The Introduction of the brain stem tranquilizing principle serotonin

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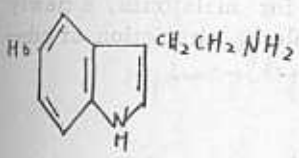
Introduction: Since Ladwig and Schmidt extracted a potent Vasoconstrictor agent from human blood, a further reaching works had been made by their Contemporary. On the basis of chemical tests as well as analytical and Spectal data, the substance has been designated as Serotonin (5-hydroxy-3-β-aminoethyl indole) by Rapport. Serotonin plays an important function in physiology and is considered as a regularly metabolite in human being. Its neurohumoral function and pharmacological significancy awoke a widely reaching in the recent years.



Distribution: Serotonin is found in many tissues of the body, but is particularly concentrated in brain, blood platelets and mucosa of the gastro-intestinal tract. Its concentration is the highest in brain stem particularly in the hypothalamus.

Physiological function:

In the brain system, serotonin is a neurohumoral agent which plays a role in the transmission of nervous impulses in the brain in a manner analogous to that of epinephrine and acetylcholine in the transmission of Peripheral impulses. If the transmission (serotonin) are blocked by inhibitor agent a model psychoses are produced

Experiment has been indicated that alcohol, cannabis, cocaine, especially lysergic acid diethylamide are capable of inducing toxin psychoses " Schizophrenia" characterized by various degrees of disturbance in think, mood, posture. The case are found also in metabolism disease such as phenylketourics, tryptophane dificiening.

Advances in this field have aroused hope that it may be possible ultimately to serious mental disorder in terms of biochemical disturbances in the brain rather than attributing such disturbances entirely to enviromental trauma and congential factor as has been done in classical psychiatry.

The studies of Hess on the hypothalamus have indicated the presence in diencephalon of two opposing systems designated as ergotropic and trophotropic which integrated the basic life function ordinary beyond voluntary control. Activation of ergotropic nervous system increases skeletal muscle activity, induce arousal and activates states. The opposing trophotropic system integrates mechanisms that have a protective dssimulative function. Activation of this system stimulates the parasympathetic system and decreases motor activity, sensitivity to external stimuli and drowsiness akin to natural sleep. The serotonin set off a syndrome similar to those abscribed to stimulation of trophotropic system.

However established a peace, quiet states in brain function, it is high concentration in the lower forms life, where it is present in the brain in high amount than in mammal explain that serotonin serves a role in

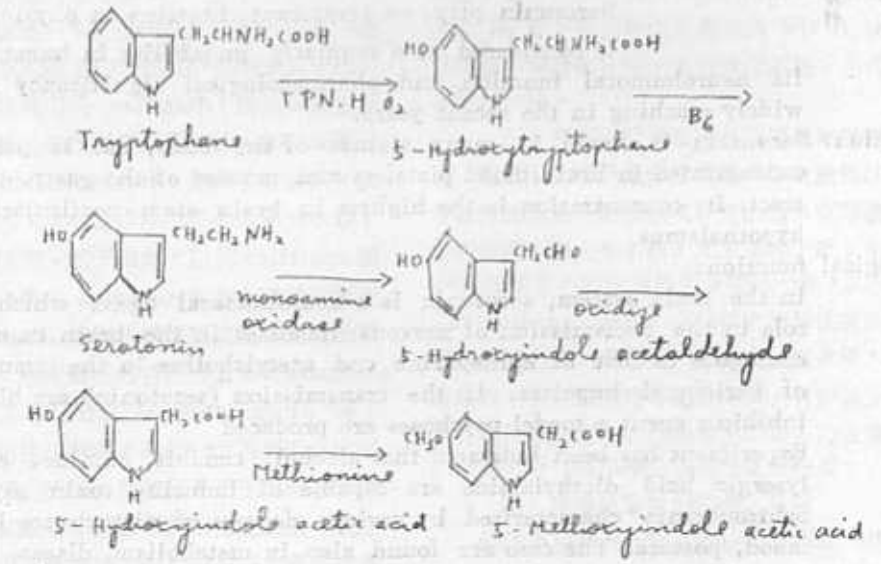
the defense mechanism and living expression. Serotonin would potentiate the sedative effect of hexobarbital in animals. The sedative mechanism of Reserpin might be mediated through the freeing of serotonin from its bound to its inactive form resulting first in a serotonin-like action.

