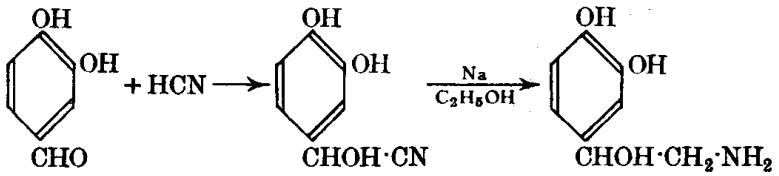
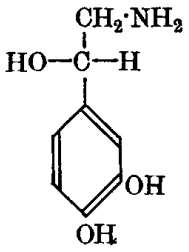


(±)-noradrenaline

According to Dalgliesh (1953), the configuration of (—)-noradrenaline is

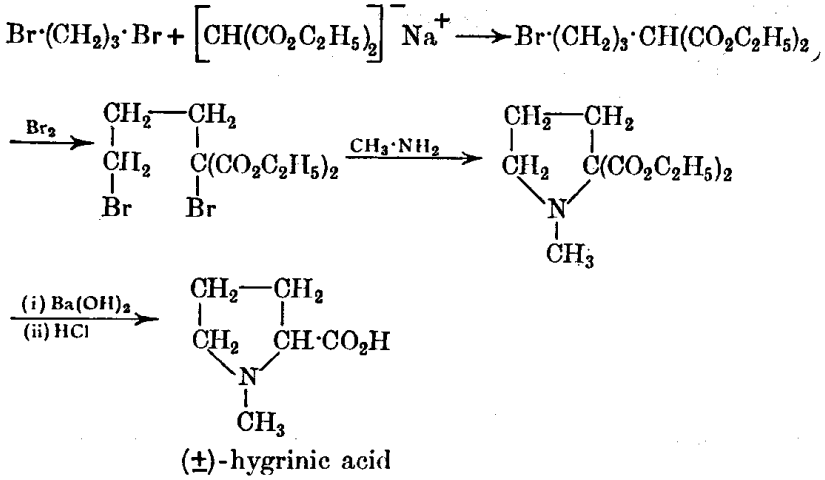


PYRROLIDINE GROUP

§13. Hygrine, $C_8H_{15}ON$, b.p. 193–195°, is one of the coca alkaloids. Its reactions show the presence of a keto group and a tertiary nitrogen atom, and when oxidised with chromic acid, hygrinic acid is formed.

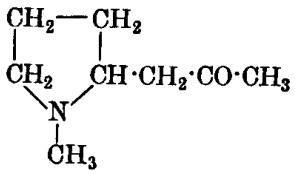
$$C_8H_{15}ON \xrightarrow{[O]} C_6H_{11}O_2N$$
hygrinic acid

Hygrinic acid was first believed to be a piperidinecarboxylic acid, but comparison with the three piperidine acids showed that this was incorrect. When subjected to dry distillation, hygrinic acid gives *N*-methylpyrrolidine; hence hygrinic acid is an *N*-methylpyrrolidinecarboxylic acid. Furthermore, since the decarboxylation occurs very readily, the carboxyl group was assumed to be in the 2-position (by analogy with the α-amino-acids). This structure, 1-methylpyrrolidine-2-carboxylic acid, for hygrinic acid was confirmed by synthesis (Willstätter, 1900).

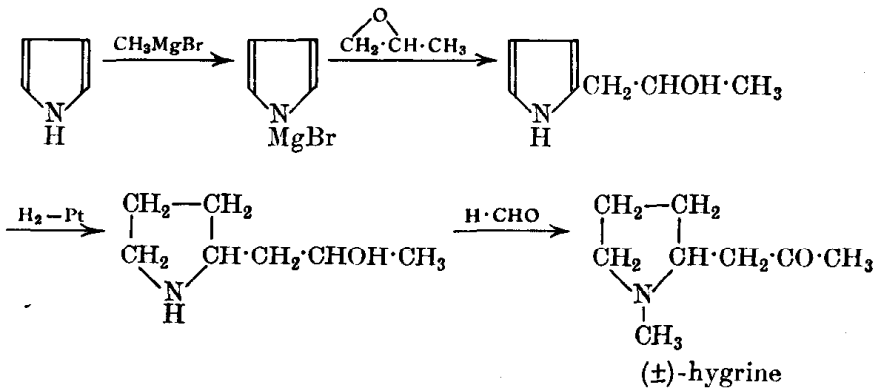


(±)-hygrinic acid

Thus a possible structure for hygrine is

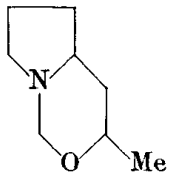


Hess (1913) claimed to have confirmed this structure by synthesis; his synthesis starts with pyrrylmagnesium bromide and propylene oxide to form pyrrylpropanol (note the rearrangement that occurs). This compound is then catalytically hydrogenated and then treated with formaldehyde; the imino nitrogen is methylated and the secondary alcoholic is oxidised to a keto group.



