, but 3-hydroxymethyl- β -car-



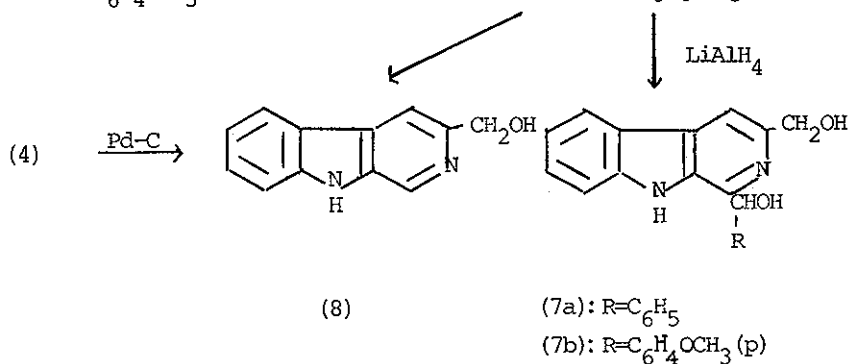
- (1): $R' = \text{CO}_2\text{C}_2\text{H}_5$, $R'' = \text{COC}_6\text{H}_5$, $R''' = \text{CO}_2\text{CH}_3$
 (2): $R' = R''' = \text{CH}_2\text{OH}$, $R'' = \text{CH}_2\text{C}_6\text{H}_5$
 (3): $R' = \text{H}$, $R'' = \text{CH}_2\text{C}_6\text{H}_5$, $R''' = \text{CH}_2\text{OH}$
 (4): $R' = \text{CH}(\text{OH})\text{CH}_2\text{OH}$, $R'' = \text{H}$, $R''' = \text{CH}_2\text{OH}$

Pyridindolol (9)**



- (5a): $R = \text{C}_6\text{H}_5$
 (5b): $R = \text{C}_6\text{H}_4\text{OCH}_3$ (p)

- (6a): $R = \text{C}_6\text{H}_5$
 (6b): $R = \text{C}_6\text{H}_4\text{OCH}_3$ (p)



** 1-[1-(R), 2-dihydroxyethyl]-3-hydroxymethyl- β -carboline

boline (8) (mp 225–228°C) and any other method of dehydrogenation to obtain 9 was unsuccessful.

Amides (5a,b) were prepared by condensation of tryptophan methyl ester and phenylacetic acid or p-methoxyphenylacetic acid with diethyl phosphorocyanidate (DEPC)³ in good yields. Cyclization of amides (5a,b) with phosphoryl chloride yielded the ring-closed compounds, which were immediately oxidized by air to form 1-aryl-3-methoxycarbonyl- β -carboline (6a) [mp 245°C, yield; 29%, UV_{max}^{EtOH} nm (log ϵ); 225 (3.47), 283 (4.05)] and (6b) [mp 249°C, yield; 50%, UV_{max}^{EtOH} nm (log ϵ); 221 (3.76), 293 (3.77)]. By LAH reduction of 6a and 6b, 1-(α -hydroxyarylmethyl)-3-hydroxymethyl- β -carboline (7a) (mp 165°C) and (7b) (mp 167°C) were obtained respectively.

In the above syntheses it was often observed that hydroxymethyl or alkoxy-carbonyl groups were eliminated by LAH reduction, for instance, from 1 to 3, from 4 to 8 and from 6 to 8, and that their yields varied with the reaction conditions. Since there are several reports⁴ concerning the decarboxylation of amino acid, we are now investigating these dehydroxymethylation.

The hydrochloride of 2 has an antinflammatory activity, whose effectivity is almost equal to that of oxyphenbutazone.

Elemental analysis of all the new compounds gave satisfactory result.

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