The constitution of cytisine, the alkaloid of Cytisus laburnum. Pt. 1. The synthesis of [alpha]-cytisolidine and of [beta]-cytisolidine / by Arthur James Ewins.

Contributors

Ewins, Arthur James.
Royal College of Surgeons of England

Publication/Creation

London : Wellcome Physiological Research Laboratories, 1913.

Persistent URL

https://wellcomecollection.org/works/mghupp5t

Provider

Royal College of Surgeons

License and attribution

5.

THE
CONSTITUTION OF CYTISINE, THE
ALKALOID OF CYTISUS LABURNUM
Part 1.   THE SYNTHESIS OF
α–CYTISOLIDINE AND OF
β–CYTISOLIDINE

BY

ARTHUR JAMES EWINS, B.Sc.
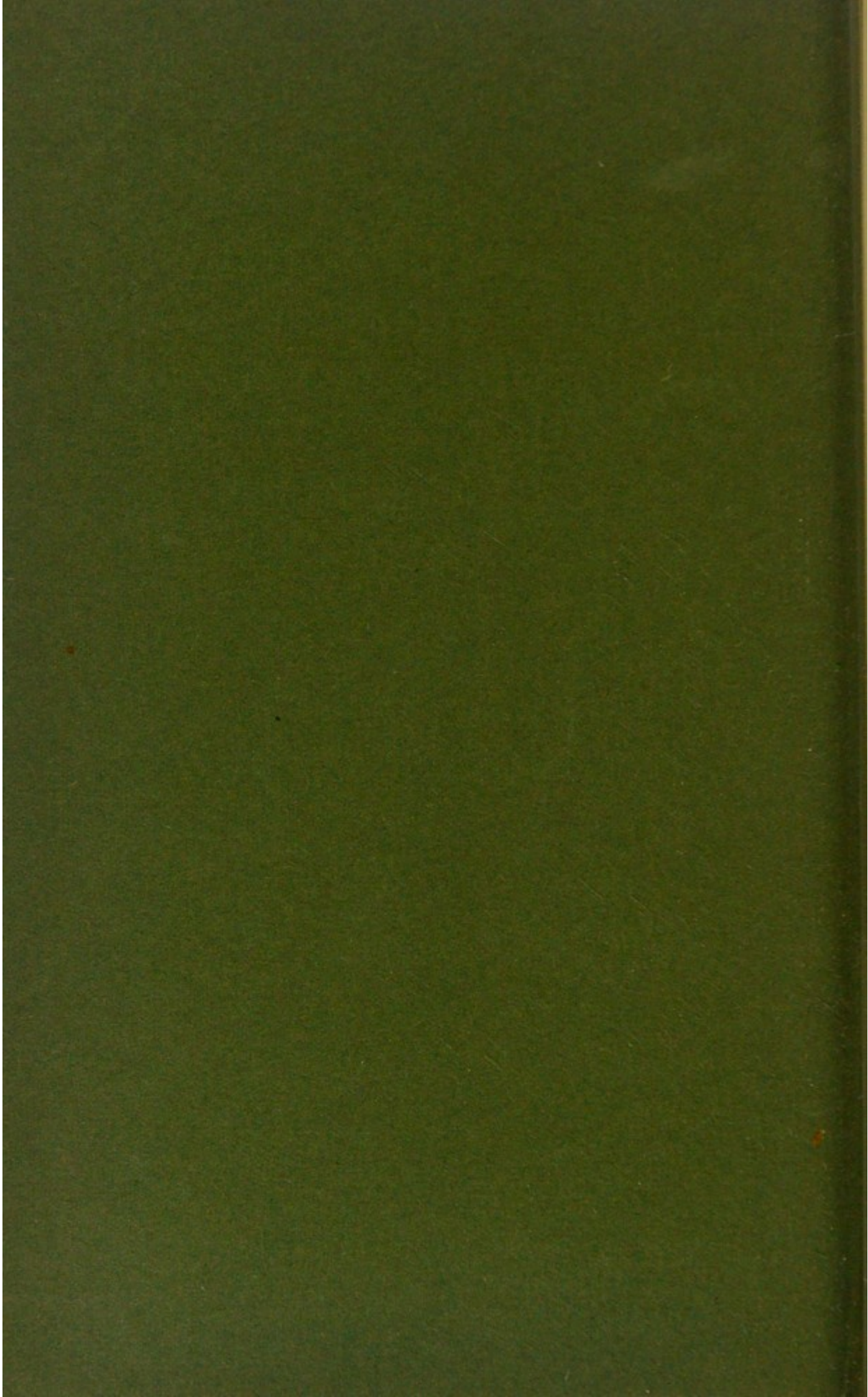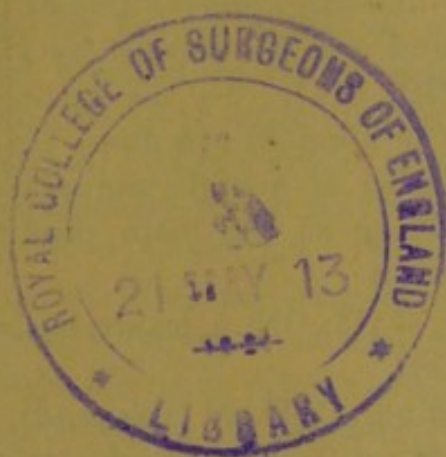
XIV.—*The Constitution of Cytisine, the Alkaloid of Cytisus Laburnum. Part I. The Synthesis of α-Cytisolidine and of β-Cytisolidine.**

