T: Chem (13)

Chemical nature and biosynthesis of catecolamine (Epinephrine and norepinephrine)

The pathways of catecholamine biosynthesis of the Central Nervous system (CNS) Sympathetic postganglionic neurons, and adrenal chromaffin tissue appear to be identical.

Phenylalanine is converted into tyrosine, in the presence of phenylalanine hydroxylase. The conversion of tyrosine to epinephrine involves four steps (1) Hydroxylation at the three position of phenolic ring
(2) side chain decarboxylation.
(3) side chain hydroxylation.
(4) N-methylation.

(1) Hydroxylation at the three position of phenolic ring

Hydroxylation of phenylalanine although essential for tyrosine production, may not make an important contribution to tyrosine availability within Sympathetic neuron and chromaffin cells. Tyrosine, the precursor, is also derived primarily from dietary sources. Tyrosine is transported into the cell where it is converted by dihydroxyphenylalanine (DOPA). The first step in the biosynthesis pathway, ie the conversion of tyrosine to dopa, is the rate-limiting reaction; this reaction is catalyzed by the enzyme. tyrosine hydroxylase which is found only in neuroectodermal tissue. Tyrosine hydroxylase is the rate-limiting enzyme in catecholamine biosynthesis.

The activity of this enzyme is regulated by feedback (end product) inhibition by cytoplasmic catecholamines.

② Side chain decarboxylation

In the subsequent step dihydroxyphenylalanine (DOPA) is decarboxylated to dopamine (DA) by by L-aromatic amino acid decarboxylase (DBH) or (DOPA decarboxylase). (DBH is a non specific decarboxylase found in many tissues.)

③ Side chain hydroxylation :— Dopamine is then hydroxylated by dopamine β-hydroxylase (DBH) by addition of an -OH group to the side-chain carbon. (β-carbon adjacent to the phenolic ring). forming norepinephrine (NE) Dopamine is an important neurotransmitter within the CNS. In dopaminergic neurons DA is the final step in catecholamine biosynthesis. In noradrenergic cells neurons DA is then converted to NE within the chromaffin granule. Fig ○

④ N-methylation :— The NE produced is converted to epinephrine (E) by phenylethanolamine N-Methyl transferase (PNMT) outside the granule; this enzyme is found only in the cells that synthesize E (adrenal chromaffin tissue & many vertebrates, and within specific neuronal tract in the brain.).

It should be noted that NE is a primary amine, whereas E is a N-methylated secondary amine these differences provide an important structural basis for the differing potency of these two Catecholamines on adrenoreceptors.

In species where the chromaffin tissue is separated from the adrenal steroidogenic tissue NE is usually the main synthetic product. In those species where the chromaffin cells are contiguous with steroidogenic tissue, (eg human, rat) however E is the predominant catecholamine synthesized.

Storage and release of catecholamines

Unlike the adrenocortical steroid, which are released almost as soon as they are synthesized, catecholamines are stored in the adrenal medullary cells (within granules). They remain present in membrane-enclosed secretory vesicle and are complex with ATP (1 mole of ATP for 4 molecules of catecholamines) and a specific protein chromogranin (mol. weight of 40,000) and DBH. Besides the vesicles also contain a Ca^{+2} and Mg^{2+} dependent ATPase these subcellular vesicles take up epinephrine and norepinephrine by a transport process. The vesicle take up mechanism is blocked potently by reserpine, an antihypertensive drug.

All the contents of the storage granules are released during vesicular exocytosis. The hormones contained within the secretory vesicle can be released in response to an appropriate stimulus, which in the case of adrenal, is acetylcholine secreted by the preganglionic nerve fibres that terminate in medulla. other agents include histamine and glucagon which can also stimulate the release of epinephrine. In response to these signals the chromaffin cells release the catecholamines into the adjacent blood vessels.

Note — Dopa is a neurotransmitter substance used in the treatment of Parkinson's disease.

