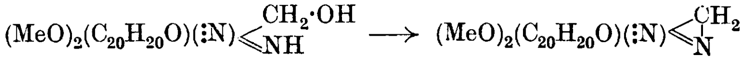
CCXI.—*Strychnine and Brucine. Part V.*

By JOHN MASSON GULLAND, WILLIAM HENRY PERKIN, jun., and ROBERT ROBINSON.

THE present communication contains the description of part of a general investigation of the reduction products of brucine, our knowledge of which is comparatively scanty. Reduction by hydrogen in presence of colloidal palladium yields dihydrobrucine (Skita and Franck, *Ber.*, 1911, **44**, 2864), and Tafel and Naumann (*Ber.*, 1901, **34**, 3291) have described the preparation by electrolytic reduction of a substance which they designate "tetrahydrobrucine."

The starting point of the research now to be described is brucidine, a substance which Tafel and Naumann (*loc. cit.*) claim to have prepared from "tetrahydrobrucine" by the elimination of water at 215°. The two substances were thus considered to be analogous to tetrahydrostrychnine and strychnidine and were represented by the scheme:



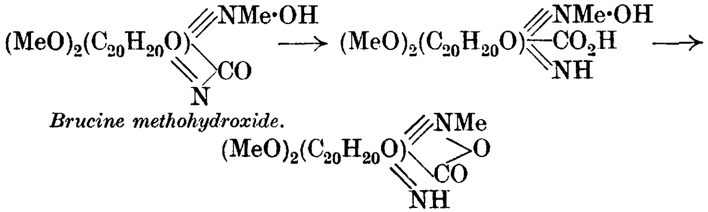
$$(MeO)_2(C_{20}H_{20}O)(\vdots N)\Big\langle\begin{matrix}CH_2\cdot OH\\ NH\end{matrix} \longrightarrow (MeO)_2(C_{20}H_{20}O)(\vdots N)\Big\langle\begin{matrix}CH_2\\ |\\ N\end{matrix}$$

Tetrahydrobrucine. *Brucidine.*

The properties of these substances as described by Tafel are extremely similar, and he was unable to demonstrate by the preparation of a nitrosoamine the presence of an imino-group in the secondary amine, tetrahydrobrucine. We have repeated the electrolytic reduction of brucine, using the modified apparatus described in a previous communication (J., 1924, **125**, 1798), and our results show that Tafel's "tetrahydrobrucine," m. p. 200—201°, should be re-named brucidine. It is clear, however, that his "brucidine," m. p. 198°, was correctly named, although it was not quite homogeneous and was identical with his supposed "tetrahydrobrucine." We have now obtained two products, (i) *brucidine*, m. p. 203—203·5°, which shows all the properties of Tafel's "tetrahydrobrucine," and (ii) *tetrahydrobrucine*, m. p. 177°, which is a secondary amine yielding a *nitrosoamine*. The second substance, moreover, yields brucidine when dehydrated by means of phosphorus oxychloride, and the two compounds are thus entirely analogous to the corresponding derivatives of strychnine. Tafel's analyses of " tetrahydrobrucine " are in agreement with the theory for brucidine containing a molecule of methyl alcohol, and we have found that the base when crystallised from methyl alcohol does in fact retain one molecule of the solvent.

Tetrahydrobrucine and brucidine are di-acid bases each of which forms a *dihydrochloride* and a *dihydriodide*, but only a mono-methiodide when heated with an excess of methyl iodide in boiling methyl alcohol.

The starting materials in the experiments described in this communication are the brucidine metho-salts, and of these the *metho-sulphate*, prepared by the direct combination of the base with methyl sulphate, is the most easily obtained in practice. Brucidine metho-salts, however, have also been prepared by the electrolytic reduction of methylbrucine. This substance was first obtained (Moufang and Tafel, *Annalen*, 1899, **304**, 42) by the decomposition of brucine methiodide with silver sulphate, followed by the removal of the sulphuric acid by baryta, and Tafel represented it as a betaine according to the scheme :



Brucine methohydroxide.

Methylbrucine.

