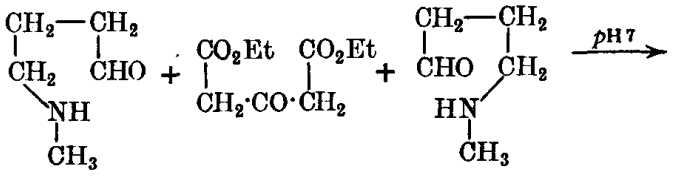
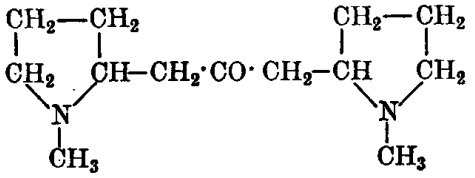
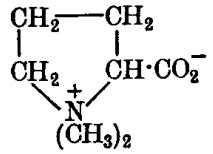


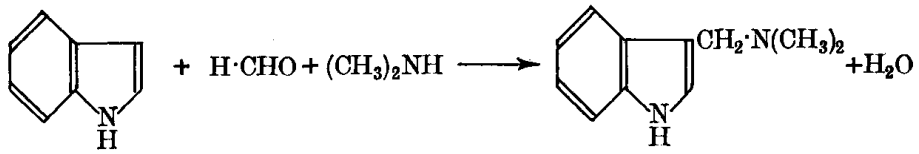


cuscohygrine

§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.

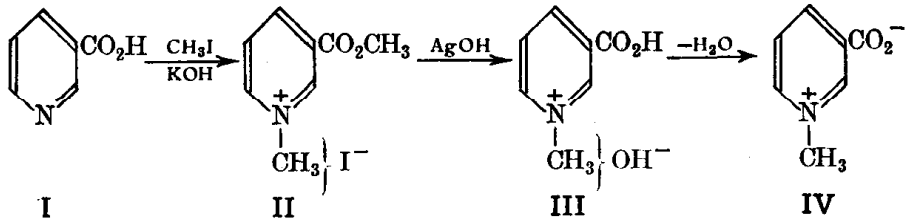


§14. Gramine has been found in barley mutants; it raises the blood-pressure in dogs when administered in small doses. Gramine has been synthesised by allowing indole to stand in an aqueous solution containing formaldehyde and dimethylamine (Snyder *et al.*, 1944).

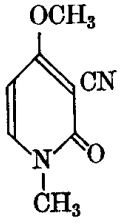


PYRIDINE GROUP

§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.

