It should be noted that in many cases different alkaloids obtained from the same plant often have similar chemical structures, and so sometimes the source of the alkaloids may indicate chemical similarity.

PHENYLETHYLAMINE GROUP

Many compounds of this group are known, some natural and others synthetic. Their outstanding physiological action is to increase the blood-pressure; hence they are often referred to as the *pressor drugs*.

§6. β-Phenylethylamine. This is the parent substance of this group of alkaloids, and occurs in putrid meat (it is formed by the decarboxylation of phenylalanine, an amino-acid). β-Phenylethylamine may be readily synthesised as follows:

$$C_6H_5{\cdot}CH_2Cl + KCN \longrightarrow C_6H_5{\cdot}CH_2{\cdot}CN \xrightarrow[C_2H_5OH]{Na} C_6H_5{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$$

β-Phenylethylamine is a colourless liquid, b.p. 197°.

§7. (−)-Ephedrine, m.p. 38·1°. (−)-Ephedrine occurs in the genus *Ephedra*; it is one of the most important drugs in *Ma Huang* (a Chinese drug). Physiologically, its action is similar to that of adrenaline (§12), and it can be taken orally.

The molecular formula of ephedrine is $C_{10}H_{15}ON$, and since on oxidation ephedrine forms benzoic acid, the structure therefore contains a benzene ring with only one side-chain. When treated with nitrous acid, ephedrine forms a nitroso-compound; therefore the compound is a secondary amine. Since ephedrine forms a dibenzoyl derivative, one hydroxyl group must be present (one benzoyl group is accounted for by the imino group). Finally, when heated with hydrochloric acid, ephedrine forms methylamine and propiophenone.

$$C_{10}H_{15}ON \xrightarrow{HCl} CH_3{\cdot}NH_2 + C_6H_5{\cdot}CO{\cdot}CH_2{\cdot}CH_3$$

The formation of these products can be explained if the structure of ephedrine is either I or II.

$$C_6H_5{\cdot}CHOH{\cdot}CH_2{\cdot}CH_2{\cdot}NH{\cdot}CH_3 \qquad \text{I}$$

$$C_6H_5{\cdot}CHOH{\cdot}CH(NH{\cdot}CH_3){\cdot}CH_3 \qquad \text{II}$$

It has been observed, however, that compounds of structure II undergo the *hydramine fission* to form propiophenone when heated with hydrochloric acid. Thus II is more likely than I. This is supported by the fact that when subjected to the Hofmann exhaustive methylation method, ephedrine forms *sym.*-methylphenylethylene oxide, III; this cannot be produced from I, but is to be expected from II.

$$\underset{\text{II}}{C_6H_5{\cdot}CHOH{\cdot}CH(CH_3){\cdot}NHCH_3} \xrightarrow[\text{(ii) AgOH}]{\text{(i) } CH_3I} C_6H_5{\cdot}CHOH{\cdot}CH(CH_3){\cdot}N(CH_3)_3\}^+OH^- \xrightarrow[(-H_2O)]{\text{heat}}$$

$$\underset{\text{III}}{C_6H_5{\cdot}\overset{\diagup O \diagdown}{CH{\cdot}CH}{\cdot}CH_3} + (CH_3)_3N$$

Further support for II is afforded by the following evidence. Structure I contains one asymmetric carbon atom, and so replacement of the hydroxyl

group by hydrogen will result in the formation of an optically inactive compound. Structure II, however, contains two asymmetric carbon atoms, and so the replacement of the hydroxyl group by hydrogen should still give a compound that can be optically active. Experimentally it has been found that when this replacement is effected in (—)-ephedrine, the product, deoxyephedrine, is optically active. Thus II agrees with all the known facts, and this structure has been confirmed by synthesis, *e.g.*, Späth *et al.* (1920):

$$CH_3{\cdot}CH_2{\cdot}CHO \xrightarrow{Br_2} CH_3{\cdot}CHBr{\cdot}CHO \xrightarrow[HBr]{CH_3OH}$$

$$CH_3{\cdot}CHBr{\cdot}CH(OCH_3)(Br) \xrightarrow{C_6H_5MgBr} CH_3{\cdot}CHBr{\cdot}CH(OCH_3)(C_6H_5) \xrightarrow{CH_3{\cdot}NH_2}$$

$$CH_3{\cdot}CH(NH{\cdot}CH_3){\cdot}CH(OCH_3)(C_6H_5) \xrightarrow{HI} C_6H_5{\cdot}CHOH{\cdot}CH(CH_3){\cdot}NH{\cdot}CH_3$$

(±)-ψ-ephedrine

The racemic modification of ψ-ephedrine (see below) was resolved by means of tartaric acid.