Leuchs and Anderson (*Ber.*, 1911, **44**, 3046), however, prepared this compound more simply by the action of sodium hydroxide on brucine methosulphate, and we have employed a slight modification of their method. The electrolytic reduction of methylbrucine in dilute sulphuric acid is followed by the removal of the sulphuric acid by means of barium carbonate. In this way, *brucidine metho-hydrogencarbonate* is obtained, and from it may be prepared *brucidine methohydroxide* by the action of alkali, and also *brucidine methiodide* by means of sodium iodide. This methiodide is identical with a specimen prepared by the interaction of the base with methyl iodide, and it is therefore evident that the nitrogen atom which is involved in the production of brucidine metho-salts is not that which forms part of the group $-CO-N:$ of brucine.

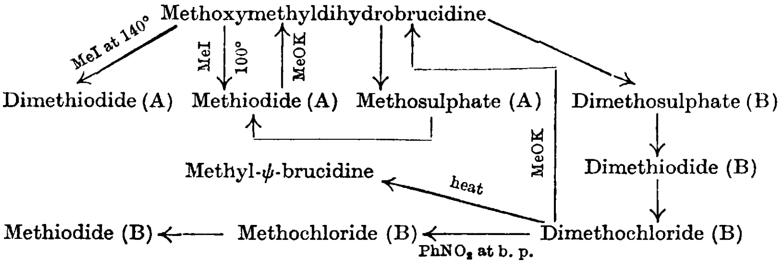
When brucidine methochloride or methosulphate,

$$C_{23}H_{28}O_3N_2,Me_2SO_4,$$

is digested with methyl-alcoholic potassium hydroxide it is converted into *methoxymethyldihydrobrucidine*, $C_{25}H_{34}O_4N_2$, m. p. 115°, which is derived from brucidine by the introduction of a methyl group and the addition of methyl alcohol. Unlike the corresponding derivative of strychnidine, this substance is a di-acid base, yielding a *dihydriodide*, but here, as in the case of brucidine, one molecule only of methyl iodide enters easily into combination with the base. The formation of this *methiodide* (A) by the action of methyl iodide at 100° takes place smoothly in the absence of a solvent, but when methyl alcohol is employed in the preparation, a small quantity of *oxymethoxymethyldihydrobrucidine*, $C_{25}H_{34}O_5N_2$, m. p. 277°, is produced, and a little of the same substance may be isolated from the mother-liquors when the methiodide, prepared in the absence of a solvent, is recrystallised from methyl alcohol. By far the greater proportion of the product of the action of methyl iodide on methoxymethyldihydrobrucidine under either set of conditions is the methiodide (A), and in this the brucidine derivative differs greatly from the parallel strychnidine one (compare this vol., p. 1591). Indications have been obtained of the formation in these reactions of a second iodine-free *base*, melting at about 218°, which may correspond to oxymethoxymethyldihydrostrychnidine (A), but this substance has not been obtained in a pure condition, because recrystallisation from methyl alcohol converts it into oxymethoxymethyldihydrobrucidine, m. p. 277°. Oxymethoxymethyldihydrobrucidine is probably formed by an atmospheric oxidation which is catalysed by small quantities of iodine, since it has recently been obtained in much greater yield when an ethyl-alcoholic solution of methoxymethyldihydrobrucidine containing a few small crystals of iodine is exposed to the air for some days. A parallel experiment in which the iodine was omitted yielded no oxymethoxymethyldihydrobrucidine in the same space of time.

Further atmospheric oxidation takes place in boiling methyl-alcoholic solution, and a *dioxymethoxymethyldihydrobrucidine* (X), $C_{25}H_{34}O_6N_2$, m. p. 270°, has been isolated. This substance is isomeric with two *dioxymethoxymethyldihydrobrucidines*, namely (Y) and (Z) (p. 1631), which are produced by oxidation of methoxymethyldihydrobrucidine by permanganate. The investigation into the constitution of these substances, their relationship, and the significance of their formation has not yet been completed.

