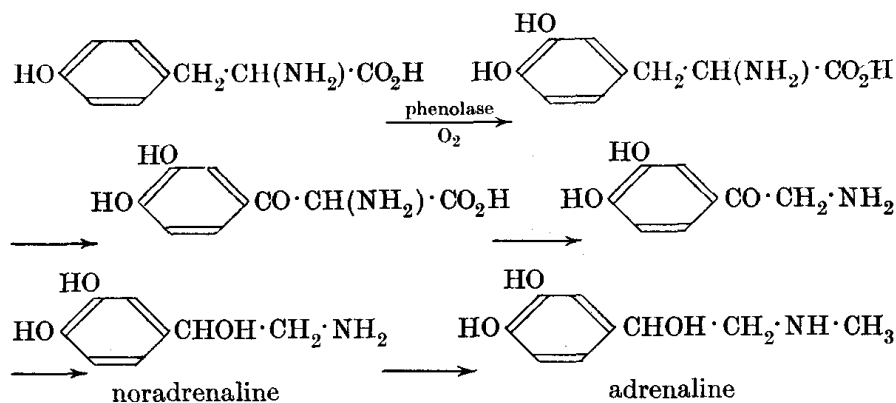


Gates *et al.* (1956) have now synthesised morphine.

§28. Biosynthesis of alkaloids. As more and more structures of alkaloids were elucidated, it became increasingly probable that the precursors in the biosynthesis of alkaloids were amino-acids and amino-aldehydes and amines derived from them. A particularly interesting point is that the consideration of biosynthesis has led to deductions in structure, *e.g.*, Woodward (1948) proposed a biosynthesis of strychnine, and from this Robinson (1948) deduced the structure of emetine which was later confirmed by the synthetic work of Battersby *et al.* (1950).

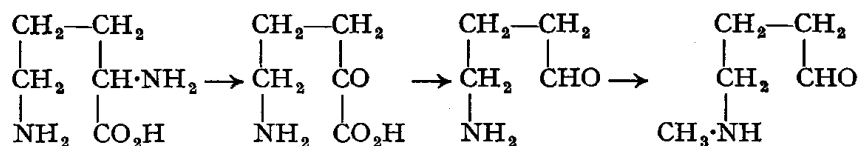
We have already seen (§18. XIII) how keto-acids may be converted into amino-acids, and *vice versa*. There are also enzymes which bring about the decarboxylation of amino-acids to amines and the decarboxylation of α -keto-acids to aldehydes. Thus amino-acids, amines and amino-aldehydes, together with formaldehyde (or its equivalent) are believed to be the units involved in the biosynthesis of alkaloids. The general technique has been to administer labelled precursors to plants and to isolate the alkaloid after some time has elapsed for the growth of the plant.

The following examples of biosynthesis illustrate the principles outlined above. Alkaloids containing a benzene ring are believed to be products of the shikimic acid route (§18. XIII); the amino-acids phenylalanine and tyrosine are the starting points for the biosynthesis of, *e.g.*, ephedrine, hordenine, mezcaine, etc. As an example, we may describe the biosynthesis of adrenaline (§12) from tyrosine; the route is possibly:

