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A Synthesis of 6-Methoxy-2-methyl-1,2,3,4-tetrahydro-β-carboline

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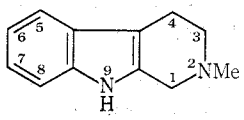
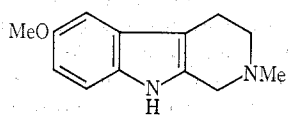
Abstract

A convenient, larger-scale preparation of 6-methoxy-2-methyl-1,2,3,4-tetrahydro-β-carboline, an alkaloid occurring in the pasture grass, *Phalaris tuberosa* L., is described. DL-5-Methoxytryptophan is condensed with formaldehyde and the product, DL-6-methoxy-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid, treated with dichromate to form 6-methoxy-β-carboline. The methiodide of this base is reduced with borohydride to the required alkaloid in *c.* 60% overall yield.

The bases, 2-methyl-1,2,3,4-tetrahydro-β-carboline (1) and 6-methoxy-2-methyl-1,2,3,4-tetrahydro-β-carboline (2), are common, though minor, alkaloidal constituents of several strains of the pasture grass, *Phalaris tuberosa* L., grown in Australia.[1]



(1)



(2)

The major alkaloids present in *P. tuberosa* are the related bases, *N,N*-dimethyltryptamine and its 5-methoxy derivative,[1,2] and these are presumed to be the toxic principles responsible for the sudden collapse and rapid death of sheep grazing the grass at certain stages of its growth cycle.[3,4] Sheep grazing *P. tuberosa* may also contract the chronic neurological disorder known as 'phalaris staggers', but it seems less likely, from tests in which *N,N*-dimethyltryptamine and 5-methoxy-*N,N*-dimethyltryptamine were administered to experimental animals, that these substances are also responsible for this other toxic response.[3–5]

It was therefore necessary that other known constituents of the grass be tested for their possible toxic effects and we have now prepared the above tetrahydro-β-carbolines in quantities of approximately 30 g each. Base (1) was synthesized

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[2] Culvenor, C. C. J., Dal Bon, R., and Smith, L. W., *Aust. J. Chem.*, 1964, **17**, 1301.
[3] Gallagher, C. H., Koch, J. H., Moore, R. M., and Steel, J. D., *Nature*, 1964, **204**, 542.
[4] Gallagher, C. H., Koch, J. H., and Hoffmann, H., *Aust. Vet. J.*, 1966, **42**, 279.
[5] Lee, H. J., and Kuchel, R. E., unpublished data.

following published procedures by condensing tryptophan with formaldehyde (Pictet–Spengler reaction) and treating the product, 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid, with dichromate to form β-carboline (norharman).[6] This was converted into its methiodide[7,8] which was then reduced with borohydride to the required base (1).[8] The analogous synthesis of base (2) from 5-methoxytryptophan does not appear to have been reported, but we have found that it proceeds satisfactorily.

There seems, however, to be no cheap commercial source of 5-methoxytryptophan, but it was conveniently synthesized in the required amounts by the method of Suvorov *et al.*,[9] starting with 4-methoxyphenylhydrazine, which can be prepared in consistently good yield, as described in the preceding communication,[10] after a small modification of the conventional method for preparing arylhydrazines.

Base (2) has been synthesized by other methods which, for economic reasons, were not considered for larger-scale preparation. Shannon and Leyshon[11] prepared it by converting 6-methoxy-1,2,3,4-tetrahydro-β-carboline into its 2-ethoxycarbonyl derivative and reducing this with lithium aluminium hydride. The base also results from the condensation of 5-methoxy-*N*-methyltryptamine with formaldehyde[12] and, in poor yield, by rearrangement of the *N*-oxide of 5-methoxy-*N*,*N*-dimethyltryptamine in the presence of ferrous sulphate.[13]

Experimental

Diethyl Acetamido(formylethyl)malonate

This was prepared by reaction of diethyl acetamidomalonate[14] with acrolein as described by Suvorov *et al.*,[9] sodium methoxide being used as catalyst.