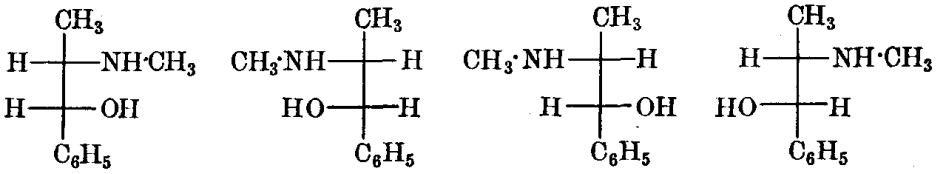
(—)-Ephedrine itself has been synthesised by Manske *et al.* (1929) by the catalytic reduction of 1-phenylpropane-1 : 2-dione (benzoylacetyl) in the presence of methylamine in methanol solution.

$$C_6H_5{\cdot}CO{\cdot}CO{\cdot}CH_3 + CH_3{\cdot}NH_2 \rightarrow C_6H_5{\cdot}CO{\cdot}C(=N{\cdot}CH_3){\cdot}CH_3 \xrightarrow{H_2—Pt} C_6H_5{\cdot}CHOH{\cdot}CH(CH_3){\cdot}NH{\cdot}CH_3$$

(±)-ephedrine

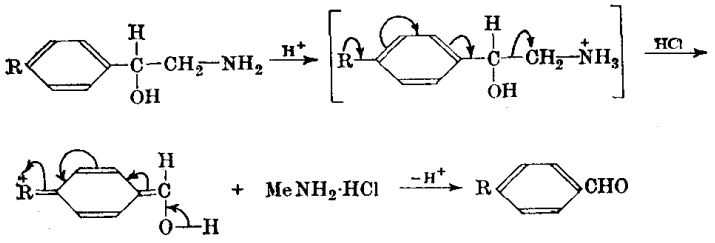
The racemic ephedrine was resolved by means of mandelic acid. Some (±)-ψ-ephedrine was also obtained in this synthesis.

Since the ephedrine molecule contains two dissimilar asymmetric carbon atoms, four optically active forms (two pairs of enantiomorphs) are theoretically possible. According to Freudenberg (1932), the configurations of ephedrine and ψ-ephedrine are:

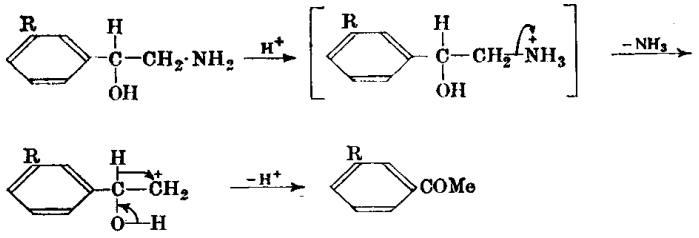


(—)-ephedrine (+)-ephedrine (—)-ψ-ephedrine (+)-ψ-ephedrine

Various mechanisms have been proposed for the hydramine fission. Chatterjee *et al.* (1961) have suggested two different mechanisms according to whether the aryl nucleus contains (i) an electron-releasing group in the *o* and/or *p*-position, *e.g.*, R = OMe, OH, Me:

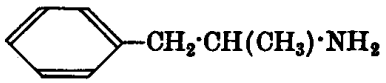


(ii) R in the *m*-position:



Thus hydramine fission gives an aldehyde or a ketone according to the nature and position of groups in the aryl nucleus. With a 4-nitro group the product is 4-nitroacetophenone (yield: very poor).

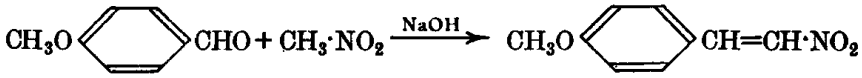
§8. **Benzedrine** (*Amphetamine*) was originally introduced as a substitute for ephedrine, but it is now used in its own right since it apparently produces a feeling of confidence.



