Biological Activities of Some 5-Substituted N,N-Dimethyltryptamines, α-Methyltryptamines, and Gramines*

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Summary. Three series of derivatives of N,N-dimethyltryptamine, α-methyltryptamine and gramine bearing substituents of varying electronic nature on the C-5 position were tested for acute toxicity, effect on barbiturate sleeping time, antireserpine effect, swim maze, variable interval conditioned behavior, and inhibition of monoamine oxidase. No correlation could be made between the electronic effects and their pharmacological activities. It was thus suggested that there exist different pharmacological receptors for the tryptamines and gramines.

Key-Words: 5-Substituted N,N-Dimethyltryptamines, α-Methyltryptamine, and Gramines — Monoamine Oxidase Inhibitors — Psychopharmacology.

Introduction

The antiserotonin activities of some substituted N,N-dimethyltryptamines, α-methyltryptamines, and gramines have been investigated (Erspamer, 1953; Quadbeck and Röhm, 1954; Gaddum et al., 1955; Ehrhart and Henning, 1961). N,N-Dimethyltryptamine and its 5-methoxy and 5-hydroxy (Bufotenine) derivatives were found to cause behavior changes in animals (McIsaac, 1961; Gessner and Page, 1962; Gallagher et al., 1965; Gessner et al., 1968). Moreover, the inhibitory activities towards monoamine oxidase of N,N-dimethyltryptamine, α-methyltryptamine, their 5-hydroxy and 5-methoxy analogs, and gramine have been reviewed (Zirkle and Kaiser, 1964). Curious as to the versatile activities of these compounds, we collected and synthesized a number of derivatives of N,N-dimethyltryptamine and gramines bearing C-5 substituents and

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studied the influence of their electron with-drawing or electron donating properties on pharmacological activity and monoamine oxidase inhibitory activity.

Method

Compounds

Compounds listed in Table 1 were obtained commercially, except nitrogramine (VIII) and cyanogramine (IX) which were synthesized in our laboratory.

5-Cyanogramine (IX). To a solution of 4.3 g (0.03 mole) of 5-cyanoidole in 15 ml of glacial acetic acid were added successively 6.0 g (0.033 mole) of 25% aqueous dimethylamine, 2.8 g (0.03 mole) of 33% aqueous formaldehyde, and 5 ml of glacial acetic acid. The mixture was stirred at 50°C for 3 hr, cooled, made distinctively alkaline with 10% aqueous potassium hydroxide, and first extracted with 500 ml of ether then 200 ml of benzene. The combined extracts were dried with anhydrous sodium sulfate and evaporated under reduced pressure leaving 5.2 g (86.6% of product, m.p. 138—141°C. Recrystallization of this product with benzene gave 4.3 g (71% of solid, m.p. 144—145°C (corrected).

Anal. Calcd. for C_{12}H_{13}N_8: C, 72.3; H, 6.57; N, 21.1. Found: C, 72.3; H, 6.39; N, 20.9.

5-Nitrogramine (VIII). 5-Nitroindole (5.0 g, 0.031 mole) was treated with dimethylamine and formaldehyde in a similar manner as described in the preparation of IX. The product was extracted into 500 ml of ether. After the removal of ether, the crude solid was recrystallized from benzene yielding 5.0 g (74.7% of yellow needles, m.p. 154—156°C (corrected) (lit. Cavallini and Ravenna, 1958, m.p. 169—170°C).

Anal. Calcd. for C_{12}H_{13}N_8O_2: C, 60.3; H, 5.97; N, 19.2. Found: C, 60.4; H, 6.04; N, 19.3.

Pharmacology

a) Acute Toxicity. All compounds in 30% propylene glycol (10 ml/kg mouse) were administered intraperitoneally at an average of 5 to 6 doses to groups of 10 male albino Yale-Swiss mice weighing 17—23 g. The LD_{50} within a 24-hr period was determined graphically according to the method of Miller and Tainter (1944).

b) Effect on Barbiturate Sleeping Time. Mice in groups of 10 were injected intraperitoneally with 5 μmoles/kg of compounds in 30% propylene glycol. After 5 min, sodium pentobarbital (40 mg/kg) in saline was given via the same route. Controls were treated first with 30% propylene glycol then with pentobarbital in saline. The pre-sleeping time and sleeping time (loss of the righting reflex) were recorded and treated statistically.