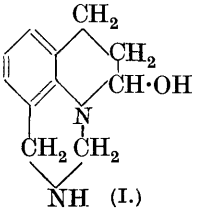
CCXCVIII.—*Cytisine. Part I.*

By Harry Raymond Ing.

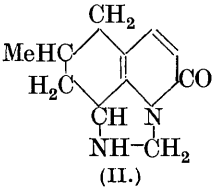
Cytisine occurs in the seeds of *Cytisus laburnum* and of a large number of other *Leguminosæ*. It was first isolated in a pure state by Husemann and Marmé (*Edin. Med. J.*, 1862, **7**, 908, 1025) and has since been extensively investigated by Partheil (*Arch. Pharm.*, 1892, **230**, 448; 1894, **232**, 167; *Ber.*, 1890, **23**, 3202; 1891, **24**, 635), Freund and his collaborators (*Ber.*, 1901, **34**, 605; 1904, **37**, 16; 1906, **39**, 814; *Arch. Pharm.*, 1918, **256**, 33), Ewins (J., 1913, **103**, 97) and Späth (*Monatsh.*, 1919, **40**, 15, 93).

Cytisine has the formula $C_{11}H_{14}ON_2$. It forms mono-*N*-acyl derivatives and yields a mononitroso-compound, and contains, therefore, one secondary nitrogen atom, which is shown by exhaustive methylation (see below) to form part of a ring. The common salts of cytisine are monoacidic, but a dihydrochloride has been described (Partheil), and the *N*-acyl derivatives form salts but no methiodides. The second nitrogen atom is thus tertiary and feebly basic.

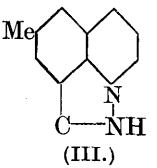
The most illuminating facts about the structure of cytisine are derived from its behaviour on reduction by hydriodic acid and red phosphorus, whereby it yields ammonia, cytisoline, $C_{11}H_{11}ON$, and β-cytisolidine, $C_{11}H_{11}N$ (Freund, *loc. cit.*). It has been proved by synthesis that the latter organic compound is 6 : 8-dimethylquinoline (Ewins, *loc. cit.*), and the former 2-hydroxy-6 : 8-dimethylquinoline (Späth, *loc. cit.*). On the basis of these results, formula (I) for cytisine was put forward by Freund and formula (II) by Späth. Ewins had previously suggested that cytisine was formed by the fusion of quinoline and pyrazole rings (III) but he did not discuss the allocation of the hydrogen and oxygen atoms.



(I.)



(II.)



(III.)

Objections can be raised to each of these formulæ. There is no evidence for the hydroxy-group of formula (I). Only Ewins's partial formula (III) contains the 6 : 8-dimethyl carbon atoms in the positions which they occupy in cytisoline, and there is no reason to assume that a methyl group attached to the quinoline nitrogen will migrate either to the 6-position as required by Freund's formula (I) or to the 8-position as required by Späth's (II). Indeed, Späth himself failed to obtain such migrations when *N*-methyl-α-quinolones were heated with hydriodic acid under the conditions of the reduction process.

Moreover, any partially reduced quinoline formula for cytisine would be expected to involve ease of oxidation of the alkaloid to a completely aromatic structure and (I), in particular, should lead to a benzene-carboxylic acid. This has never been observed. Cytisine is easily oxidised but degradation products more complex than ammonia and oxalic acid have never been isolated. Späth (*loc. cit.*) claimed to have obtained *iso*valeric acid among the products of its oxidation with barium permanganate, but the only evidence for this consisted in the odour of an ethyl ester. Distillation of cytisine with zinc dust or soda–lime yields pyrrole and pyridine but no quinoline bases.

Oxidation with silver oxide, iodine in alcohol, and similar reagents was studied in the present investigation, but in no case could a crystalline product be isolated and consequently this line of attack was abandoned. Hydrogen peroxide oxidises cytisine to hydroxycytisine, $C_{11}H_{14}O_2N_2$, in which the imino-group is converted into $>N\cdot OH$ (Freund, *loc. cit.*). This result is difficult to reconcile with Späth's formula (II) when it is remembered with what ease the iminazole ring is formed in preference to its hydrogenated analogue.

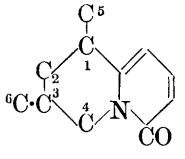
These objections suggest that previous authors have been wrong in concluding that the quinoline nucleus exists preformed in the alkaloid. The only evidence for this assumption is the production of cytisoline and β-cytisolidine in the phosphorus and hydriodic acid reduction, and this result is equally consistent with the view that the quinoline nucleus is formed during the reduction process itself by some intramolecular change. But if the view that cytisine contains a quinoline skeleton is rejected, there is good evidence for the presence of one aromatic nucleus in the alkaloid.