(±)-hygrine

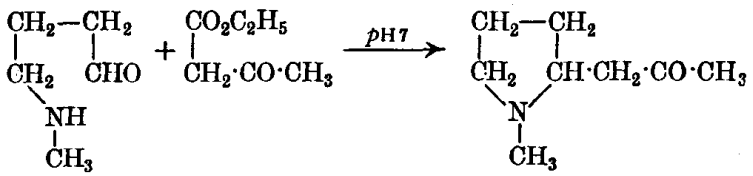
Lukeš *et al.* (1959) have repeated Hess's work and have shown that the



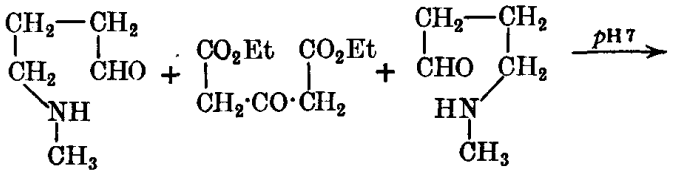
I

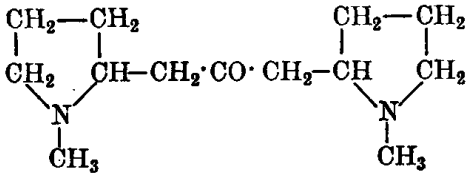
product is not hygrine but the tetrahydro-oxazine (I); it is the last stage of Hess's interpretation that has been shown to be incorrect.

Anet *et al.* (1949) have also synthesised (±)-hygrine by condensing γ-methylaminobutyraldehyde with ethyl acetoacetate in a buffered solution at a *p*H of 7 (physiological conditions).



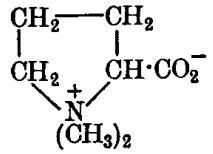
§13a. Cuscohygrine (*Cuskhygrine*), b.p. 169–170°/23 mm., occurs with hygrine. Its structure is established by the following synthesis (Anet *et al.*, 1949); γ-methylaminobutyraldehyde is condensed with acetonedicarboxylic ester:



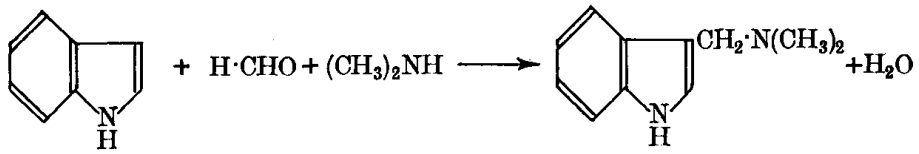


cuscohygrine

§13b. Stachydrine is obtained from the roots of *Stachys tuberifa*, from orange leaves, etc. It is the betaine (§4 C. XIII) of the quaternary ammonium compound of hygrinic acid.



§14. Gramine has been found in barley mutants; it raises the blood-pressure in dogs when administered in small doses. Gramine has been synthesised by allowing indole to stand in an aqueous solution containing formaldehyde and dimethylamine (Snyder *et al.*, 1944).



PYRIDINE GROUP

§15. Trigonelline, $C_7H_7O_2N$, m.p. 130°, is widely distributed in plants; the best source is the coffee bean. When boiled with barium hydroxide solution trigonelline produces methylamine; thus the molecule contains an *N*-methylamino group. On the other hand, when heated with hydrochloric acid at 250° under pressure, trigonelline forms methyl chloride and nicotinic acid; this suggests that the alkaloid is the methyl betaine of nicotinic acid. This structure for trigonelline has been confirmed by synthesis (Hantzsch, 1886). When heated with methyl iodide in the presence of potassium hydroxide, nicotinic acid, I, is converted into methyl nicotinate methiodide, II. II, on treatment with " silver hydroxide " solution, forms nicotinic acid methohydroxide, III, which then spontaneously loses a molecule of water to give trigonelline (a betaine), IV.