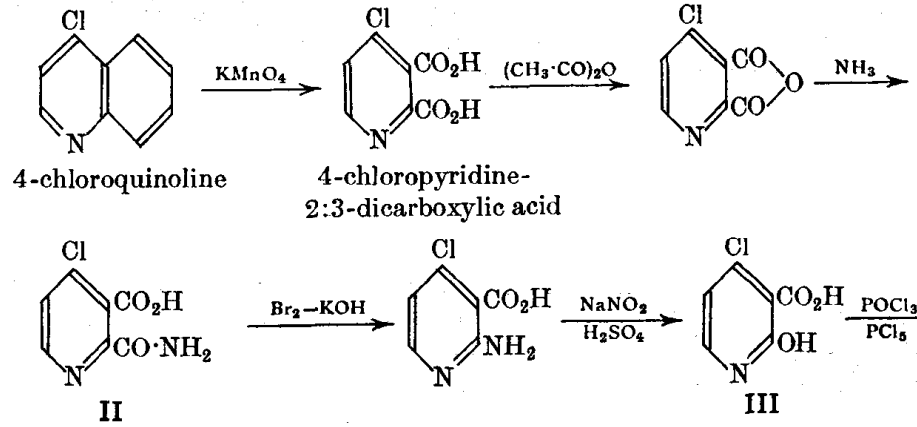


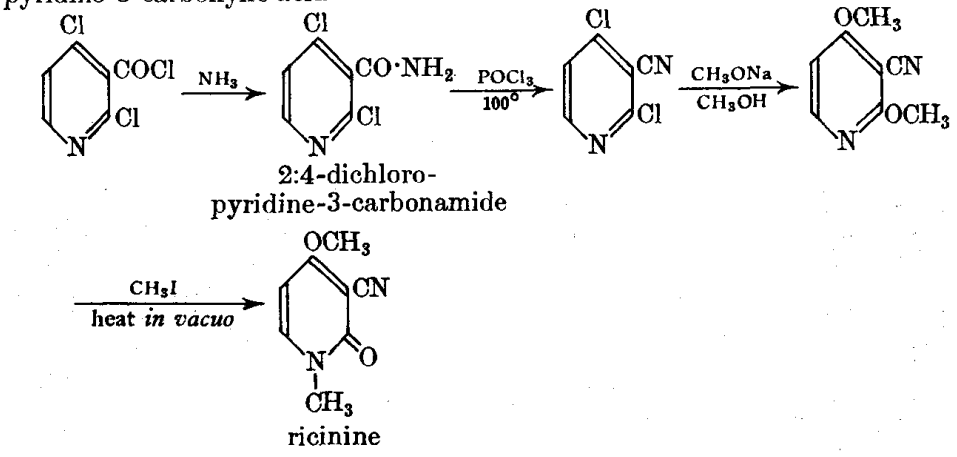
§16. Ricinine, $C_8H_8O_2N_2$, m.p. 201·5°, has been isolated from castor-oil seed; it is not a very toxic alkaloid. Degradative and synthetic work led to the suggestion that I is the structure of ricinine.



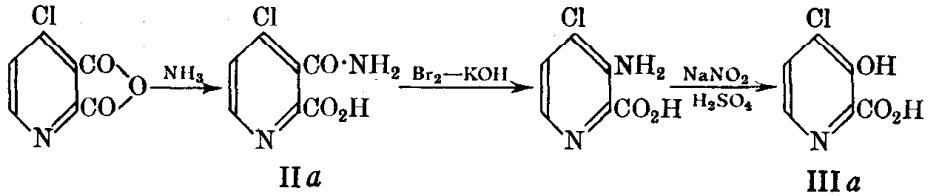
I

This has been confirmed by synthesis, *e.g.*, Späth *et al.* (1923);

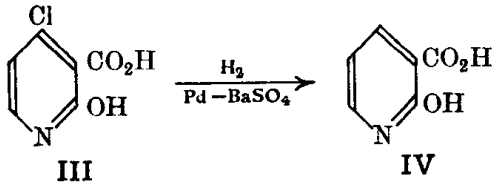




This is not an unambiguous synthesis, since II could have been 3-carbonamido-4-chloropyridine-2-carboxylic acid, II*a*, and consequently III would have been III*a*.

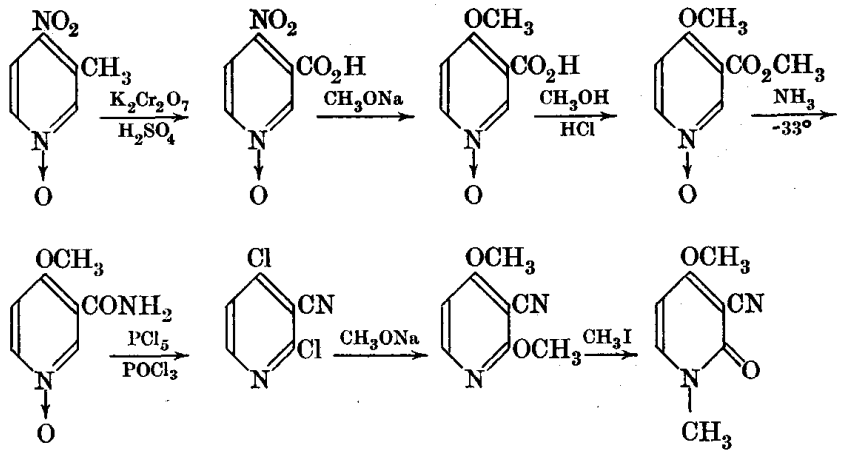


The structure of III was proved by the fact that on hydrogenation in the presence of Pd—$BaSO_4$, it gave 2-hydroxypyridine-3-carboxylic acid, IV.

