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Synthesis of 5-Hydroxykynuramine Hydrochloride (Mausamine)

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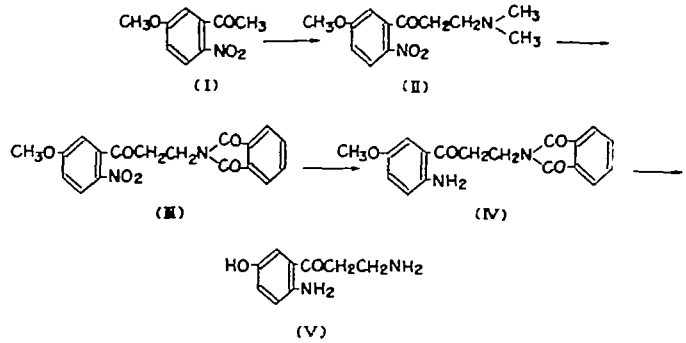
5-Hydroxykynuramine (mausamine) (V) was recently identified in mice urine (*1*) and brain (*2*) with authentic sample in our laboratory. The relationship between the biosynthesis of mausamine and tryptophan metabolism is now under investigation in our laboratory. The fact that mausamine is contained in mouse brain suggests its important role in the function of brain. 5-Hydroxykynurenine which is supposed to be a precursor of mausamine has been recently detected in a human urine though only in very small amount. Mausamine seems to have nearly the same degree of blood pressure effect and promoting action of the contraction of small intestines as serotonine, showing much more remarkable effect than dimethylkynuramine (*3*) or 5-hydroxydimethylkynuramine (*4*). Mausamine (band A on ppc) was easily converted to a new substance which we call mausamine B (*1*, *2*) in dilute aqueous solution (pH 7.0) as can be easily proven by paper chromatography (Table I) or ultraviolet absorption spectrum (band A: λ_{max} 224 mμ and 400 mμ at pH 7.0. band B: λ_{max} 241 mμ and 335 mμ at pH 7.0). The color reactions of band A were positive with Pauli-Monda's reagent (*1*) and Ehrlich's reagent (*1*). Band B had strong fluorescence, and the color reaction was positive with Pauli-Monda's reagent, but color reactions with Ehrlich's reagent and ninhydrin were negative.

Table I

R_f Values of 5-Hydroxykynuramine (Mausamine) A and B Obtained with Various Solvent Systems as Developers

Solvent systems	R_f	
	Band A	Band B
a	0.15	0.49
b	0.06	0.19
c	0.01	0.14
d	0.00	0.04
e	0.36	0.66
Fluorescence	yellow	white

a : *n*-butanol, acetic acid and water (4 : 1 : 5);
b : *n*-butanol saturated with water;
c : isoamyl alcohol, acetic acid and water (4 : 1 : 5);
d : isoamyl alcohol saturated with water;
e : *n*-propanol, acetic acid and water (4 : 1 : 1).



The synthesis of 5-hydroxykynuramine hydrochloride (mausamine) was carried out as follows.

EXPERIMENTAL

2-Nitro-5-Methoxy-β-Dimethylaminopropiophenone Hydrochloride (*II*)—19.5 g. (0.1 mole) of 2-nitro-5-methoxyacetophenone (*5*) were refluxed in 30 ml. of butanol with 4.2 g. (0.14 mole as HCHO) of paraformaldehyde and 8.2 g. (0.1 mole) of dimethylamine hydrochloride for 2 hours. Additional 3 g. (0.1 mole as HCHO) of paraformaldehyde in one interval and a few drops of concentrated hydrochloric acid were added to the mixture near the end of the reaction. After removing the bulk of the solvent *in vacuo*, 60 ml. of acetone were added to the residue and warmed to dissolve and then cooled to get precipitates, m.p. 208°C, yield 22 g. (76.3%).