In blood platelets: a considerable amount of serotonin derived from disintegrating platelets. Its Vaso constriction participates in hemostasis and hypertension.

In gastro-intestinal tract: on the mucosa of gastro-intestinal tract a great amount of serotonin present. It exerted stimulation on smooth muscle of stomach. Serotonin may be a gastro-intestinal hormone for digestive system.

In electrolyte balance: Serotonin is a precursor for melatonin, a newly substance derived from the pineal. Melatonin blocks the action of ado-

a.



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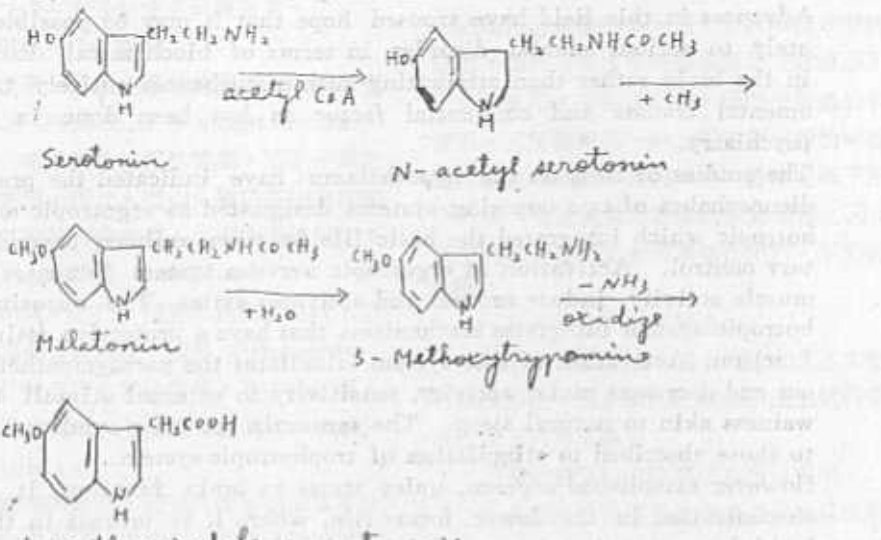

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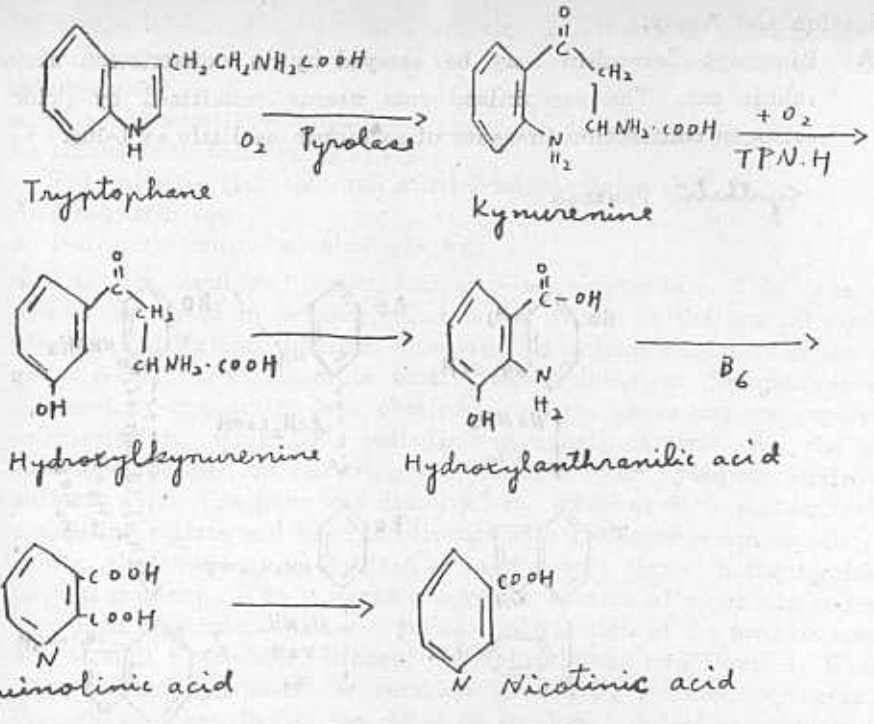


ncorticotropic hormone, consequently induces a retent of sodium ions by the kidney.