Methoxymethyldihydrobrucidine combines readily at 100° with one molecule of methyl iodide, as has been stated above, but when the temperature is raised to 140° and the reaction prolonged for some hours, the *dimethiodide* (A), m. p. 215°, is formed. In a similar way, methoxymethyldihydrobrucidine reacts slowly with methyl sulphate at 100° to form the *monomethosulphate* (A), but if the reaction is continued for a day the base is converted quantitatively into the *dimethosulphate* (B). This substance has not been obtained in a crystalline form, but when sodium iodide is added to its aqueous solution the *dimethiodide* (B), m. p. 290°, is precipitated and easily obtained in a pure condition. The *dimethochloride* (B), prepared from the dimethiodide by the action of silver chloride, is a horny mass which has been decomposed in three different ways. When boiled with methyl-alcoholic potassium hydroxide, it loses two molecules of methyl chloride, and methoxymethyldihydrobrucidine is regenerated. When the dimethochloride is heated for a short time in boiling nitrobenzene, the chief product is *methoxymethyldihydrobrucidine methochloride* (B), produced by the liberation of one molecule of methyl chloride. Sodium iodide converts this substance into the *methiodide* (B), which is isomeric with the methiodide (A) mentioned above. When, thirdly, the dry dimethochloride (B) is heated, it loses two molecules of methyl chloride and one of methyl alcohol and yields *methyl-ψ-brucidine* (p. 1631). It will be observed that methoxymethyldihydrobrucidine not only forms two series of metho-salts, depending probably upon which of the two nitrogen atoms is involved, but also two series of dimetho-salts, which are probably stereoisomeric. The relationships existing in this complex group of substances are readily understood from the following scheme :



A consideration of the colour reactions of the reduced brucidine derivatives, especially that given with ferric chloride (see p. 1661), leads to the conclusion that the methiodide (A) has the formula $(MeO)_2(C_{20}H_{20}O)(OMe)(\vdots NMe){<}\left.\begin{matrix}CH_2\\|\\NMe\end{matrix}\right\}I$, whilst the methiodide (B) is $(MeO)_2(C_{20}H_{20}O)(OMe)(\vdots NMe_2){<}\left.\begin{matrix}CH_2\\|\\N\end{matrix}\right\}I$. This is noteworthy and implies that the more basic of the two nitrogen atoms of brucidine becomes the less basic of the two nitrogen atoms of methoxymethyldihydrobrucidine.

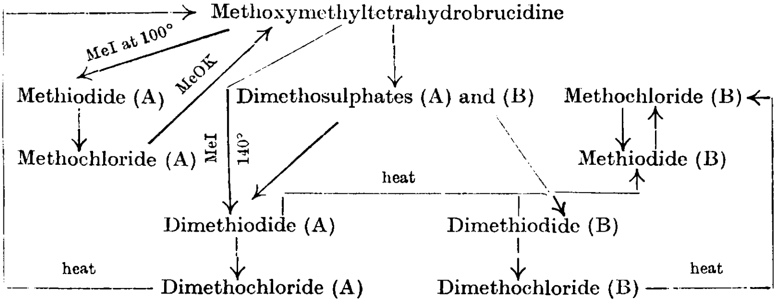
Dilute nitric acid has apparently little oxidising action on methoxymethyldihydrobrucidine, as this reagent at 100° yields only *nitromethoxymethyldihydrobrucidine*, $C_{25}H_{33}O_6N_3$. When, however, the oxidation is brought about by means of potassium permanganate in acetone, two isomeric *dioxymethoxymethyldihydrobrucidines*, $C_{25}H_{34}O_6N_2$, are produced, namely (Y), m. p. 185—186°, and (Z), m. p. 110—111°. The first of these substances (Y) is a base and yields a *methiodide*, which has the interesting property of existing simultaneously in two interconvertible forms; one contains solvent of crystallisation, the other does not. This base is not altered by boiling for a short time with acetic anhydride, and attempts to form a semicarbazone resulted in a dark red, uncrystallisable oil. The second substance (Z) shows more feebly basic properties, since, although it is readily soluble in dilute hydrochloric acid, it does not react with methyl iodide at 100°.