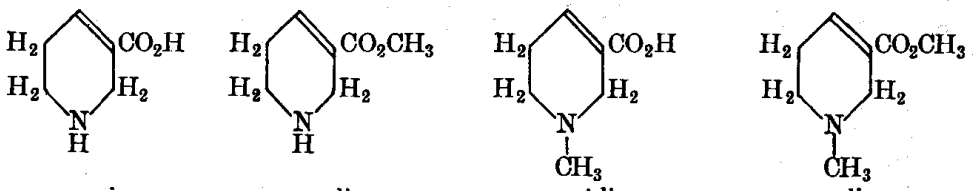


III IV

A more recent synthesis of ricinine is that of Taylor *et al.* (1956).

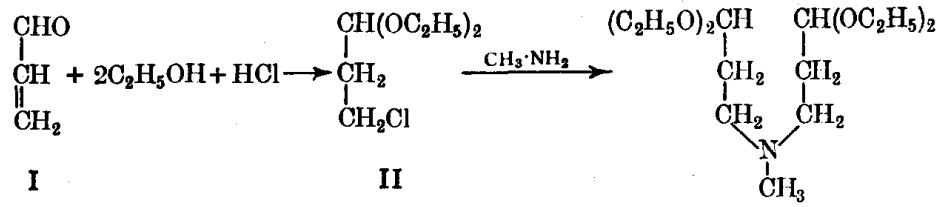


§17. Areca (or Betel) nut alkaloids. The betel nut is the source of a number of alkaloids which are all partially hydrogenated derivatives of nicotinic acid, *e.g.*,

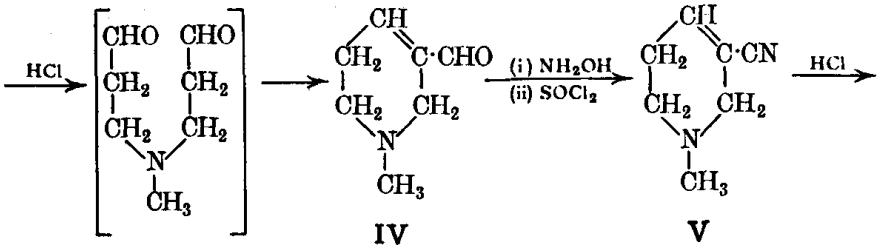


guvacine, m.p. 271-272° | guvacoline, b.p. 114°/13 mm. | arecaidine, m.p. 223° | arecoline, b.p. 209°

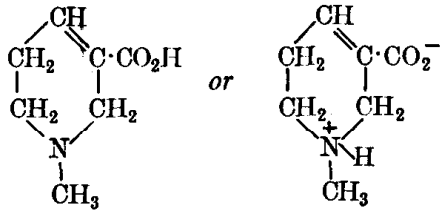
Let us consider arecaidine; its molecular formula is $C_7H_{11}O_2N$. When distilled with zinc dust, guvacine gives 3-methylpyridine; therefore this alkaloid is a pyridine derivative. Now guvacine is converted into arecaidine on heating with potassium methyl sulphate and sodium methoxide (Jahns, 1888, 1890); thus arecaidine is a methyl derivative of guvacine, and consequently is also a pyridine derivative. The usual tests show that arecaidine contains one carboxyl group, an *N*-methyl group and one double bond; hence the formula for arecaidine may be written as $C_5H_7N(CH_3)\cdot CO_2H$. Since the alkaloid is a pyridine derivative, the fragment C_5H_7N could be tetrahydropyridine. This was proved to be so by synthesis, and at the same time the positions of the double bond and carboxyl group were also established (Wohl *et al.*, 1907). Acraldehyde, I, on treatment with ethanol in the presence of hydrogen chloride, forms 3-chloropropionaldehyde acetal, II. II reacts with methylamine to form β-methyliminodipropionaldehyde tetra-acetal, III, which, on treatment with concentrated hydrochloric acid, ring closes to form 1 : 2 : 5 : 6-tetrahydro-1-methylpyridine-3-aldehyde, IV. This gives the cyano compound V on treatment with hydroxylamine, followed by dehydration of the oxime with thionyl chloride, and V is then converted into