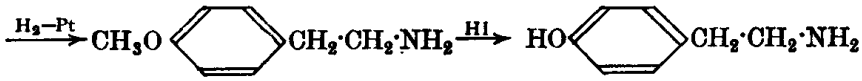
Benzedrine has been synthesised in many ways, *e.g.*, Mingoia (1940):

$$C_6H_5{\cdot}CH_2{\cdot}COCH_3 \xrightarrow[150-190^\circ]{HCONH_2} C_6H_5{\cdot}CH_2{\cdot}CH(CH_3){\cdot}NH{\cdot}CHO \xrightarrow{HCl} C_6H_5{\cdot}CH_2{\cdot}CH(CH_3){\cdot}NH$$

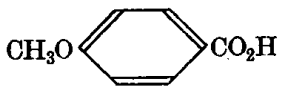
§9. **β-*p*-Hydroxyphenylethylamine** (*tyramine*), m.p. 160°, occurs in ergot, and is produced by the putrefaction of proteins (by the decarboxylation of tyrosine). Tyramine has been synthesised in various ways, *e.g.*,



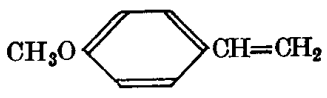
anisaldehyde



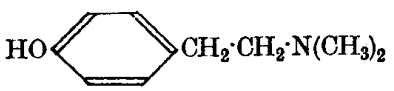
§10. **Hordenine** (*β-p*-hydroxyphenylethyldimethylamine, *Anhaline*), m.p. 117–118°, occurs naturally in germinating barley. The molecular formula of hordenine is $C_{10}H_{15}ON$; the routine tests show that hordenine is a tertiary base and that it contains a phenolic group. Since the methylation of hordenine, followed by oxidation (with alkaline permanganate), gives anisic acid, I, it therefore follows that the hydroxyl group is in the *para*-position with respect to the side-chain. Furthermore, since the methylated compound gives *p*-vinylanisole, II, after the Hofmann exhaustive methylation, the structure of hordenine is probably III.



I

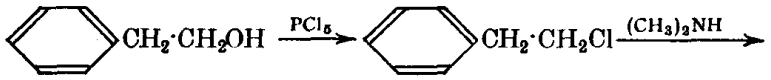


II

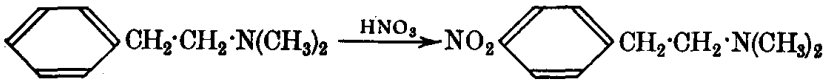


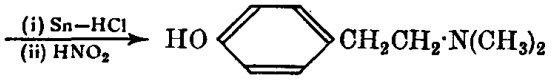
III

This has been confirmed by synthesis, *e.g.*, Barger (1909):

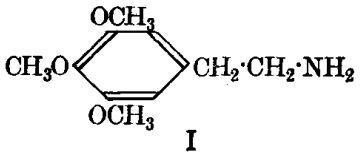


2-phenylethanol



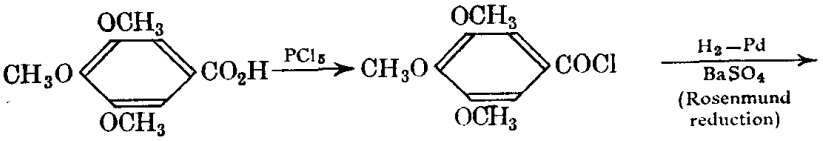


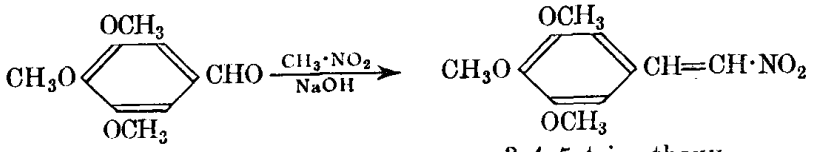
§11. **Mezcaline** (mescaline), $C_{11}H_{17}O_3N$, b.p. 180–180·5°/12 mm., occurs naturally in " mezcal buttons ". The routine tests show that mezcaline contains a primary aliphatic amino-group and three methoxyl groups. On oxidation with alkaline permanganate, mezcaline gives 3 : 4 : 5-trimethoxybenzoic acid, and thus the probable structure of mezcaline is I.



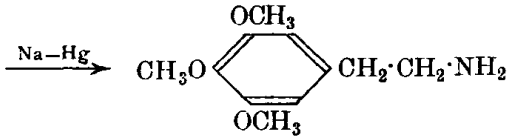
I

This has been confirmed by synthesis (Späth, 1919):