In order to determine whether a process similar to the formation of methoxymethyldihydrobrucidine would occur if ethyl alcohol were substituted for the methyl alcohol used in the preparation of this substance, brucidine methosulphate was digested with sodium ethoxide in ethyl alcohol. A sandy powder was obtained which showed no tendency to crystallise, and was therefore analysed in the form of its crystalline methiodide. This proved to be *ethoxymethyldihydrobrucidine methiodide*, $C_{26}H_{36}O_4N_2$,MeI. The reaction thus follows a course similar to that observed when methyl alcohol is used, but the product was not further investigated.

When methoxymethyldihydrobrucidine is boiled with dilute sulphuric acid, methyl alcohol is eliminated, and as no precipitate is formed on the addition of ammonia or sodium hydroxide the solution evidently contains a quaternary sulphate. On addition of an excess of sodium iodide *methyl*neo*brucidinium iodide*, $C_{24}H_{31}O_3N_2I$, m. p. 298°, is precipitated, and the investigation of the mother-liquors yielded only a further quantity of the same iodide. It would thus appear that, in contrast to the behaviour of methoxymethyldihydrostrychnidine under similar conditions (this vol., p. 1593), only one iodide is formed, which, it should be noted, is isomeric with brucidine methiodide, m. p. 322°. *Methyl*neo*brucidinium chloride*, prepared from the iodide by means of silver chloride, may be decomposed in two ways. When digested with methyl-alcoholic potassium hydroxide, it gains methyl alcohol and loses hydrogen chloride, forming methoxymethyldihydrobrucidine. On the other hand, if the dry chloride is heated it loses hydrogen chloride, forming *methyl-ψ-brucidine*.

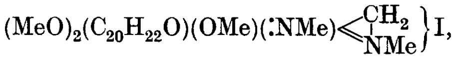
Methyl-ψ-brucidine, $C_{24}H_{30}O_3N_2$, m. p. 198—199°, is obtained either in the manner described above, or by heating methoxymethyldihydrobrucidine dimethochloride (B). It is a base, forming a *dihydriodide*, but only a *methiodide* when combined directly with methyl iodide in the cold. Small quantities of the base and also of its methochloride are formed during the decomposition of methoxymethyldihydrobrucidine dimethochloride (B) in boiling nitrobenzene; the methochloride, which was not isolated, yields the above-mentioned methiodide when treated with sodium iodide. Methyl-ψ-brucidine is unchanged by electrolytic reduction or by shaking in an atmosphere of hydrogen in presence of colloidal palladium, but it is readily oxidised by potassium permanganate to brucidone, $C_{23}H_{28}O_5N_2$, one atom of carbon being lost during the process. This most interesting substance, the analogue of strychnidone, is unfortunately an oil, but a crystalline *monosemicarbazone* was obtained and analysed. The stability of methyl-ψ-brucidine towards reducing agents is noteworthy and cannot, at present, be explained.

Methoxymethyltetrahydrobrucidine, $C_{25}H_{36}O_4N_2$, m. p. 133—135°, is derived from methoxymethyldihydrobrucidine by electrolytic reduction. It is characterised by the facility with which it crystallises, and also shows greater stability to light and air than the methoxydihydro-derivative. It is a di-acid base yielding a *dihydrochloride* and a *dihydriodide*, and like the methoxydihydro-derivatives it forms two series of metho-salts, namely (A) and (B), and also two series of dimetho-salts, namely (A), which are comparatively low-melting, and (B), which are high-melting. The *methiodide* (A) is produced by the direct combination of the base with methyl iodide at 100°, and in contrast to the behaviour of methoxymethyldihydrobrucidine under similar conditions no oxidation accompanies this reaction (compare p. 1629). This methiodide yields the *methochloride* (A) by the action of silver chloride, and it was observed that both of these substances readily revert to the parent base. The methiodide loses methyl iodide quantitatively at 170°, whilst methyl chloride is eliminated when the methochloride is boiled with methyl-alcoholic potassium hydroxide. Methoxymethyltetrahydrobrucidine combines slowly with methyl sulphate when heated with an excess of the reagent in dry benzene for 24 hours, and yields a glassy mass which is a mixture of two *dimethosulphates*, namely, (A) and (B). These have not been separated, but the addition of sodium iodide to their aqueous solution precipitates the *dimethiodide* (B), m. p. 287°, the isomeride (A) remaining in solution. The dimethiodide (B) and the *dimethochloride* (B), which is prepared from it by means of silver chloride, each lose one molecule of methyl iodide, or methyl chloride, when heated, and yield respectively the *methiodide*, or *methochloride*, of the series (B). Attempts to prepare methyl-ψ-dihydrobrucidine by further decomposition of the dimethochloride (B) or the methochloride (B) were unsuccessful, because decomposition of the rest of the molecule precedes the elimination of methyl chloride; this behaviour is in marked contrast to that of the corresponding strychnidine derivatives (compare this vol., p. 1592). *Methoxymethyltetrahydrobrucidine dimethiodide* (A), m. p. 230—232°, is precipitated in a very crude condition by the addition of a large excess of potassium hydroxide to the mother-liquors from the preparation of the dimethiodide (B). It may also be obtained by the direct combination of the base with methyl iodide at 140°. When heated at its melting point, it loses one molecule of methyl iodide with the formation of the methiodide (B), and it is converted by silver chloride into the *dimethochloride* (A). When this substance is heated, two molecules of methyl chloride are liberated and methoxymethyltetrahydrobrucidine is regenerated. The relationships of these substances are illustrated by the following scheme:—