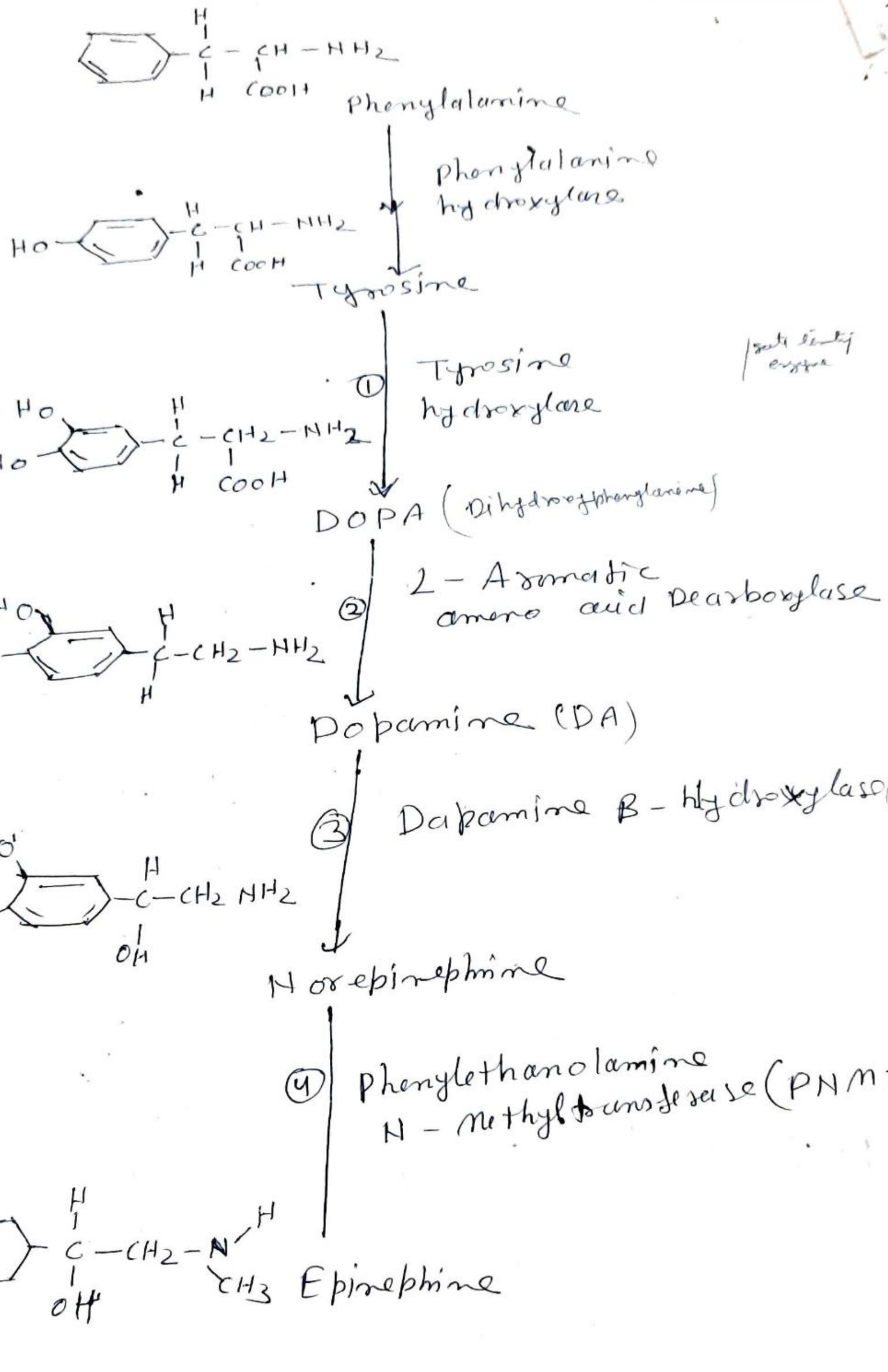

Fig ① Pathway of Catecholamine biosynthesis.

(Fig. 14-3 HJ.