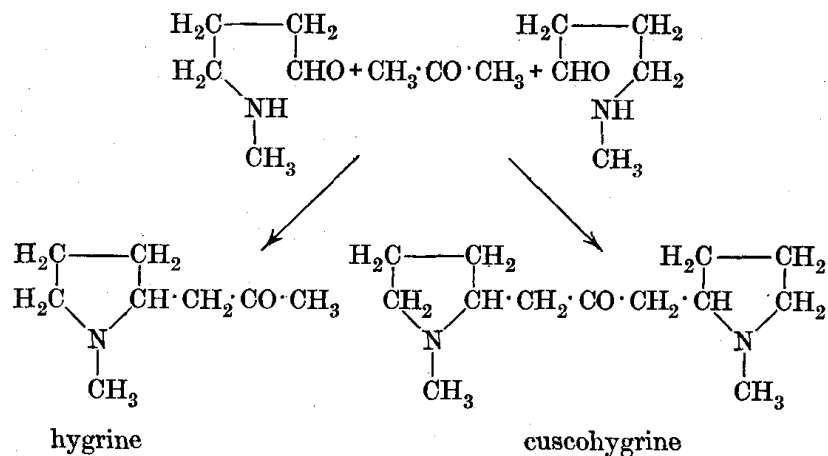


Leete *et al.* (1952-) have shown, using labelled compounds, that phenylalanine, tyrosine and 3,4-dihydroxyphenylalanine are precursors for the alkaloids of the phenylalanine and *isoquinoline* groups (see also later).

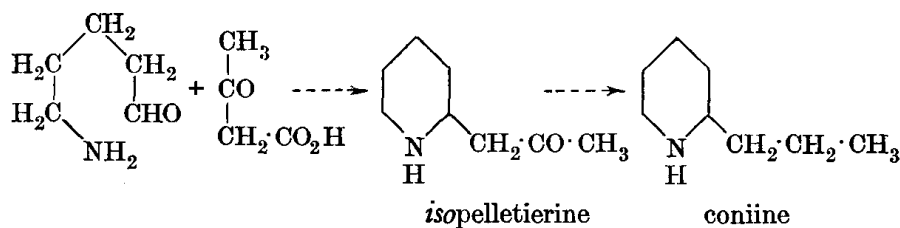
A study of the formulæ of hygrine (§13) and cuscohygrine (§13a) shows that the two most reasonable units are acetone and pyrrolidine. The biosynthesis of acetone occurs *via* acetoacetic acid (see §32a. VIII), but the precursor of the pyrrolidine fragment is less certain. The most likely amino-acid precursor appears to be ornithine, which could undergo the following reactions to give 4-methylaminobutanal (see also later):



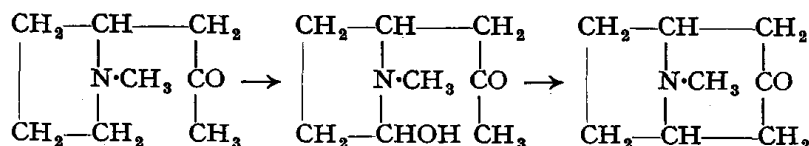
This compound may then be imagined to condense with acetone (or acetoacetic acid) to form hygrine and cuscohygrine (*cf.* §§13, 13a).



In the same way, the pelletierine group of alkaloids (§19) may all be imagined to be formed from 5-aminopentanal, *e.g.*, Anet *et al.* (1949) have condensed this aldehyde with acetoacetic acid at *pH* 11 to give *isopelletierine*; and 5-methylaminopentanal with acetoacetic acid at *pH* 7 to give methyl*isopelletierine*. The amino-acid precursor of 5-aminopentanal is most likely lysine (the homologue of ornithine). It should also be noted that conversion of the keto group in *isopelletierine* into a methylene group gives coniine:

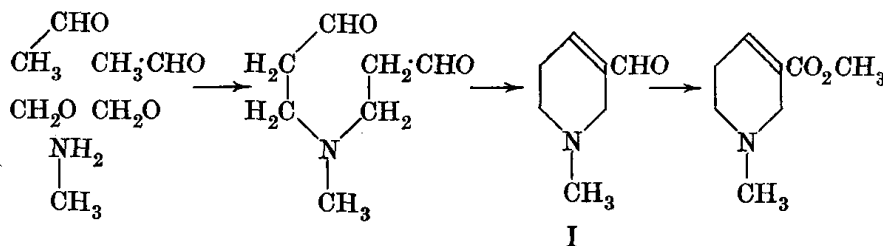


Now let us consider tropinone. Since this compound contains the hygrine skeleton, one possible mode of biosynthesis of tropinone could be *via* hygrine as the precursor:



On the other hand, tropinone has been synthesised from succinaldehyde, methylamine and acetonedicarboxylic acid under physiological conditions (§22). In this case, the problem is the nature of the precursor of succinaldehyde. Glutamic acid is one possibility, and succinic acid is another. The biosynthesis of cocaine (§23) is similar to that of tropinone.