I II III



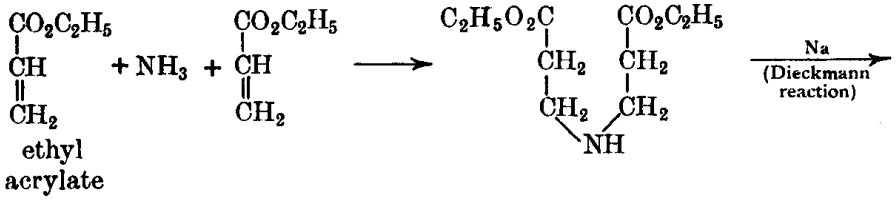
IV V



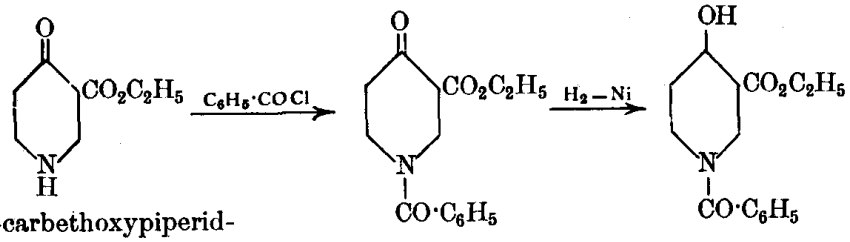
VI VI *a*

arecaidine by hydrolysis. Arecaidine is VI, or possibly VI*a*, the dipolar ion structure (*cf.* amino-acids and betaines).

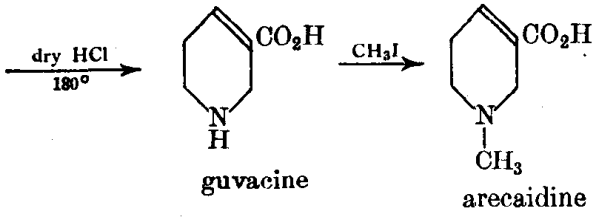
A more recent synthesis of arecaidine (and guvacine) is that of McElvain *et al.* (1946).



ethyl acrylate



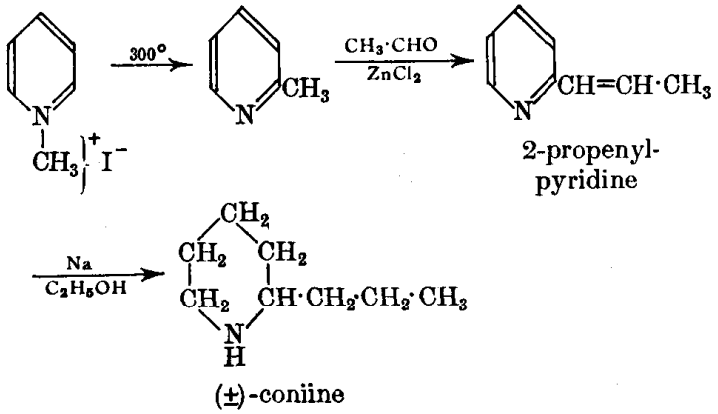
3-carbethoxypiperid-4-one



guvacine arecaidine

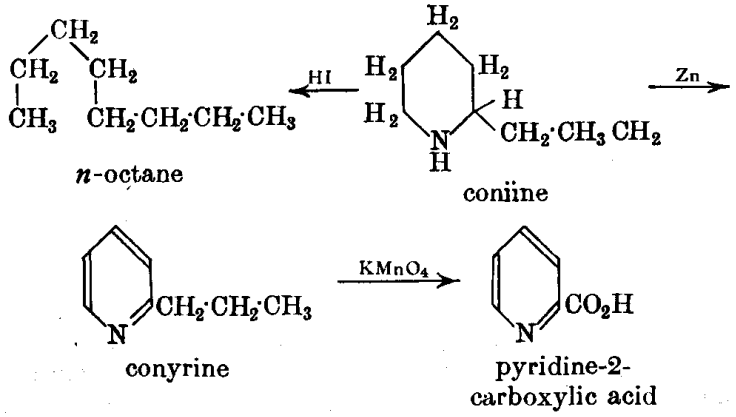
§18. Hemlock alkaloids. The most important alkaloid of this group is **coniine;** it was the first alkaloid to be synthesised. Oil of hemlock was drunk by Socrates when he was condemned to death in 399 B.C.