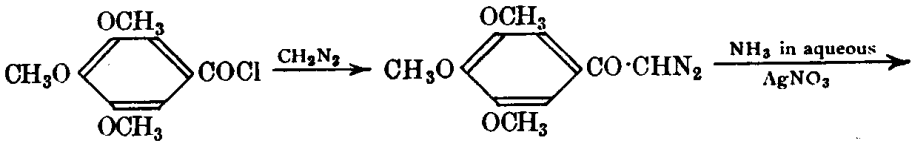


3:4:5-trimethoxy-ω-nitrostyrene

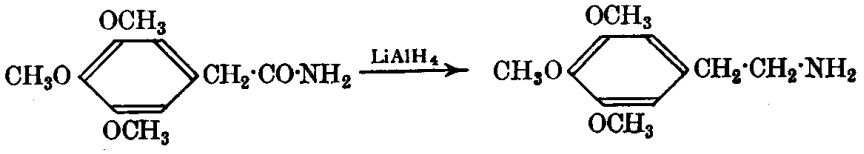


mezcaline

A more recent synthesis of mezcaline is that of Banholzer *et al.* (1952); this makes use of the Arndt–Eistert synthesis.



diazoketone

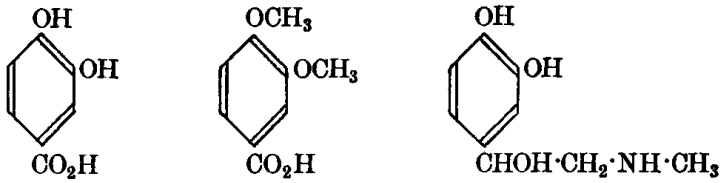


N-Methylmezcaline and *N*-acetylmezcaline also occur naturally in mezcal buttons.

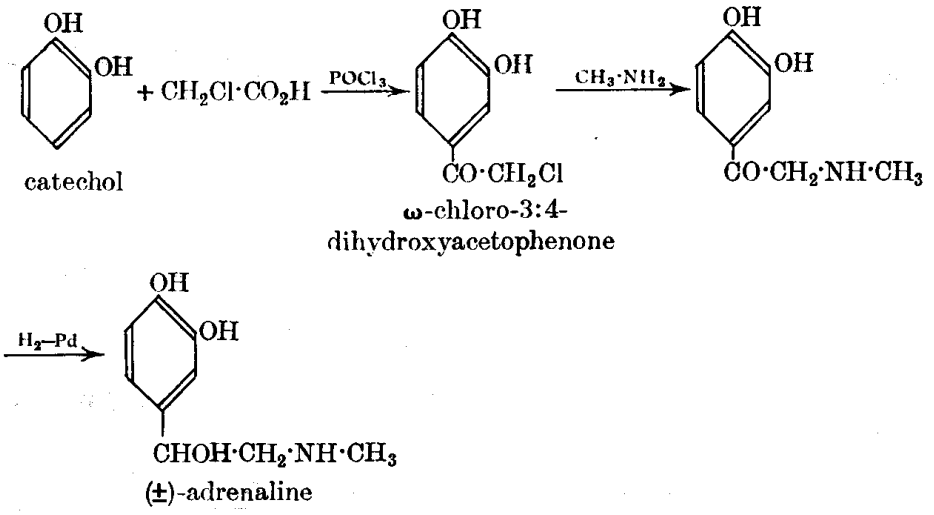
§12. Adrenaline (*Epinephrine*), $C_9H_{13}O_3N$, is a non-steroid hormone. The adrenal medulla is the source of the hormones adrenaline and noradrenaline. Adrenaline was the first hormone to be isolated in a crystalline form (Takamine, 1901; Aldrich, 1901). Adrenaline is active only when given by injection; it raises the blood-pressure, and is used locally to stop hæmorrhage.

Adrenaline is a colourless crystalline solid, m.p. 211°, and dissolves in acids and alkalis (it is insoluble in water); it is also optically active, having a lævorotation.

The phenolic character of adrenaline is indicated by its solubility in sodium hydroxide and its reprecipitation by carbon dioxide. Since it gives a green colour with ferric chloride, this led to the suggestion that adrenaline is a catechol derivative. When boiled with aqueous potassium hydroxide, adrenaline evolves methylamine; thus a methylamino group is probably present. On the other hand, when fused with potassium hydroxide, the product is protocatechuic acid, I (Takamine, 1901); methylation, followed