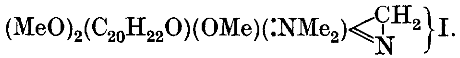
The ferric chloride reactions suggest that the metho-salts (A) and (B) are constituted analogously to the related series from methoxymethyldihydrobrucine.

The methiodide (A) will have the formula



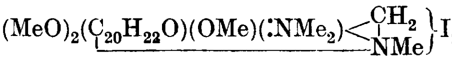
$$(MeO)_2(C_{20}H_{22}O)(OMe)(:NMe)<\begin{matrix}CH_2\\ |\\ NMe\end{matrix}\Big\}I,$$

whilst the methiodide (B) should be

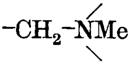


$$(MeO)_2(C_{20}H_{22}O)(OMe)(:NMe_2)<\begin{matrix}CH_2\\ |\\ N\end{matrix}\Big\}I.$$

This is in agreement with the production of the methiodide (B) from each of the stereoisomeric dimethiodides (A) and (B), since the decomposition, on the suggested hypothesis, occurs at the nitrogen atom which becomes asymmetric (N*abcd*) on the formation of the dimethiodides. A glance at the formula of the dimethiodides,



$(MeO)_2(C_{20}H_{22}O)(OMe)(:NMe_2)<\begin{matrix}CH_2\\ |\\ NMe\end{matrix}\Big\}I_2$, will show that the $:NMe_2$ group is not a new asymmetric centre, whilst the nitrogen atom of the

 $-CH_2-NMe$ group can give rise to enantiomorphism. If the formulæ for the methiodides (A) and (B) were transposed, we should anticipate that the dimethiodides (A) and (B) would give rise to stereoisomeric methiodides on decomposition.

The *methyl*neo*dihydrobrucidinium salts* could not be prepared directly from methoxymethyltetrahydrobrucidine because this substance, unlike the methoxydihydro-base, is unaffected by boiling dilute sulphuric acid. Attempts to obtain these salts by the reduction of the methyl*neo*brucidinium salts were unsuccessful, as the sulphate was unchanged by electrolytic reduction. Methoxymethyltetrahydrobrucidine dihydrochloride, however, decomposes above its melting point in boiling mesitylene, yielding hydrogen chloride, methyl alcohol, and *methyl*neo*dihydrobrucidinium chloride*. This substance is amorphous, and its aqueous solution forms no precipitate with ammonia or potassium hydroxide. When the dry chloride is heated, it decomposes without producing methyl-ψ-dihydrobrucidine (compare this vol., p. 1592). The crystalline *methyl*neo*dihydrobrucidinium iodide* is prepared from the chloride by means of sodium iodide.