By Arthur James Ewins.

Cytisine, the poisonous alkaloid of the common laburnum (*Cytisus laburnum*), was first isolated in a pure state by Husemann and Marmé (*Zeitsch. f. Chem.*, 1865, **1**, 161), who gave it the formula $C_{20}H_{27}ON_3$. Partheil (*Ber.*, 1890, **23**, 3201), however, showed the true composition of the alkaloid to be $C_{11}H_{14}ON_2$, and

* This communication forms part of an investigation which is being carried out in collaboration with Dr. G. Barger.

this formula was confirmed by Buchka and Magelhaës (*Ber.*, 1891, **24**, 273, 674), as well as by subsequent workers.

The alkaloid is present in many other plants, for example, in other kinds of cytisus and in *Ulex europaeus*, the common gorse, the "ulexine" of which, isolated by Gerrard (*Ber.*, 1886, **19**, 838), was shown by Partheil and others to be identical with cytisine.

The interest attaching to this alkaloid has been very considerably increased by the recent work of Dale and Laidlaw (*J. Pharm. Expt. Ther.*, 1912, **3**, 205), who have shown that its physiological action is in all respects qualitatively and almost quantitatively indistinguishable from that of the very poisonous alkaloid nicotine. The question of its chemical constitution accordingly becomes of interest in so far as one might perhaps expect some chemical relationship with that of the latter alkaloid.

The chemical constitution of cytisine has previously been worked at chiefly by two investigators: Partheil (*loc. cit.*), and more especially by M. Freund and his co-workers (*Ber.*, 1901, **34**, 615; 1904, **37**, 16; 1906, **39**, 814). To the latter the following main facts with regard to the alkaloid are due. On treatment with hydriodic acid and phosphorus at a high temperature (230°) the alkaloid is decomposed, yielding as the main products of the reaction the following substances:

(*a*) Cytisoline, $C_{11}H_{11}ON$, a feebly basic, crystalline solid, melting when pure at 198°.

(*b*) β-Cytisolidine, $C_{11}H_{15}N$ (Freund), a basic oil, yielding a crystalline picrate (m. p. 229°) and platinichloride (m. p. 234°).

(*c*) A mixture of hydrocarbons melting at 185—230°.

(*d*) Ammonia.

Of these products, cytisoline on reduction with sodium and alcohol gives a base, α-cytisolidine, $C_{11}H_{15}N$, considered by Freund to be isomeric with β-cytisolidine. This base yielded an oily picrate and a crystalline platinichloride melting at 216°. Further, cytisoline on oxidation with chromic acid gives an acid, cytisolinic acid, $C_{10}H_8ON(CO_2H)$, obviously by oxidation of a methyl group in the molecule.

Lastly, Freund (*Ber.*, 1904, **37**, 16; 1906, **39**, 814) showed that on electrolytic reduction, cytisine, $C_{11}H_{14}ON_2$, was converted into a base, tetrahydrodeoxycytisine, $C_{11}H_{20}N_2$. Experiments soon showed that the main hope of gaining any further knowledge of the constitution of the alkaloid lay in the elucidation of the constitution of the products obtained by Freund by the action of hydriodic acid. Many attempts were made to obtain some product of oxidation from cytisine which would throw some light on the problem of its constitution. Cytisine is very readily attacked by oxidising agents,

such as potassium permanganate and chromic acid, but, however the conditions of oxidation were varied, no pure product could be isolated except oxalic acid.