(+)-Coniine, $C_8H_{17}N$, b.p. 166–167°, is the form that occurs in oil of hemlock. When distilled with zinc dust, coniine is converted into conyrine, $C_8H_{11}N$ (Hofmann, 1884). Since the oxidation of conyrine with permanganate gives pyridine-2-carboxylic acid (α-picolinic acid), it follows that a pyridine nucleus is present with a side-chain in the 2-position. Thus coniine is probably a piperidine derivative with a side-chain in the 2-position. This side-chain must contain three carbon atoms, since two are lost when conyrine is oxidised. This side-chain is therefore either *n*-propyl or *iso*propyl, and it was actually shown to be *n*-propyl by the fact that when heated with

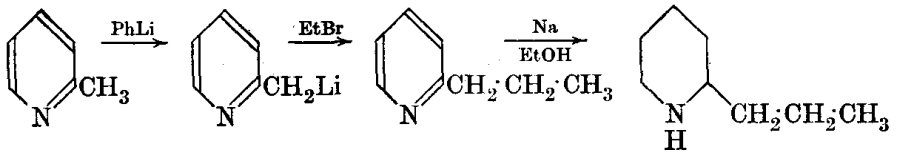


hydriodic acid at 300° under pressure, coniine forms *n*-octane. Had the side-chain been *iso*propyl, then the expected product would be *iso*-octane. From this evidence it therefore follows that coniine is 2-*n*-propylpiperidine, and this has been confirmed by synthesis (Ladenburg, 1885). The racemic coniine was resolved by means of (+)-tartaric acid, and the (+)-coniine so obtained was found to be identical with the natural compound.

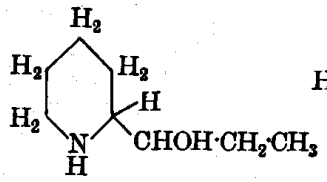
The reactions of coniine described above can therefore be formulated as follows:



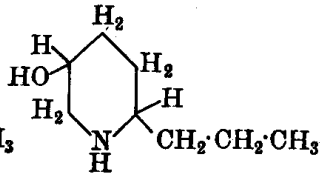
Coniine has also been synthesised from 2-methylpyridine and phenyllithium as follows (Bergmann *et al.*, 1932):



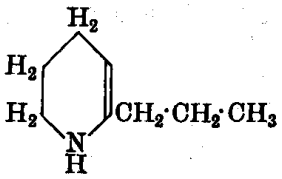
Other hemlock alkaloids are:



conhydrine

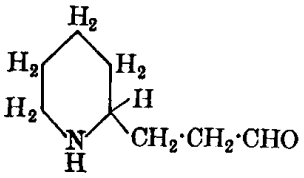


ψ-conhydrine

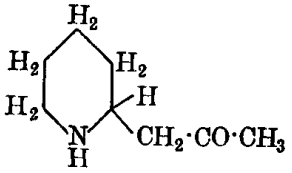


γ-coniceine

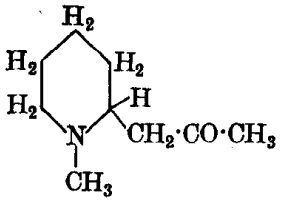
§19. Pomegranate alkaloids. The root bark of the pomegranate tree contains a number of alkaloids, the most important of which is pelletierine; three others are *iso*pelletierine, methyl*iso*pelletierine and pseudo-pelletierine. The last of these is related to atropine (§22).