2-Nitro-5-Methoxy-β-Phthalyliminopropiophenone (*III*)—28.8 g. (0.1 mole) of crude 2-nitro-5-methoxy-β-dimethylaminopropiophenone hydrochloride dissolved in 260 ml. of water were decomposed with 2 *N* sodium hydroxide solution under cooling and the free base in the alkaline solution was extracted with 260 ml. of ether. The ether extracts, after being dried with anhydrous sodium sulfate, was added with 14.7 g. (0.1 mole) of phthalimide and evaporated to dryness. The residue was then refluxed in 65 ml. of absolute ethanol with a bit of sodium ethylate for 2 hours. The reaction solution was allowed to stand overnight in a refrigerator. The precipitates thus formed were collected and washed with diluted hydrochloric acid, 2 *N* sodium hydroxide and water. The crude products were recrystallized from glacial acetic acid or a large amount of ethanol, m.p. 199°C, yield 8 g. (22.6%).

Analysis;
Calcd. for $C_{18}H_{14}O_6N_2$: C: 61.0; H: 4.0; N: 7.9
Found: C: 61.8; H: 4.0; N: 7.9

2-Amino-5-Methoxy-β-Phthalyliminopropiophenone (*IV*)—10.6 g. (0.03 mole) of 2-nitro-5-methoxy-β-phthalyliminopropiophenone dissolved in 100 ml. of glacial acetic acid were added with 27 g. (0.12 mole) of stannous chloride dissolved in 32 ml. of concentrated hydrochloric acid and boiled for a few minutes. The yellowish clear solution was diluted with about 300 ml. of boiling water and cooled in a refrigerator. The yellowish precipitates were collected and recrystallized from glacial acetic acid or a large amount of ethanol, m.p. 216°C, yield 8 g. (82.5%).

Analysis;
Calcd. for $C_{18}H_{16}O_4N_2$: C: 66.7; H: 5.0; N: 8.1
Found: C: 66.9; H: 5.0; N: 8.5

5-Hydroxykynuramine Hydrochloride (*Mausamine*) (*V*)—3.2 g. (0.01 mole) of 2-amino-5-methoxy-β-phthalyliminopropiophenone and 25 ml. of hydrobromic acid (*d.* 1.48) were boiled in a round bottom flask with a reflux condenser under carbon dioxide until it dissolved (about 1.30 hours) to remove phthalyl group. The reaction mixture was subsequently boiled for 20 minutes and then hydrobromic acid was removed *in vacuo* under carbon dioxide, the residue was dissolved in 40 ml. of concentrated hydrochloric acid, then filtered in glass filter to remove phthalic acid. The crude products were boiled with 15 ml. of glacial acetic acid to remove the remaining reactant and the mixture while it was still hot was filtered by suction. After cooling the precipitates were collected and recrystallized from concentrated hydrochloric acid (in this recrystallization, instead of dissolving in concentrated hydrochloric acid the crude product may as well be dissolved in a bit of water followed with adding concentrated hydrochloric acid to it), m.p. 169°C, yield 1.92 g. (76.8%).

5-Hydroxykynuramine Dipicrate—2.0 g. of 5-hydroxykynuramine hydrochloride dissolved in 20 ml. of water were added to a solution of 6 g. of sodium picrate dissolved in 150 ml. of water, and were stand overnight at room temperature. The precipitated yellowish products were collected and recrystallized from water, and then ethanol, m.p. 135°C, yield 3.0 g. (83.0%).

Analysis;
Calcd. for $C_9H_{12}O_2N_2 \cdot 2C_6H_3O_7N_3 \cdot H_2O$:
C: 38.41; H: 3.07; N: 17.08
Found: C: 38.77; H: 3.50; N: 17.50

Decomposition of 5-Hydroxykynuramine Dipicrate—1 g. of 5-hydroxykynuramine dipicrate was dissolved in 200 ml. of 10% hydrochloric acid and extracted several times with ether to remove picric acid completely. The water phase was concentrated to 20 ml. under carben dioxide, then cooled overnight in a deepfreezer. The product was recrystallized from concentrated hydrochloric acid, m.p. 184°C, yield 0.5 g. (94.5%).

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