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

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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 antiflammatory agent.

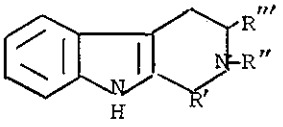
Several biologically active hydroxymethyl-β-carbolines were found in the natural world.[1] One of them, pyridindolol[1a] (9) which was recently isolated from Actinomycetes, is a β-galactosidase inhibitor.

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

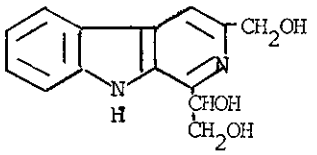
The reduction with $LiAlH_4$ (LAH reduction) of cis-1,3-dialkoxycarbonyl-2-benzoyl-1,2,3,4-tetrahydro-β-carboline[2] (1) afforded cis-1,3-bis(hydroxymethyl)-2-benzyl-1,2,3,4-tetrahydro-β-carboline (2) (hydrochloride; mp 222°C) and 3-hydroxymethyl-2-benzyl-1,2,3,4-tetrahydro-β-carboline (3) (monohydrate; 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 condenzation of tryptophanol and glycerylaldehyde.

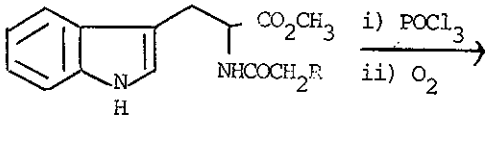
Dehydrogenation of 4 with Pd-C did not afford 9, but 3-hydroxymethyl-β-car-



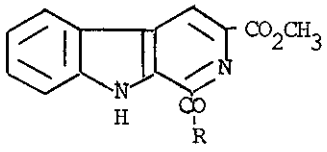
(1): R′=$CO_2C_2H_5$, R″=COC_6H_5, R‴=CO_2CH_3
(2): R′=R‴=CH_2OH, R″=$CH_2C_6H_5$
(3): R′=H, R″=$CH_2C_6H_5$, R‴=CH_2OH
(4): R′=CH(OH)CH_2OH, R″=H, R‴=CH_2OH



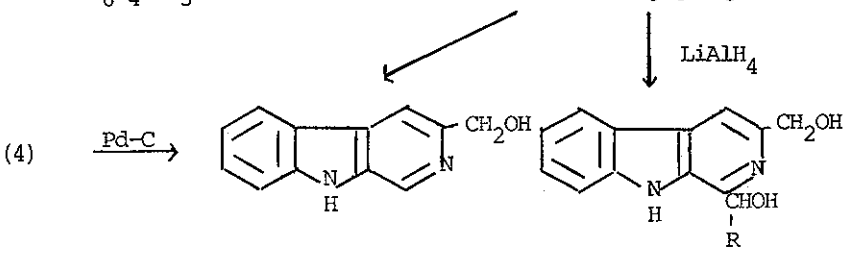
Pyridindolol (9)**



(5a): R=C_6H_5
(5b): R=$C_6H_4OCH_3$(p)



(6a): R=C_6H_5
(6b): R=$C_6H_4OCH_3$(p)



(8)

(7a): R=C_6H_5
(7b): R=$C_6H_4OCH_3$(p)

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

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

Amides (5a,b) were prepared by condenzation of tryptophan methyl ester and phenylacetic acid or p-methoxyphenylacetic acid with diethyl phosphorcyanidate (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-aroyl-3-methoxycarbonyl-β-carbolines (6a) [mp 245°C, yield; 29%, UV_{max}^{EtOH}nm (logε); 225 (3.47), 283 (4.05)] and (6b) [mp 249°C, yield; 50%, UV_{max}^{EtOH}nm (logε); 221 (3.76), 293 (3.77)]. By LAH reduction of 6a and 6b, 1-(α-hydroxyarylmethyl)-3-hydroxymethyl-β-carbolines (7a) (mp 165°C) and (7b) (mp 167°C) were obtained respectively.

In the above syntheses it was often observed that hydroxymethyl or alkoxycarbonyl 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 reports[4] concerning the decarboxylation of amino acid, we are now investigating these dehydroxymethylation.

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

Elemental analysis of all the new compounds gave satisfactory result.

REFERENCES

1 a) T. Aoyagi, M. Kumagai, T. Hazato, M. Hamada, T. Takeuchi and H. Umezawa, J. Antibiotics, 1975, XXVIII, 557. b) Y. Kondo and T. Takemoto, Chem. Pharm. Bull. (Tokyo), 1973, 21, 837.

2 F. Hamaguchi, T. Nagasaka and S. Ohki, Yakugaku Zasshi, 1974, 94, 351.

3 T. Shioiri, Y. Yokoyama, Y. Kasai and S. Yamada, Tetrahedron, 1976, 32, 2211.

4 a) H. Akimoto, K. Okamura, M. Yui, T. Shioiri, M. Kuramoto, Y. Kikugawa and

S. Yamada, Chem. Pharm. Bull. (Tokyo), 1974, 22, 2614. b) P. Rajagopalan and B. G. Advani, Tetrahedron Letters, 1965, 2197. c) S. Yamada and H. Akimoto, Tetrahedron Letters, 1969, 3105.

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