A number of efforts were made to prepare *methyl-ψ-dihydrobrucidine* by heating either (i) methoxymethyltetrahydrobrucidine methochloride (B), or (ii) methoxymethyltetrahydrobrucidine dimethochloride (B), or (iii) methyl*neo*dihydrobrucidinium chloride In each case, it was evident that decomposition of the rest of the molecule preceded the liberation of methyl chloride or of hydrogen chloride as the case might be, although the corresponding derivatives of strychnidine yield methyl-ψ-dihydrostrychnidine. We hoped, therefore, that the less stable *methoxymethyltetrahydrobrucidine dimethohydrogencarbonates* would decompose more readily, and this proved to be the case. The *dimethohydrogencarbonates* (A) and (B) may be prepared by evaporating in an open basin aqueous solutions of the corresponding *dimethohydroxides*, prepared by the action of silver hydroxide on the dimethiodides (A) and (B). They are also obtained by the action of silver carbonate on the dimethiodides. When heated over a flame, the dimethohydrogencarbonate (A) regenerates methoxymethyltetrahydrobrucidine, whilst the dimethohydrogencarbonate (B) yields methyl-ψ-dihydrobrucidine, $C_{24}H_{32}O_3N_2$, m. p. 220—221°, which has been characterised further by the preparation of a *dihydriodide*. When heated less vigorously (at 135°), the dimethohydrogencarbonate (B) loses only one molecule of carbon dioxide and forms *methoxymethyltetrahydrobrucidine methohydrogencarbonate* (B), which was not purified, but was isolated in the form of the methiodide (B) by the action of sodium iodide.

EXPERIMENTAL.

Brucine Methosulphate.—Leuchs and Anderson (*Ber.*, 1911, **44**, 3046) have described the preparation of small quantities of this substance by the combination of brucine with methyl sulphate in chloroform. The following process was found convenient for large-scale operations. Pure methyl sulphate (50 c.c.) is added to a suspension of brucine (125 g.) in methyl alcohol (200 c.c.). The base dissolves with evolution of heat, and the methosulphate, which separates over-night, is collected, washed with a little methyl alcohol, and dried first in a vacuum and then at 100°. A further quantity is obtained on concentrating the mother-liquors (total yield, about 90%). The methosulphate crystallises from ethyl alcohol in colourless needles, m. p. 278° (decomp.) (Found : C, 58·2; H, 6·5. Calc. : C, 58·5; H, 6·5%). Leuchs and Anderson give m. p. 268°.

Brucine methiodide is obtained by adding sodium iodide solution to an aqueous solution of the methosulphate. It crystallises from water in needles, m. p. 295° (decomp.), after drying at 100° (Found : C, 53·4; H, 5·4. Calc.: C, 53·7; H, 5·4%). Claus and Röhre (*Ber.*, 1881, **14**, 772) prepared this compound by the interaction of brucine and methyl iodide, and give the melting point as 290° (decomp)., whereas Hanssen (*Ber.*, 1884, **17**, 2267) gives 270°.

Brucine methohydrogencarbonate is prepared from the methiodide by shaking a hot aqueous solution with excess of silver carbonate, evaporating the filtrate to dryness under reduced pressure on the water-bath, and crystallising the residue from ethyl alcohol. It forms creamy-yellow plates, m. p. 202—203° (decomp.), which retain a molecule of alcohol after drying in a vacuum desiccator, and dissolve readily in water (loss at 120°, 10·5. 1EtOH requires loss, 9·8%. Found in dried material : C, 63·6; H, 6·5. $C_{23}H_{26}O_4N_2$, $MeHCO_3$ requires C, 63·8; H, 6·4%).

The Electrolytic Reduction of Brucine. Brucidine and Tetrahydrobrucine.

The success of this reduction depends largely on the temperature of the cathode chamber. Thus at 18°, the lowest temperature at which the battery of cells could be kept during a prolonged period in the absence of ice-cooling, about 68% of the weight of brucine used was isolated in the form of practically pure brucidine and tetrahydrobrucine. If, on the other hand, the temperature rose to 21°, the yield dropped to about 55% of the weight of brucine, and further the isolation of the tetrahydrobrucine was made more difficult by the presence of gummy substances, which caused the products to become red when exposed to light and air. The formation of these could never be entirely avoided, but their amount was diminished considerably at the lower temperature. Tafel and Naumann (*loc. cit.*) were troubled by similar unstable by-products if their reduction was carried out above 15°.