Equally disappointing were the attempts which were made to decompose the alkaloid by the action of acids or alkalis at high temperatures. Towards these reagents cytisine is stable to a remarkable degree. After heating with concentrated or dilute sulphuric or hydrochloric acids to temperatures of from 200° to 250°, or higher, for some time, the greater part of the alkaloid was recovered unchanged. Only with a saturated solution of hydrogen bromide in acetic acid, at a temperature of 250°, was there any indication of the formation of a new crystalline derivative, and even in this case the yield was extremely small. These experiments were consequently abandoned.

In repeating the experiments of Freund it was noticed that the base α-cytisolidine, obtained by the reduction of cytisoline by the action of sodium in alcohol, when dissolved in sulphuric acid and treated with a drop of nitric acid, gave a carmine-red colour shading to blue at the edge of the liquid. This reaction is somewhat similar to that given by tetrahydroquinoline, and it was considered probable that α-cytisolidine might be a substituted tetrahydroquinoline. Freund himself had considered the possibility of its being 1:8-dimethyltetrahydroquinoline, but synthesis of the latter compound had shown that this was not the case (*Ber.*, 1904, **37**, 22). The absence of a methyl group attached to the nitrogen atom of the base was easily shown, since a determination carried out according to the method of Herzig and Meyer for such a grouping gave a negative result. Moreover, since cytisoline has been shown to contain a methyl group, it follows that α-cytisolidine must be a dimethyltetrahydroquinoline if it is indeed a derivative of tetrahydroquinoline, and cytisoline a hydroxydimethylquinoline. The general properties of cytisoline gave considerable support to the above hypothesis when compared with those of the corresponding hydroxyquinolines already described in the literature. Like these derivatives, cytisoline is a feeble base. Its salts are dissociated by water, it gives a brownish-red coloration with ferric chloride solution, and on reduction it loses oxygen, taking up four atoms of hydrogen to give a base volatile in steam.

Excluding the bases containing a methyl group attached to the nitrogen atom, there are possible twenty-one isomeric dimethyltetrahydroquinolines. Of these, some ten are mentioned in the literature, but few of these are by any means well characterised. The task of identifying the base was therefore no light one. The synthesis of what were considered to be the more likely of these

dimethyltetrahydroquinolines was commenced in collaboration with Mr. H. King, and some of the results of this work are described in the succeeding paper (Ewins and King, p. 104).

The work carried out in this direction unexpectedly threw a further light on the relationship of α-cytisolidine to β-cytisolidine, the basic oil obtained by the action of hydriodic acid on cytisine. The last-mentioned authors found a well-marked and fairly constant difference in the properties of the dimethyltetrahydroquinolines and the corresponding dimethylquinolines, chiefly in the melting points and solubilities of their salts. A similar relationship was observed to exist between the α- and β-cytisolidines, and a closer examination and analysis showed that the latter possessed the composition $C_{11}H_{11}N$, and not $C_{11}H_{15}N$, as stated by Freund (*loc. cit.*). It was therefore very probable that α-cytisolidine was the dimethyltetrahydroquinoline corresponding with the dimethylquinoline, β-cytisolidine, a relationship which was readily confirmed, β-cytisolidine on reduction with sodium in alcoholic solution giving a base identical with α-cytisolidine.

The problem thus resolved itself into the identification of β-cytisolidine as (probably) a dimethylquinoline. Here, again, there are twenty-one possible isomerides, of which about a dozen have been described, but again for the most part very imperfectly.

Finally, after a number of these dimethylquinolines had been prepared, the synthesis of 6:8-dimethylquinoline from *m*-4-xylidine was carried out. The base so obtained proved to be identical with β-cytisolidine, and on reduction yielded another base identical with α-cytisolidine. The constitution of these two bases is thus established beyond doubt. Further, cytisoline must be a corresponding hydroxydimethylquinoline. This is confirmed by the fact that on distillation with zinc dust β-cytisolidine is obtained. The position of the hydroxy-group is, however, as yet undetermined; but it is most probably either in the 3- or 4-position, since 2-hydroxy-6:8-dimethylquinoline prepared by the action of hypochlorous acid on 6:8-dimethylquinoline, although agreeing closely in general properties with cytisoline, was found to be different. 5-Hydroxy-6:8-dimethylquinoline was also synthesised, but the properties of this substance differ considerably from cytisoline, owing to the phenolic character of the hydroxy-group, for which reason also 7-hydroxy-6:8-dimethylquinoline may most probably be eliminated. Experiments to determine the constitution of cytisoline are in progress.