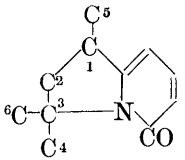
Cytisine can be nitrated, and nitrocytisine yields on reduction an aminocytisine capable of diazotisation (Freund, *loc. cit.*). It can also be readily brominated to form dibromocytisine, $C_{11}H_{12}ON_2Br_2$. This substance was studied by Partheil (*loc. cit.*) and Lammers (*Arch. Pharm.*, 1897, **235**, 275), who found that no hydrobromic acid was removed by boiling it with baryta, silver oxide, or alcoholic

potassium hydroxide. Reduction with sodium amalgam or zinc and sulphuric acid reconverts dibromocytisine into cytisine. These results, which have been confirmed by the present author, suggest that both bromine atoms enter an aromatic nucleus, and it is noteworthy that neither formula (I) nor (II) affords suitable positions for disubstitution.

The formation of the α-quinolone nucleus in the reduction of cytisine, together with the failure of several authors to obtain evidence for the existence of benzene-carboxylic acids in the permanganate oxidation products of the alkaloid, make it fairly certain that the aromatic nucleus in cytisine is an α-pyridone ring. This view is supported by the fact that cytisine gives a red colour with ferric chloride which is discharged by hydrogen peroxide with the slow production of a blue-green, since Späth found this colour reaction to be characteristic of a number of *N*-alkyl-α-pyridones and -α-quinolones.

In order to account for the production of cytisoline from cytisine, it is necessary to assume that the carbon skeleton C·C(·C)·C·C·C is attached to the α-pyridone nitrogen and to another atom in the pyridone ring in such a way as to make possible the completion of the quinoline nucleus. The partial formulæ (IV) and (V) represent the simplest ways of fulfilling these conditions.

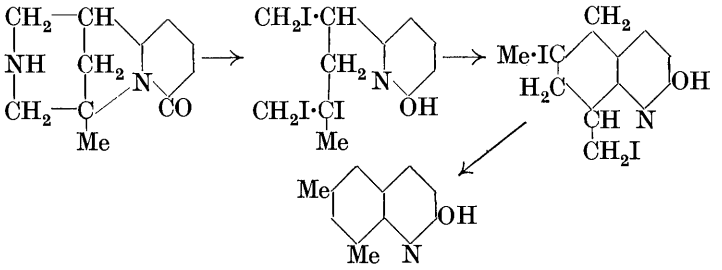
(IV.) 

 (V.)

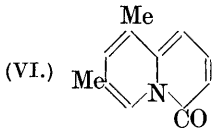
The pyridocoline nucleus as in (IV) is known to occur in certain alkaloids of the berberine type, and although the pyrrocoline nucleus as in (V) has not so far been demonstrated to occur in natural products, derivatives of it have been synthesised (compare Clemo and Ramage, this vol., p. 49). The development of the partial formulæ (IV) and (V) requires the linking of two carbon atoms of the numbered rings by NH< and the complete saturation of the bridged-ring system so formed by hydrogen. In (IV) the imino-group may be assumed to link one of the following pairs of carbon atoms : 1 : 4; 1 : 6; 3 : 5; 4 : 5 and 5 : 6, and in (V) either of the pairs 1 : 6 or 5 : 6.

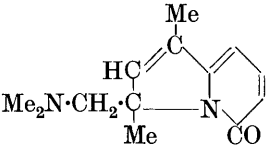
The formulæ (IV) and (V) afford a simple explanation of the formation of the 6 : 8-dimethylquinoline nucleus in the reduction of cytisine by phosphorus and hydriodic acid. The effect of these reagents is to remove the imino-group as ammonia and to break the carbon linkage to the pyridone nitrogen. Hydriodic acid is then lost

between carbon atom 4 or 6 and the para-position to the 2-hydroxy-group of the pyridine ring, followed by further loss of hydriodic acid from the newly formed ring. This is illustrated for a formula of type (V), but similar mechanisms will hold for formulæ of type (IV).



In deciding between formulæ (IV) and (V) it is instructive to consider what would be the results of the exhaustive methylation of such structures. All the five possible formulæ for cytisine of type (IV) should yield the same dimethylpyridocoline derivative (VI) if the appropriate rearrangements of double bonds to form a second aromatic ring are assumed. The two possible formulæ of type (V)





(NH< linking carbon atoms 1 : 6 or 5 : 6) lead to no such simple result. The first stage of the exhaustive methylation should yield a de-*N*-dimethyl compound (VII), but as this structure contains no hydrogen in the β-position to nitrogen it is difficult to predict the subsequent course of the degradation.