The biosynthesis of some alkaloids containing a piperidine ring has already been discussed. Mannich (1942) has suggested that arecoline (§17) is formed as follows:

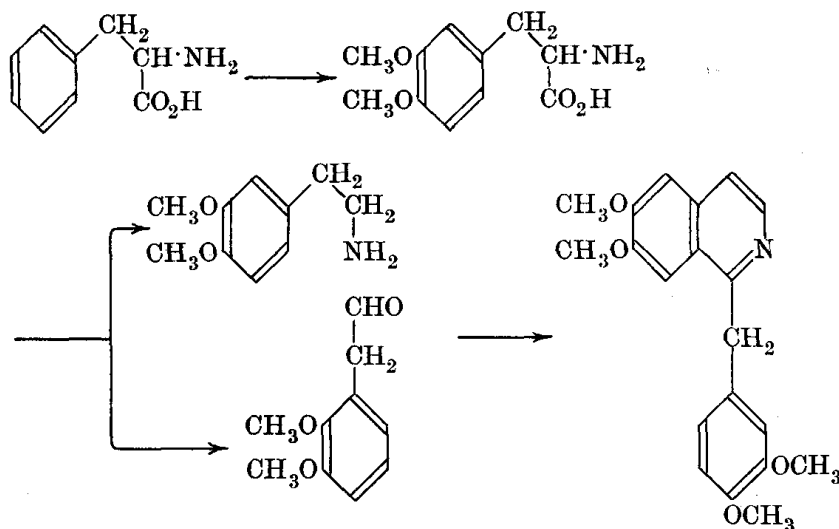


Mannich obtained I by carrying out the condensation with a mixture of acetaldehyde, formaldehyde and methylamine at room temperature at pH 3.

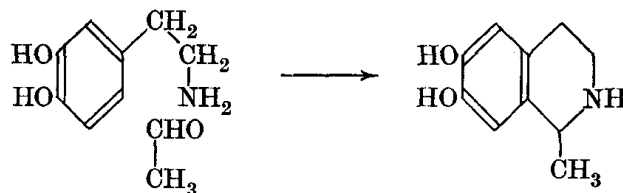
Leete (1955–1958) has shown, using labelled ornithine, that this amino-acid is a good precursor for the pyrrolidine ring in nicotine, and has also suggested that putrescine, glutamic acid and proline are incorporated into the pyrrolidine ring, but are less efficient precursors than ornithine. Marion *et al.* (1954) have also shown that labelled ornithine is incorporated into hyoscyamine (§22). Kaczowski *et al.* (1960), using labelled compounds, have found that acetate is incorporated into the tropane ring in hyoscyamine, possibly *via* acetoacetate. Leete (1960) has shown that phenylalanine is a precursor of tropic acid.

The origin of the pyridine ring is still obscure. Some suggestions have been described above. It appears that alanine and aspartic acid are precursors of nicotinic acid, and experiments using tritium-labelled nicotinic acid support the hypothesis that it is converted into nicotine *via* a 6-pyridone derivative (Dawson *et al.*, 1958).

It has been pointed out above that phenylalanine, etc. are precursors for the *isoquinoline* alkaloids. Thus, *e.g.*, papaverine (§26) might possibly undergo biosynthesis as follows:



Support for the plausibility of this mechanism is given, *e.g.*, by the formation of the tetrahydroisoquinoline from the condensation between 3 : 4-dihydroxyphenylethylamine and acetaldehyde at *pH* 3-5 (Schöpf *et al.*, 1934).



Rapoport *et al.* (1960), using labelled carbon dioxide (^{14}C), have shown that the primary product of synthesis in the morphine alkaloids is apparently thebaine, which is later converted into codeine and morphine.

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