The constitution of cytisine itself still remains an open question. It is to be noticed, however, that cytisoline, $C_{11}H_{11}ON$, which, from the results recorded in this communication, must be a hydroxydimethylquinoline, is formed from cytisine by the loss of the elements

of ammonia alone. The manner in which this elimination takes place is at present quite unknown. The most simple explanation is perhaps that cytisine is formed by the fusion of three rings (benzene, pyridine, and pyrazole rings), somewhat according to the following scheme :
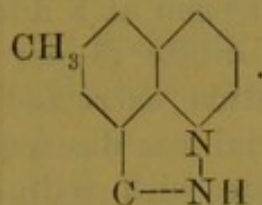
Such a compound might conceivably lose ammonia under the conditions described, to yield dimethylquinoline derivatives; but there is so far no direct evidence in support of such a structure.

EXPERIMENTAL.

The Action of Hydriodic Acid and Phosphorus on Cytisine.

The method employed by Freund (*Ber.*, 1904, **37**, 16) to obtain cytisoline was as follows: Two grams of cytisine, 1 gram of red phosphorus, and 10 c.c. of hydriodic acid (D 1·7) were heated in sealed tubes for four hours at 225—230°. In this way 5 grams of cytisoline were obtained from 40 grams of cytisine. Experiment confirmed these results, but a slight modification was adopted by which the yield was somewhat increased. This consisted in heating 2 grams of cytisine, 0·4 gram of phosphorus, and 4 c.c. only of hydriodic acid to 230—235° for three hours. In this way, an average yield of 3·5 grams of cytisoline (m. p. 180°) was obtained from 20 grams of cytisine. At a slightly lower temperature a somewhat less pure product was obtained consisting of cytisoline, together with a substance or substances possessing very similar properties which render purification a matter of considerable difficulty. The reaction product was treated in a manner somewhat different from that employed by Freund. The contents of the tubes were poured into water, and on keeping the crystalline cytisoline separated out and was collected. The acid filtrate, on neutralisation, yielded a further small quantity of cytisoline. The solution was finally rendered alkaline with sodium hydroxide and distilled in a current of steam, when β-cytisolidine, together with a little α-cytisolidine, passed over. The yield of the base was small. From the residue in the distilling flask a considerable amount of unchanged cytisine could be recovered by extraction with chloroform.

The Formation of β-Cytisolidine from Cytisoline by Distillation with Zinc Dust.

Four grams of cytisoline were distilled over zinc dust and zinc pumice in a current of hydrogen at a dull red heat. The red, oily distillate was dissolved in dilute (5 per cent.) hydrochloric acid, and the filtered acid solution extracted with ether. The small amount of extracted material was discarded. The aqueous solution was then rendered alkaline with sodium hydroxide, and again extracted with ether. The ethereal solution was washed with water, dried over anhydrous potassium carbonate, and the ether evaporated. The residue was distilled, and 0·9 gram of a colourless, limpid oil boiling at 132—133°/14 mm. was obtained. This base was easily shown to be identical with β-cytisolidine by comparison of its salts. The identity is shown in the following table:

	Base from cytisoline.	β-Cytisolidine.
Picrate......................	224°	224—225° (Freund 229°)
Platinichloride	234—235	234—235
Nitro-derivative......	104	104—105

The melting points of mixtures in all these cases showed no depression.

The Synthesis of β-Cytisolidine (6 : 8-*Dimethylquinoline*).

6 : 8-Dimethylquinoline was originally obtained by Leeds (*Ber.*, 1873, **16**, 289) by the dry distillation of xylidineacrolein, and was by him termed kryptidin. It was then obtained by Berend (*Ber.*, 1874, **17**, 2716) from *m*-4-xylidine by the Skraup synthesis.

For the preparation of the base the latter method was employed. Ten grams of *m*-4-xylidine, 5 grams of nitrobenzene, and 24 grams of glycerol were heated together in a large flask on a sand-bath, and 20 grams of concentrated sulphuric acid were gradually run through a dropping funnel into the heated mixture. In this way the reaction proceeded quite smoothly. The product was worked up in the usual manner, and 6·5 grams of a base boiling at 133—134°/14 mm. were obtained. (Found, C = 83·9; H = 7·1. Calc., C = 84·0; H = 7·0 per cent.)