The exhaustive methylation of cytisine was studied by Partheil (*loc. cit.*), who found that it yielded first methylcytisine, a crystalline substance, m. p. 134°, which on further degradation gave an amorphous de-*N*-dimethylcytisine. The amorphous methiodide of the latter on heating with potassium hydroxide lost trimethylamine and formaldehyde and left an amorphous base, $C_{10}H_{13}O_2N$, analysed as its amorphous chloroplatinate. It has now been found that de-*N*-dimethylcytisine methohydroxide decomposes smoothly in boiling amyl alcohol with loss of trimethylamine, and the main product is a crystalline *substance*, m. p. 300°, of empirical composition $C_{11}H_{11}ON$, a formula which corresponds to cytisine less the elements of ammonia. No formaldehyde could be detected in this decomposition. A small amount of soluble base was also formed which gave an amorphous

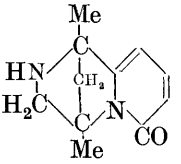
methiodide but insufficient was obtained for further investigation. No hydroxy-compound could be detected by means of phenyl *iso*cyanate.

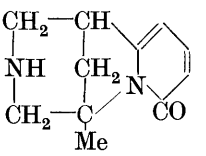
The substance, m. p. 300°, is a weak base, insoluble in water, but dissolving in concentrated acid and crystallising on dilution. It gives the red colour with ferric chloride characteristic of cytisine, and therefore contains the α-pyridone ring intact. The molecular weight in camphor corresponds to the double formula $C_{22}H_{22}O_2N_2$. This result is peculiar. The only other instances of the polymerisation of the residue on decomposition of a quaternary ammonium hydroxide appear to be fluorenyl-9-trimethyl- and -9-triethyl-ammonium hydroxides, which yield *oo'*-bisdiphenylylene-ethylene (Ingold and Jessop, J., 1929, 2357).

The studies of Ingold and his collaborators on the course of exhaustive methylation degradations indicate that, for ammonium hydroxides (>CH·NR_3OH) containing no H_β, three reactions are possible : (1) conversion to the tertiary amine (>CH·NR_2 + ROH), (2) loss of NR_3 and conversion to the alcohol (>CH·OH), and (3) methylenic elimination followed by isomerisation or polymerisation (*e.g.*, >C:C< + 2NR_3 + 2H_2O). All three reactions occur with fluorenyl-9-trimethylammonium hydroxide. Absence of H_β in an ammonium hydroxide does not necessarily involve methylenic elimination, but the latter has only been observed for ammonium hydroxides containing no H_β.

Consequently, it appears justifiable to conclude that the formation of $C_{22}H_{22}O_2N_2$ in the decomposition of de-*N*-dimethylcytisine methohydroxide implies the absence of H_β, a condition which is satisfied only by formulæ of type (V), of which two are possible, *viz.*, (VIII) and (IX).

(VIII.)





(IX.)

It is impossible at present to decide definitely between these alternative formulæ, although the author prefers (IX). The advantages claimed for these new formulæ may be briefly summarised. They contain the α-pyridone ring with two positions (3 and 5) free for substitution. They will account in a simple manner for the formation of cytisoline in the phosphorus and hydriodic acid reduction. Exhaustive methylation can only yield a de-*N*-dimethylcytisine containing no H_β, which makes plausible the polymerisation of the residue after loss of trimethylamine. At the same time, they are

consistent with all the other well-established facts about cytisine and are free from the objections raised against previously suggested formulæ.

The synthesis of ring systems such as those indicated in formulæ (VIII) and (IX) is being investigated. The experimental section of this paper gives an account of work dealing with the synthesis of quiniminazole derivatives related to Späth's cytisine formula (II), which was begun before the theoretical ideas now adumbrated were developed.

EXPERIMENTAL.

Extraction of Cytisine.—Previous workers have extracted cytisine from laburnum seeds by means of dilute aqueous or alcoholic acid. It was found more convenient to use chloroform, in which the alkaloid is very soluble. The seeds (1 kg.), ground to pass a 20-mesh sieve, were intimately mixed with slaked lime (100 g.), and water (500 c.c.) was added. The mixture was kneaded into a coarse powder and extracted with chloroform for 20 hours. The chloroform extract was evaporated finally in a vacuum to remove the last traces of solvent, and the residue stirred with light petroleum (1 litre) and left over-night. Most of the alkaloid crystallised and was separated, the mother-liquor being extracted with dilute acid. The crude alkaloid was purified by boiling its solution in dilute hydrochloric acid with charcoal, filtering it, making it strongly alkaline, and extracting with chloroform. The chloroform solution was dried with sodium sulphate and evaporated, the alkaloid crystallising at once (yield 20 g.). Cytisine is best purified by distillation in a vacuum, followed by crystallisation from dry acetone; m. p. 154·5—155·5° (Found : C, 69·3; H, 7·4; N, 14·7. Calc. for $C_{11}H_{14}ON_2$: C, 69·5; H, 7·4; N, 14·7%). *p-Toluenesulphonylcytisine* is insoluble in cold water but can be recrystallised from hot. It is soluble in dilute acid and in warm alcohol; prisms m. p. 207—208° (Found : N, 8·1. $C_{18}H_{20}O_3N_2S$ requires N, 8·1%).