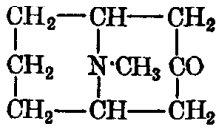
pelletierine



*iso*pelletierine

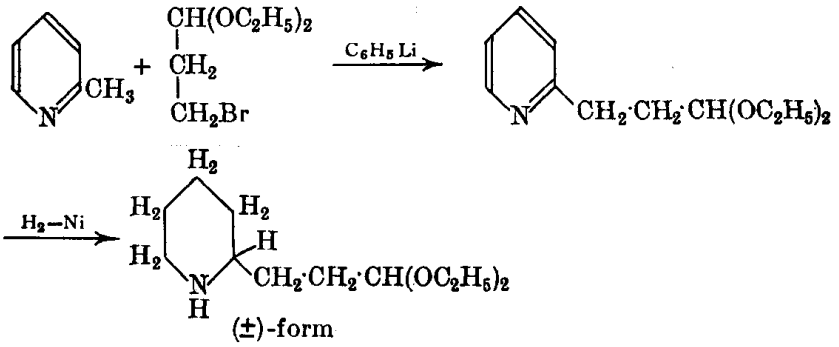


methyl*iso*pelletierine



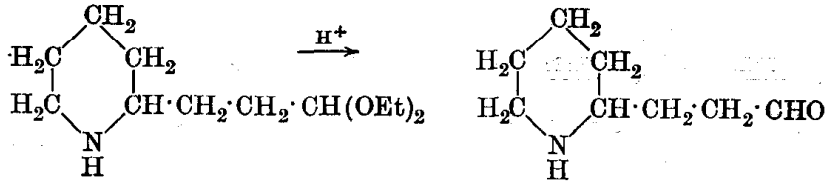
pseudo-pelletierine

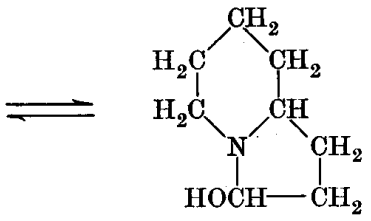
Pelletierine acetal has been synthesised by Spielman *et al.* (1941) by the action of 3-bromopropionaldehyde acetal on 2-methylpyridine (α-picoline) in the presence of phenyl-lithium, followed by catalytic reduction.



(±)-form

Pelletierine acetal was also prepared by Wibaut *et al.* (1940) who attempted to hydrolyse it to the free aldehyde; they obtained only viscous oils. Spielman *et al.* also failed to obtain the free aldehyde. Beets (1943) has therefore suggested that pelletierine can, and probably does, exist as some bicyclic structure such as I.



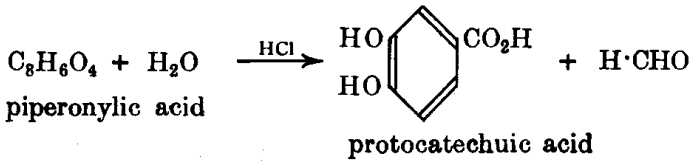


I

§20. Piperine, $C_{17}H_{19}O_3N$, m.p. 128–129·5°, occurs in pepper, especially black pepper (*Piper nigrum*). Hydrolysis of piperine with alkali gives

$$C_{17}H_{19}O_3N + N_2O \xrightarrow{KOH} \underset{\text{piperic acid}}{C_{12}H_{10}O_4} + \underset{\text{piperidine}}{C_5H_{11}N}$$

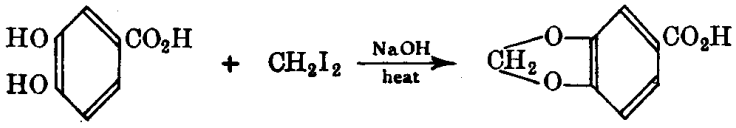
piperic acid and piperidine; thus the alkaloid is the piperidine amide of piperic acid (Babo *et al.*, 1857). Since piperidine is hexahydropyridine, the structure of piperine rests on the elucidation of that of piperic acid. The routine tests show that piperic acid contains one carboxyl group and two double bonds. When oxidised with permanganate, piperic acid gives first piperonal and then piperonylic acid. The structure of the latter is deduced from the fact that when heated with hydrochloric acid at 200° under pressure, piperonylic acid forms protocatechuic acid (3 : 4-dihydroxybenzoic acid) and formaldehyde.