The following is a description of a typical experiment, but it must be realised that variations occurred in the yields from different preparations. A solution of brucine (100 g.) in dilute sulphuric acid (300 g. of concentrated acid in 300 c.c. of water) is reduced in the usual apparatus (J., 1924, **125**, 1798) for 16 hours by a current of 5 amps., while the temperature is maintained at 17—18° by immersing the cells in running water. The contents of the cathode chambers and the aqueous washings of the cells are diluted to about twice the volume of the original solution, filtered in order to remove some lead sulphate, mixed with ice, and rendered alkaline by ammonia (*d* 0·880). Any rise of temperature is carefully avoided by the addition of ice and by cooling in a freezing mixture. A pale pink gum separates and adheres to the walls of the vessel. The liquid is decanted, extracted three times with chloroform (300 c.c. in all), and the mixed extracts are then used to dissolve the gum. The chloroform solution is washed with water, dried by potassium carbonate, and distilled. In order to remove the last traces of chloroform, the gummy residue is dissolved in boiling methyl alcohol (150 c.c.), and the solution evaporated to dryness on the water-bath. The product (100 g.), now a solid, is dissolved in boiling methyl alcohol (250 c.c.), and, on cooling, an almost colourless mass of crystals separates; this is collected and dried on the water-bath (45 g.). It melts at about 199° and is practically pure brucidine (see below). The mother-liquors are evaporated to dryness on the water-bath, the last traces of solvent being removed under reduced pressure; on boiling the semi-solid mass with pure ethyl acetate, a part remains undissolved, and after cooling is collected, washed with ethyl acetate, and dried in a vacuum (23 g.). It melts at 174° and is practically pure tetrahydrobrucine (see below). The mother-liquors contain the oily by-products, together with some crystalline substances, and their investigation is in progress.

Brucidine.—The product obtained from the reduction is crystallised from methyl alcohol, from which it separates in colourless needles, which, after being dried in a vacuum desiccator, shrink at 188—190° and melt at 203—203·5° without decomposition. On drying at 105° brucidine loses one molecule of methyl alcohol of crystallisation, and then melts at 203—203·5° without decomposition (loss at 105°, 7·7. 1MeOH requires loss, 7·9%. Found in dried material: C, 72·7; H, 7·3. $C_{23}H_{28}O_3N_2$ requires C, 72·6; H, 7·4%). It is very slightly soluble in boiling water, and the solution reacts alkaline to litmus. It dissolves readily in chloroform, less easily in methyl alcohol and ethyl acetate, and only very sparingly in ether. The colourless solution of a pure specimen in dilute hydrochloric acid slowly acquires a faint olive-green colour; on addition of a few drops of sodium nitrite a dark green coloration appears, which becomes reddish-brown on standing. When now excess of sodium carbonate is added, the colour changes to a very intense claret, which passes entirely into chloroform when the liquid is shaken with that solvent. These properties agree well with the reactions of the substance which Tafel and Naumann describe as "tetrahydrobrucine." A solution of brucidine in 60% sulphuric acid * to which a drop of an aqueous solution of potassium dichromate has been added becomes green on standing. The addition of ferric chloride to a solution in dilute hydrochloric acid produces a dark blue-green colour, which appears pink when examined in thin layers. These colour reactions are also shown by many derivatives of brucidine (see p. 1661) and in many cases dilute nitric acid causes the development of a similar green-pink colour.

The corresponding colour reactions of brucine may be given here for comparison. A drop of dichromate imparts a deep red colour to a solution in 60% sulphuric acid, but the addition of ferric chloride to brucine in dilute hydrochloric acid does not produce a coloration.

The *dihydrochloride* is formed when a little concentrated hydrochloric acid is added to a solution of the base in hot methyl alcohol. On cooling, the liquid sets to a mass of needles, which are collected and recrystallised from methyl alcohol. This salt forms colourless needles which begin to darken at 285°, and melt at 310° (decomp.) after drying in a vacuum desiccator. A satisfactory analysis of this substance was not obtained, as it appears to lose hydrogen chloride on drying. There is no doubt, however, that the base combines with two molecules of hydrogen chloride. A solution of the dihydrochloride in methyl alcohol is colourless, but on exposure for a short time to air it becomes green; the solution then appears pink when examined in thin layers.