Exhaustive Methylation of Cytisine (with ROBERT SIDNEY CAHN). —*Methylcytisine.* Cytisine dissolved in methyl alcohol was refluxed with excess of methyl iodide for an hour, cooled, and the solid methiodide filtered off and recrystallised from methyl alcohol; it formed pale yellow needles, m. p. 280° with previous sintering (Found : I, 38·3. Calc. for $C_{12}H_{17}ON_2I$: I, 38·3%). Partheil (*loc. cit.*) gives m. p. 270°. The methiodide was dissolved in excess of 20% sodium hydroxide and extracted with chloroform. Evaporation of the dried extract left methylcytisine, which rapidly crystallised; m. p. 134° after recrystallisation from acetone.

De-N-dimethylcytisine. Methylcytisine reacts slowly with methyl iodide, and the presence of unchanged base greatly increases the

solubility of the methiodide in methyl alcohol, but it can be separated by taking advantage of its insolubility in acetone. Methylcytisine was consequently refluxed in acetone with excess of methyl iodide. The methiodide gradually separated and was removed. The acetone mother-liquors were refluxed with more methyl iodide until, after separation of the methiodide, a negligible residue was left on evaporation of the solution. The methiodide was recrystallised from methyl alcohol in which it is sparingly soluble; m. p. 276° (decomp.) (Found : I, 36·7. Calc. for $C_{13}H_{19}ON_2I$: I, 36·7%). It was converted into the hydroxide by means of silver oxide in aqueous solution, the water removed by distillation in a vacuum, and the residual hydroxide refluxed in amyl alcohol for 4 hours. After removal of the amyl alcohol in steam, the aqueous solution was made strongly alkaline and extracted with chloroform. Evaporation of the chloroform left de-*N*-dimethylcytisine as a clear yellow gum which did not crystallise. Attempts to hydrogenate this base catalytically in aqueous, in alcoholic, and in 2% acetic acid solution with palladised charcoal were unsuccessful.

The substance, $C_{22}H_{22}O_2N_2$. De-*N*-dimethylcytisine reacted readily with methyl iodide in acetone solution, the methiodide separating in an amorphous condition. It could not be obtained crystalline, but was converted directly into its hydroxide in methyl-alcoholic solution by means of silver oxide, the alcohol being removed in a vacuum, and the residue refluxed in amyl alcohol until no more trimethylamine was evolved (3 hours). The solution of the hydroxide had a remarkable green fluorescence, and when evaporated assumed a bright purple-red colour which disappeared on boiling in amyl alcohol, although the fluorescence remained. Removal of the amyl alcohol in steam left a resinous material insoluble in water. The aqueous layer was decanted, made strongly alkaline, and extracted with chloroform. In this way a small amount of a base was obtained which gave an amorphous methiodide in acetone solution, but the quantity was insufficient for further investigation. It was probably de-*N*-dimethylcytisine methiodide.

The insoluble resinous material was dissolved in chloroform, the solution dried with sodium sulphate, and completely evaporated. The residual resin was dissolved in the minimal amount of hot benzene, and a crystalline material separated. The mother-liquor was evaporated and treated with hot dry acetone, whereupon more crystalline material separated. Repetition of this process, using benzene and dry acetone alternately, converted most of the resin into the crystalline material. No other material could be isolated, and treatment of the final mother-liquors with phenyl *iso*cyanate gave no phenylurethane. The crystalline *substance* was recrystal-

lised by solution in hot acetic acid and dilution with water; it separated slowly in a pale yellow microcrystalline condition, m. p. 300° with previous sintering (Found : C, 76·3; H, 6·5; N, 8·0; *M*, in camphor, 342. $C_{11}H_{11}ON$ requires C, 76·3; H, 6·4; N, 8·1%). $C_{22}H_{22}O_2N_2$ requires *M*, 346). The substance is a weak base, soluble in concentrated hydrochloric acid and crystallising on dilution. In alcoholic solution it gave a blood-red colour with ferric chloride, which was discharged by hydrogen peroxide with the slow production of a green colour on warming. In acetic acid solution it decolorised permanganate at once. Attempts to hydrogenate it in acetic acid solution with palladised charcoal were unsuccessful.