The identity of this base with cytisolidine is shown by the following table:

	6 : 8-Dimethylquinoline.	β-Cytisolidine.
Boiling point............	133—134°/14 mm.	132—133°/14 mm.
Picrate......................	221—224	224—225 (Freund 229°)
Platinichloride	234—235	234—235
Hydrochloride	246	250—260
Nitro-derivative.........	105	104—105

Mixed melting points in all cases showed no depression.

The formula $C_{11}H_{15}N$ assigned by Freund (*loc. cit.*) to β-cytisolidine was thus shown to be inaccurate. A specimen of β-cytisolidine picrate melting at 224—225°, obtained from cytisine by the action of hydriodic acid, was analysed with the following result:

0·1038 gave 0·2024 CO_2 and 0·0354 H_2O. C=53·2; H=3·8.

$C_{11}H_{11}N,C_6H_3O_7N_3$ requires C=52·8; H=3·6 per cent.

The Synthesis of α-Cytisolidine (6:8-*Dimethyl*-1:2:3:4-*tetra-hydroquinoline*).

Three grams of 6:8-dimethylquinoline were reduced in alcoholic solution with 5 grams of sodium. The mixture was diluted with water, the alcohol evaporated off, and the residue distilled in a current of steam. The distillate was extracted with ether, the ethereal solution washed and dried in the usual way, and the residue after evaporation of the ether distilled under diminished pressure. There were thus obtained 2·1 grams of a liquid boiling at 137°/11 mm.:

0·1582 gave 0·4746 CO_2 and 0·1328 H_2O. C=81·8; H=9·3.

$C_{11}H_{15}N$ requires C=82·0; H=9·3 per cent.

This was proved to be identical with α-cytisolidine by the preparation of a number of salts and derivatives, as shown by the following table:

	6:8-Dimethyl-1:2:3:4-tetra-hydroquinoline.	α-Cytisolidine.	
		Freund.	Ewins.
Boiling point	137°/11 mm.	—	141—142°/14 mm.
Picrate	147—148	oily	146
Platinichloride	214—215	216°	214—215
Iodide of methyl derivative	166	—	164—165
Benzoyl derivative	103	—	103

Melting points of mixtures in all cases showed no depression.

Since 6:8-*dimethyl*-1:2:3:4-*tetrahydroquinoline* has not previously been synthesised, a more detailed account of its salts and derivatives follows.

The *picrate* is best prepared by the addition of an ethereal solution of picric acid to an ethereal solution of the base. The salt is not immediately precipitated, but on addition of light petroleum and rubbing with a glass rod, a gummy, reddish-yellow solid separates, which gradually hardens, and can then be collected. It is best crystallised from benzene by careful addition of light petroleum, when it separates in large, orange-yellow, rhombic plates, melting at 147—148°.

In the presence of water this salt shows a very great tendency

to separate as an oil. Freund's failure to crystallise this salt is probably explained by this fact.

The *benzoyl* derivative is readily prepared by the Schotten-Baumann reaction, and crystallises from dilute alcohol in prisms melting at 103°:

0·1468 gave 0·4358 CO_2 and 0·0922 H_2O. C=81·0; H=7·0.

$C_{18}H_{19}ON$ requires C=81·5; H=7·2 per cent.

1:6:8-*Trimethyl*-1:2:3:4-*tetrahydroquinoline Hydriodide.*

This salt is produced by the addition of one molecule of methyl iodide to 6:8-dimethyl-1:2:3:4-tetrahydroquinoline.

6:8-Dimethyl-1:2:3:4-tetrahydroquinoline (0·4 gram) was boiled for a few minutes with a slight excess of methyl iodide. The solution was evaporated to dryness, the residue dissolved in a little methyl alcohol, and dry ether added, just insufficient to produce a precipitate. On keeping, crystals of the above salt separated out. They formed prisms melting at 164—165° (0·26 gram):

0·1242 gave 0·2156 CO_2 and 0·0638 H_2O. C=47·4; H=5·7.

$C_{12}H_{17}N,HI$ requires C=47·5; H=5·9 per cent.

THE WELLCOME PHYSIOLOGICAL RESEARCH LABORATORIES,
HERNE HILL, S.E.