In metastatic carcinoid tumor: Greatly increased production of serotonin occurs in malignant carcinoid a diseased charaterized by widely spread development of serotonin producing tumor cell in the argentaffin tissue throughout the abdomenal cavity. The serotonin in the blood of carcinoid patient occurs in the platelets is 0.5~2.7 meg/ml. The disease may be diagnosed by the presence of large amount of 5-hydroxyindole acetic acid in the urine.

In normal condition one percent of tryptophane converted to serotonin, but in carcinoid patient as much as sixty percent followed this path way.

Metabolism : The isotopic experiment confirms that tryptophane is a precursor for serotonin. The 5-hydroxy group can be introduced by T. D. N. H. and oxygen and 5-hydroxy tryptophane are decarboxylation by pyridoxine phosphate.

Serotonin is deaminated by monoamine oxidase, and final product is 5-hydroxyindole acetic acid. The deamination of monoamine oxidase are blocked by Iponiazid. Tryptophane to serotonin cycle are inhibited by phenylalanine. The detail see the diagram!

Properties : Molecular weight 171.21. Soluble in water, glacial acetic acid, very sparingly soluble in methanol (95%.) Insoluble in absolutely acetone, chloroform, acetate, ether, benzene. Their hydrochloride, hygrospic crystals; Sensitive to light. M.p. 167~168. soluble in water, aquas solution are stable at PH2~6.4. Its complex with creatinine absorption max. 275ms PK_1=4.9, PK_2=9.8, PH of 0.01M solution=3.6.

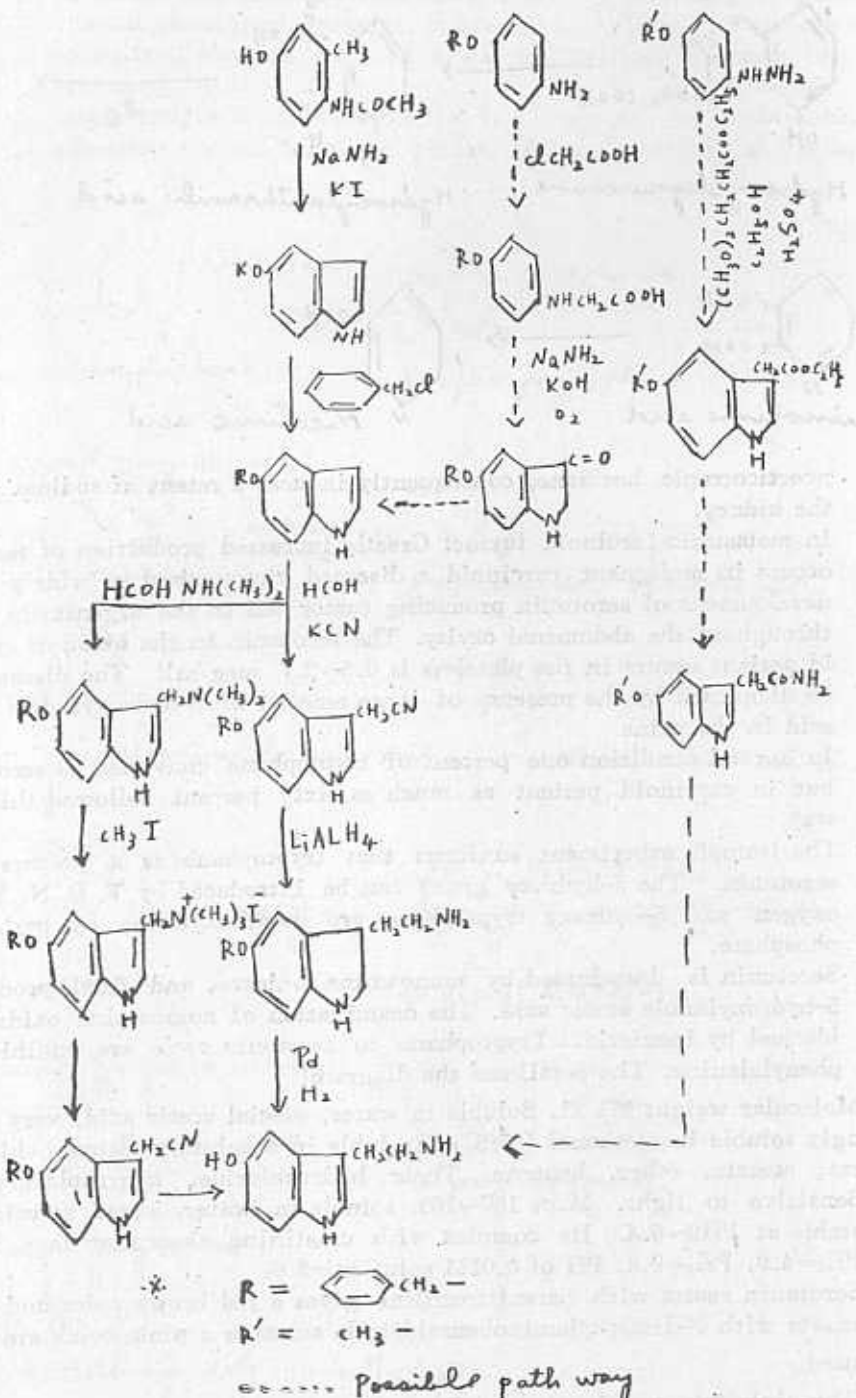
Serotonin reacts with paranitroaniline gives a red brown color and condensats with P-dimethylaminobenzaldehyde solution a pink colok are produced.