piperonylic acid

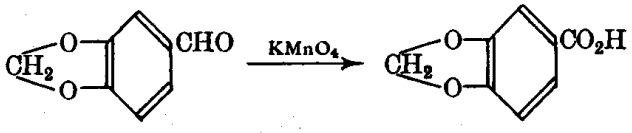
protocatechuic acid

Since one atom of carbon is eliminated, and there are no free hydroxyl groups in piperonylic acid, the structure of this acid is probably the methylene ether of protocatechuic acid, *i.e.*, piperonylic acid is 3 : 4-methylenedioxybenzoic acid; this has been confirmed by synthesis:



piperonylic acid

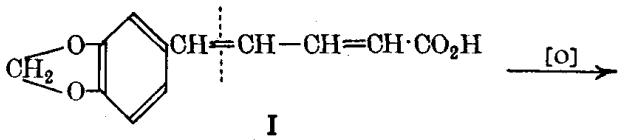
Furthermore, since piperonal (an aldehyde) gives piperonylic acid on oxidation, piperonal is therefore 3 : 4-methylenedioxybenzaldehyde.



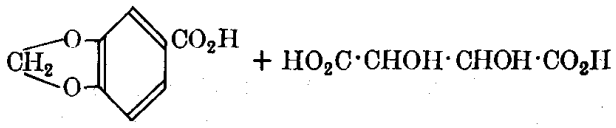
piperonal

From these results of oxidative degradation, it therefore follows that piperic acid is a benzene derivative containing only one side-chain. It is this side-chain that contains the two double bonds (the ready addition of four bromine atoms shows the presence of two *ethylenic* bonds), and since the careful oxidation of piperic acid gives tartaric acid in addition to piperonal and piperonylic acid, the side-chain is a " straight " chain. If we assume I as

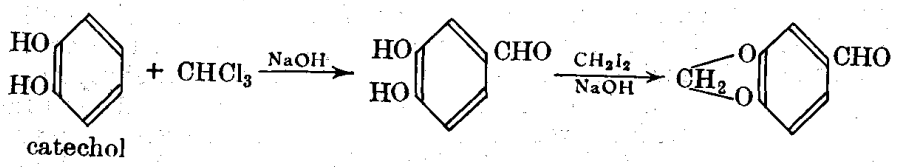
the structure of piperic acid, then all of the foregoing products of oxidation may be accounted for.



I

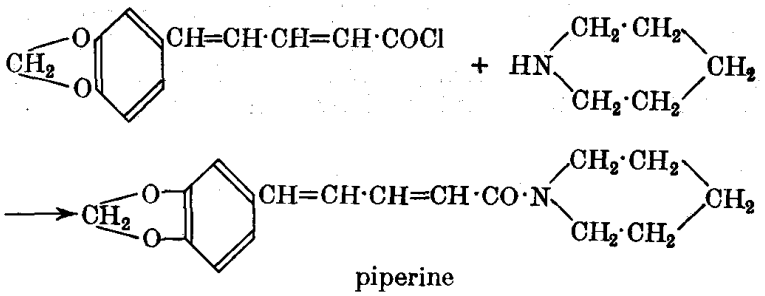


This has been confirmed by synthesis (Ladenburg *et al.*, 1894); piperonal (prepared *via* the Reimer–Tiemann reaction) is condensed with acetaldehyde in the presence of sodium hydroxide (Claisen–Schmidt reaction), and the product (a cinnamaldehyde derivative) is then heated with acetic anhydride in the presence of sodium acetate (Perkin reaction).



catechol

When the acid chloride of piperic acid (prepared by the action of phosphorus pentachloride on the acid) is heated with piperidine in benzene solution, piperine is formed; thus piperine is the piperidine amide of piperic acid.

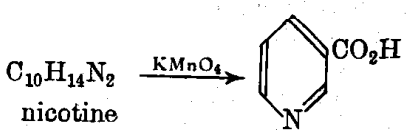


piperine

PYRROLIDINE-PYRIDINE GROUP

§21. Tobacco alkaloids. Many alkaloids have been isolated from the tobacco leaf, *e.g.*, nicotine, nicotimine (anabasine), nornicotine, etc.

Nicotine, $C_{10}H_{14}N_2$, b.p. 247°, is the best known and most widely distributed of the tobacco alkaloids; it occurs naturally as the (—)-form. When oxidised with dichromate–sulphuric acid (or permanganate or nitric acid), nicotine forms nicotinic acid (Huber, 1867).



nicotine nicotinic acid