Synthesis of Derivatives of Quiniminazole (see annexed formula).—8-Nitro-6-methylquinoline, prepared from *m*-nitro-*p*-toluidine (compare Barlow and McCollum, *J. Amer. Chem. Soc.* 1904, **26**, 700), was heated with excess of methyl sulphate on the steam-bath for 3 hours, treated with water, and extracted with ether. The aqueous solution was saturated with sodium iodide, whereupon the *methiodide* separated; it was recrystallised from water or methyl alcohol, m. p. 164° (decomp.) (Found : I, 38·5. $C_{11}H_{11}O_2N_2I$ requires I, 38·5%). The methiodide (10 g.), dissolved in alcohol (50 c.c.), was treated with 20% aqueous caustic potash (20 c.c.) and hydrogen peroxide (90—100-vol.; 40 c.c.), and the reaction completed on the steam-bath. 8-*Nitro*-1 : 6-*dimethyl*-α-*quinolone* separated and was recrystallised from methyl alcohol; yellow needles, m. p. 165—166° (Found : N, 12·8. $C_{11}H_{10}O_3N_2$ requires N, 12·8%).

Equal weights of the quinolone and phosphorus pentachloride were heated at 170—180° until effervescence ceased. The product was treated with water, and the insoluble residue recrystallised from alcohol. 2-*Chloro*-8-*nitro*-6-*methylquinoline* forms colourless needles, m. p. 150—151° (Found : N, 12·5. $C_{10}H_7O_2N_2Cl$ requires N, 12·6%). It was heated with water, made just acid, at 140° for 4 hours, and the insoluble product extracted with warm 10% potash, filtered off and made acid. The bright yellow 8-*nitro*-2-*hydroxy*-6-*methylquinoline* crystallised from alcohol as yellow plates, m. p. 200—201° (Found : N, 13·6. $C_{10}H_8O_3N_2$ requires N, 13·7%).

The foregoing compound (10 g.), dissolved in hot acetic acid (40 c.c.) and diluted with water (40 c.c.), was treated during 1 hour with iron filings (7 g.), the temperature being kept at 40—50° (compare Dikshoorn, *Rec. trav. chim.*, 1929, **48**, 147). The product was poured into water (400 c.c.), the precipitated base dissolved in warm dilute hydrochloric acid, filtered, and saturated with hydrogen chloride. 8-*Amino*-2-*hydroxy*-6-*methylquinoline hydrochloride*, which separated,

was recrystallised from dilute hydrochloric acid, and treated with ammonia; the free *base* was precipitated in an amorphous condition, and when crystallised from alcohol, it formed greenish woolly needles which did not melt below 300° (Found : N, 15·8. $C_{10}H_{10}ON_2$ requires N, 16·1%). When boiled with formic acid, this yielded, not the quiniminazole ring, but the *formyl* derivative, colourless, woolly needles from alcohol, m. p. 263—264° (Found : C, 65·4; H, 5·0; N, 13·8. $C_{11}H_{10}O_2N_2$ requires C, 65·3; H, 5·0; N, 13·8%). With boiling acetic anhydride the free base yields an *acetyl* derivative, woolly needles from alcohol, m. p. 300° (Found : N, 12·9. $C_{12}H_{12}O_2N_2$ requires N, 13·0%).

6-*Methyl*-1 : 2 : 3 : 4-*tetrahydroquiniminazole*.—Crude 8-amino-6-methyl-1 : 2 : 3 : 4-tetrahydroquinoline (Bamberger and Wulz, *Ber.*, 1891, **24**, 2071) was boiled for 2—3 hours with 100% formic acid. The product was poured into water, made alkaline, and the oil extracted with chloroform. After evaporation of the solvent, the oil was distilled in a vacuum. The fraction of b. p. 210—220°/18 mm. solidified, and was crystallised by solution in hot ether and addition of an equal volume of light petroleum (b. p. 60—80°).

6-*Methyl*-1 : 2 : 3 : 4-*tetrahydroquiniminazole* crystallises slowly in irregular prisms, m. p. 82—83° (Found : N, 16·3. $C_{11}H_{12}N_2$ requires N, 16·3%). It forms a *perchlorate*, needles from water, m. p. 240° (decomp.) (Found : N, 10·2. $C_{11}H_{12}N_2,HClO_4$ requires N, 10·3%).

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