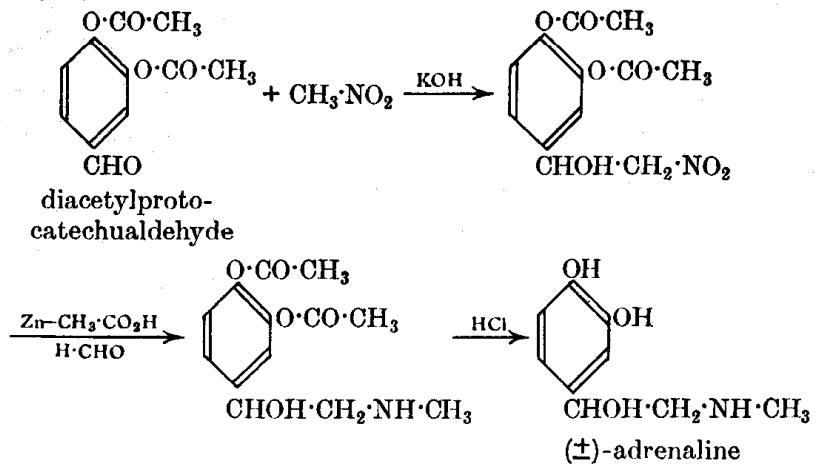


by fusion with potassium hydroxide, gives veratric acid, II, and trimethylamine (Jowett, 1904). The formation of trimethylamine indicates that the nitrogen atom must occur at the *end* of the side-chain. Since adrenaline is optically active, it must contain at least one asymmetric carbon atom. Now adrenaline contains three hydroxyl groups, two of which are phenolic (as shown by the formation of I and II). The third hydroxyl group was shown to be secondary alcoholic by the fact that when adrenaline is treated with benzenesulphonyl chloride, a tribenzenesulphonyl derivative is obtained which, on oxidation, gives a ketone (Friedmann, 1906). To account for the oxidation of adrenaline to the benzoic acid derivative, the —CHOH— group must be attached directly to the nucleus; had it been —CH_2·CHOH·, then a phenylacetic acid derivative would have been obtained. All the foregoing facts are in keeping with structure III for adrenaline, and this has been confirmed by synthesis by Stolz (1904) and Dakin (1905), with improvements by Ott (1926).

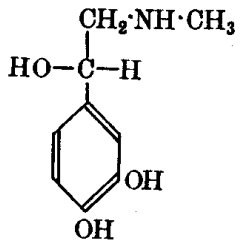


The racemic adrenaline has been resolved by means of (+)-tartaric acid.

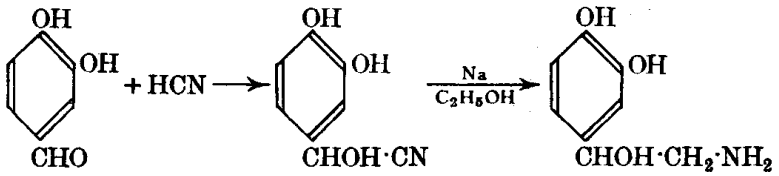
Nagai (1918) has also synthesised adrenaline as follows:



According to Dalgliesh (1953), the configuration of (−)-adrenaline is probably

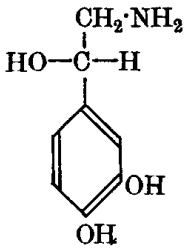


§12a. Noradrenaline (*Norepinephrine*), $C_8H_{11}O_3N$, is also present in the adrenal medulla. The natural compound is lævorotatory, and this (−)-isomer is the most powerful pressor-compound known. The structure of noradrenaline has been established by analytical work similar to that described for adrenaline, and has been confirmed by various syntheses, *e.g.*,



(±)-noradrenaline

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

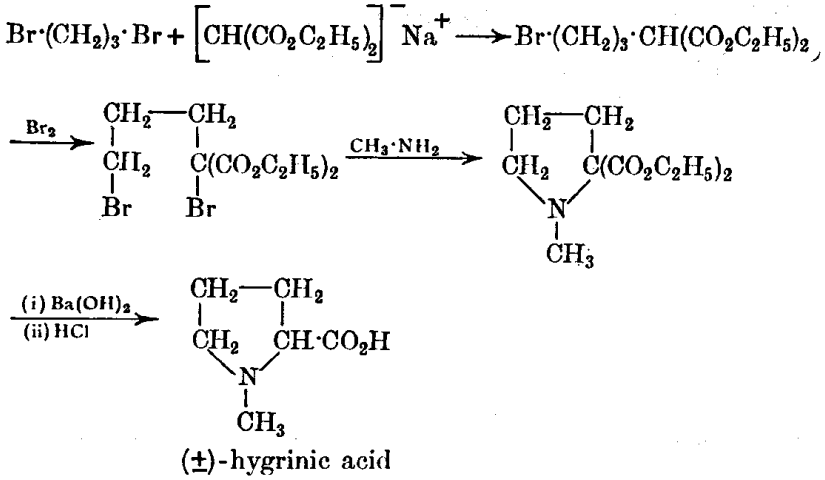


PYRROLIDINE GROUP

§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