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SYNTHESIS OF N(2)-HYDROXY-1,2,3,4-TETRAHYDRO-β-CARBOLINES

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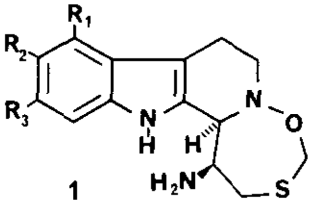
Abstract - N-Hydroxytryptamine condensed readily with a series of aldehydes in the presence of a catalytic amount of acetic acid to give the corresponding nitrones (4a-f), which in turn were cyclized by hydrochloric acid to the stable N(2)-hydroxytetrahydro-β-carbolines (5a-f). β-Carbolines of this type have not previously been synthesized, and are of interest because of their structural relationship to several potent antiviral marine alkaloids (eudistomins C, E, K and L).

A recent report described the isolation of eudistomins C, E, K, and L (1a-d) from the Caribbean tunicate Eudistoma olivaceum.[1] These new marine alkaloids, which have potent activity against Type 1 Herpes simplex virus, are structurally novel both as oxathiazepines and as *N(2)-oxytetrahydro-β-carbolines*.

In view of the antiviral properties of the eudistomins, it seemed of interest to investigate the synthesis and properties of some simple N(2)-hydroxy-1,2,3,4-tetrahydro-β-carbolines, no examples of which have been previously reported.



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1	R_1	R_2	R_3
a	H	OH	Br
b	Br	OH	H
c	H	H	Br
d	H	Br	H

The partial reduction of 3-(2'-nitroethyl)indole (2) to N-hydroxytryptamine (3) has been described,[2,3] but no transformations of 3 have been reported.

We have now found that the hydroxylamine function of 3 reacts readily with a series of representative aliphatic and aromatic aldehydes in the presence of a catalytic amount of acetic acid. The products are not cyclization products, but rather the nitrones 4a-f.[4] On treatment with mineral acid (HCl in methanol), the nitrones slowly cyclized to give the corresponding N-hydroxytetrahydro-β-carbolines (5a-f). The β-carbolines could be prepared directly in methanolic HCl from 3 and the appropriate aldehydes: nitrones were first formed in the cold and were then slowly converted into the β-carbolines on refluxing the solution. The cyclization was easily followed either by tlc, or by observing the disappearance of the α-indole proton at about δ 7.0 in the nitrones.

It is of interest to note that the N-hydroxytetrahydro-β-carbolines 5 did not undergo dehydration under the fairly vigorous acidic conditions in which they were produced. Reaction with acetic anhydride in pyridine also did not result in dehydration, but rather in O-acetylation: i.e. compound 5d gave the O-acetyl derivative (6d), mp 150-152°C, in 90% yield.

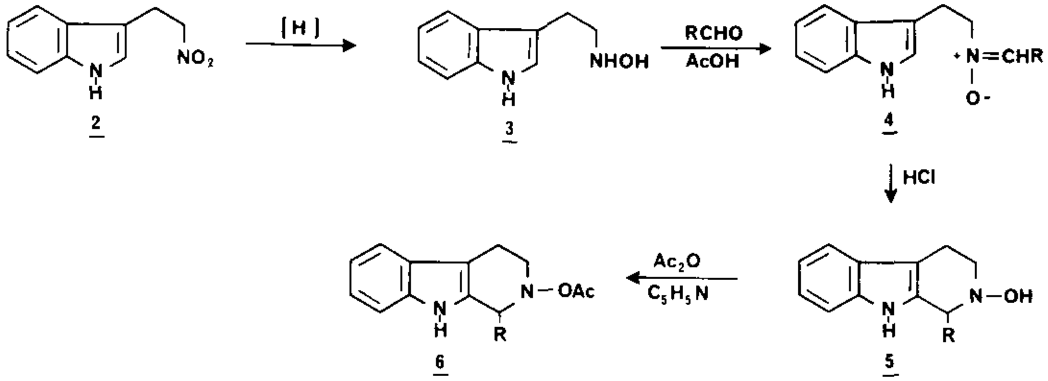

Table 1. Nitrones and N-Hydroxy-β-Carbolines from N-Hydroxytryptamine

Series	Nitrone (4) mp(°C)	Nitrone (4) Yld (%)	N-OH-β-Carboline (5) mp(°C)	N-OH-β-Carboline (5) Yld (%)	R
a	oil	100	193-194	60	CH_3
b	oil	72	oil	72	CH_3CH_2
c	oil	76	oil	66	$CH_3CH_2CH_2$
d	159-161	90	217-219	90	p-$CH_3OC_6H_4$
e	198-199	89	195-197	79	p-ClC_6H_4
f	oil	69	190-191	90	o-BrC_6H_4

Extensions of this work directed at the synthesis of natural eudistomins and their analogs are in progress.

EXPERIMENTAL

Nitrones 4a-f - The appropriate aldehyde (1.5-2.0 mmol) was added to an ice-cold, stirred solution of the hydroxylamine 3 (0.176 g, 1.0 mmol) in methanol (18 ml). Acetic acid (2 drops) was added was added, and the solution was refrigerated for 12 h. The solvent was evaporated and the residue was taken up in $CHCl_3$. The extract was washed with aqueous $NaHCO_3$, dried, evaporated, and the product was purified by chromatography ($CHCl_3$) on silica.

N(2)-Hydroxytetrahydro-β-carbolines 5a-f - The appropriate aldehyde (3-4 mmol) was added to an ice-cold, stirred solution of the hydroxylamine 3 (0.352 g, 2.0 mmol) in methanol (50 ml). Conc. aqueous HCl (20 drops) was added dropwise, and the solution was refrigerated for 6 h, and then refluxed for 34 h. The solvent was evaporated and the residue was partitioned between ether and cold dilute aqueous NH_4OH. The usual work-up was followed by silica gel chromatography ($CHCl_3$, or $CHCl_3$/hexane 3:1) and subsequent crystallization from $CHCl_3$/hexane.

REFERENCES AND NOTES

1. K. L. Rinehart, Jr., J. Kobayashi, G. C. Harbour, R. G. Hughes, Jr., S. A. Mizsak, and T. A. Scahill, J. Am. Chem. Soc., 1984, 106, 1524.

2. A. Cohen and B. Heath-Brown, J. Chem. Soc., 1965, 7179.

3. Our best procedure for the reduction of 2 to 3 employed Al/Hg in moist ether near 0°C for 4 h.

4. All new compounds were characterzied spectroscopically (nmr and ms). New crystalline compounds gave satisfactory elemental analyses.

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