The ninhydrin reaction is positive.

Indentification and Assay:

A. Bioassay: Serotonin may be assayed by its constriction action perfused rabbit ear. The atropinized rats uterus sensitized by prior inject of estrogen contraction presente of serotonin as little as 1–10r.

Synthetic process



B. Paperchromatography:

Serotonin is extended by acetic solution in up sphere column, drying in room temperature, then sparies the following reagents many differen colors appear.

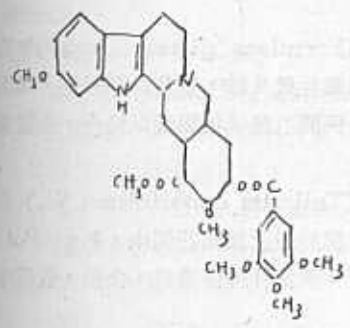
a. para-nitro aniline solution
b. Dichromate formaldehyde sol.
c. Sod. nitrite- HCl sol. and ethyl-1-naphthylame HCl
d. Ninhydrin sol.
e. P-dimethylaminobenzaldehyde sol.

Synthesis : a. The compound was prepared from 5-benzyloxyindole. This intermediate was converted to 5-benzyloxindolaceto nitrile by the general method of Mazima and Kotake. Lithium alumminium hydride reduction of the nitrile gives 5-benzyloxytryptamine which was isolated as hydrochloride. The 5-benzyloxy-tryptamine base obtained from the above salt was catalytically debenzylation using 20% palladium-charcoal catalyst. To the alcohol solution obtained on removing the catalyst was added an equivalent of sulfuric acid. The gum was dissolved in water at 60°C an equivalent of creatinine sulfate and several volumns of hot acetone added on the cooling solute, the complex crystallized as microscopic plates indistinguished for natural product. The infrared absorption spectra of synthetic and natural serotonin creatinine sulfate complex confirmation of the propose structure. (by Merrill E. Specter, Richard V. Heinzelmann and David I. Weisblat)

The Fischer synthesis: A solution of ethyl-r-r-dimethoxybutyrate and P-methoxy- phenylhydazine reflex in absolute ethanol and concentration sulfuric acid under a nitrogen atmosphere for several hours. The products are converted by intraction with ammonia into amide. This intermediates are reduced by lithium aluminium hydride to amine.

Relative compound and antogonial methanism:

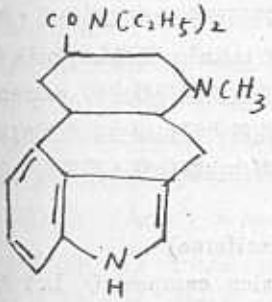
serotonin and reserpine alkaloids: Reserpine contain an indole nucleus as well as serotonin has been suggested their pharmacological acts is a result as antagonizing or potentiting effect of serotonin by displacing it is the tissues and that alteration in serotonin metabolism.



Large dose of reserpine in human causes a decline in serotonin content in the brain. The antogonized effect between serotonin and reserpine as well as Sulfonamide and P-amino benzoid acid.

The sedative and hypotensive effect of reserpine is associated to its antogonized mechanism.

Serotonin and lyserpic acid diethylamide Lysergic acid diethylamide which contain a indole structure is a very potentical Substance to serotonin in another way, The substance is accepted as a miracle hullocinogent in psychosis. The syndrom as well as serotonin inhibited in depressing mental state.



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