DL-*5-Methoxytryptophan*

Diethyl acetamido(formylethyl)malonate was condensed with 4-methoxyphenylhydrazine[10] to form the corresponding hydrazone which was cyclized and the product converted into DL-5-methoxytryptophan according to the method of Suvorov *et al.*[9]

The alkaline hydrolysis mixture obtained in the final step was acidified with hydrochloric acid to pH *c.* 5, but the precipitate which then formed did not contain the expected 5-methoxytryptophan.[15] It was removed by centrifuging and the clear supernatant passed through a column of the anion-exchange resin, Bio-Rad AG 2-X8 (Bio-Rad Laboratories, California) in the free-base form, and the column washed with water. The amino acid was eluted from the column with 1N acetic acid and recovered in 32% yield, based on 4-methoxyphenylhydrazine.

6-Methoxy-β-carboline

DL-5-Methoxytryptophan (10 g) was dissolved in 0·5N sodium hydroxide (85 ml) to give a solution of pH *c.* 7. Formalin (7 ml; 35% w/w) was added and the mixture allowed to stand at room temperature for 48 h.

It was then acidified (5N hydrochloric acid) to pH 4 and the precipitate (DL-6-methoxy-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid) dissolved by heating to *c.* 80°. Glacial acetic acid (100 ml)

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[8] Elliott, I. W., *J. Heterocycl. Chem.*, 1966, **3**, 361.
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was added, followed by the slow addition of potassium dichromate solution (450 ml; 10% w/v). The effervescing mixture was maintained at 80° and after 10 min, when the evolution of CO_2 had ceased, it was cooled in an ice bath and excess dichromate destroyed by adding solid sodium metabisulphite (40 g).

The mixture was made alkaline with sodium hydroxide solution (250 ml; 40% w/v) and shaken with chloroform (400 ml). Precipitated solids were separated and the chloroform emulsion broken by centrifuging. The lower (chloroform) layer of the supernatant, containing portion of the required product, was set aside.

The residual solids were shaken thoroughly with acetone and the mixture filtered. The acetone was evaporated from the filtrate and the aqueous residue extracted with chloroform.

The two chloroform extracts were combined and dried with anhydrous $MgSO_4$ and the solvent evaporated. The residue was recrystallized from benzene–light petroleum to give 6·3 g (75%) of needles, m.p. 205–207°; λ_{max} 215 (ε 26500), 231 (35000), 246 (25000), 257 (18000), 290 (13000), 297 nm (22200) in ethanol solution (cf.[16]).

6-Methoxy-β-carboline Methiodide

6-Methoxy-β-carboline (10 g) was dissolved in ethanol (200 ml), methyl iodide (45 ml) was added, and the mixture allowed to stand at room temperature for 2 days. Some yellow crystals of the methiodide formed during this period and more were obtained on the subsequent addition of ether (1 l.) to the reaction mixture. The methiodide (15 g; 87%) melted at 265–268° with decomposition.

6-Methoxy-2-methyl-1,2,3,4-tetrahydro-β-carboline

The above methiodide (12 g) was dissolved in methanol–water (900 ml; 1 : 1 v/v) and excess sodium borohydride (6 g) added in small portions, with stirring, over a period of 15 min. The mixture was allowed to stand for a further 15 min and then boiled for 5 min. The base crystallized on cooling and was recovered by filtration and recrystallized from aqueous methanol to yield 6·9 g (91%) of fine white needles, m.p. 215–216° undepressed on admixture with a sample of the alkaloid obtained from *P. tuberosa* and identified by mass spectrometry.[1]

The chromatographic and paper electrophoretic properties of the naturally occurring and synthetic compounds were identical, as were their ultraviolet spectra, λ_{max} 228 and 278 nm with shoulders at 289, 295 and 307 nm in ethanol solution (cf.[11]).

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