The *dihydriodide*, prepared by adding sodium iodide to a solution of the base in dilute hydrochloric acid, crystallises from water in shining, grey needles, m.p. 255° (decomp.), which are only very sparingly soluble in hot water.

The methosulphate. A short, vigorous reaction occurs when pure methyl sulphate (8 c.c.) is added to a slightly warm suspension of

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* In the case of brucine and its derivatives the colour reactions are well shown in dilute sulphuric acid of 60% by weight, and not by volume (compare Part IV, this vol., p. 1599).

powdered brucidine (20 g.) in methyl alcohol (80 c.c.), and when this has subsided the mixture is heated on the water-bath for a few moments until the base has completely dissolved. On cooling the green solution in ice, the methosulphate separates in excellent yield as a mass of colourless needles, which are collected, washed with methyl alcohol, and dried in a vacuum desiccator. It is essential that the methyl sulphate should be pure and freshly distilled; the presence of acid greatly reduces the yield. When prepared in this way, the methosulphate is sufficiently pure for most purposes. It may be recrystallised from methyl alcohol in colourless needles which begin to darken at 270° and melt at 291° (decomp.), are readily soluble in water, and become purple or green when kept for some time.

The *methiodide* is obtained either by the addition of sodium iodide to an aqueous solution of the methosulphate, or by adding methyl iodide to an ethyl-alcoholic solution of the base. In either case, the crystals which separate are recrystallised from water. The methiodide forms colourless needles, m. p. 322° (decomp.), which are sparingly soluble in methyl or ethyl alcohol (Found : C, 55·1; H, 6·0. $C_{23}H_{28}O_3N_2$,MeI requires C, 55·2; H, 5·9%).

Tetrahydrobrucine.—The product obtained from the electrolytic reduction (p. 1636) is recrystallised from ethyl acetate, in which it is sparingly soluble. When prepared in this way, tetrahydrobrucine forms colourless needles, m. p. 177° (Found: C, 69·1; H, 7·7. $C_{23}H_{30}O_4N_2$ requires C, 69·4; H, 7·5%), but one of its characteristic properties is the power of retaining solvent of crystallisation with the resulting production of comparatively low-melting crystalline forms. It melts in boiling water, dissolves fairly readily to a solution which is alkaline to litmus, and on cooling crystallises in colourless needles; after drying for a short time in a vacuum desiccator, these melt to a pasty mass at 90—92°, and evolve water briskly at 100° (loss at 100°, 14·8. $4H_2O$ requires loss, 15·3%). It is rather easily soluble in methyl alcohol, but when a concentrated solution is cooled, it crystallises in colourless needles, which, after being dried in a vacuum desiccator, melt to a pasty mass at 90—95° (loss at 100°, 10·4. MeOH requires loss, 10·8%), harden on further heating, and melt again at 177°. When crystallised from ethyl alcohol, tetrahydrobrucine forms colourless needles, which soften at 115° and melt at 120° after drying in a vacuum desiccator. These contain one molecule of ethyl alcohol which is not lost at 90° (Found in material dried at 90°: C, 68·4; H, 8·3. $C_{23}H_{30}O_4N_2$,EtOH requires C, 68·2; H, 8·2%), but is liberated at 120° (loss at 120°, 10·0. 1EtOH requires loss, 10·4%). A solution of a pure specimen in dilute hydrochloric acid is colourless, but becomes bright green on the addition of a few drops of ferric chloride; this solution does not, however, show the pink tinge in thin layers which is characteristic of brucidine and its derivatives.

The *dihydrochloride* is rather readily soluble, but is obtained when a little concentrated hydrochloric acid is added to a concentrated solution of the base in methyl alcohol. On standing over-night, it separates in colourless needles, which are collected, washed with methyl alcohol, and dried at 100°. This salt darkens at 280° and melts at 305° (decomp.) (Found: C, 58·4; H, 7·0. $C_{23}H_{30}O_4N_2,2HCl$ requires C, 58·6; H, 6·8%).

The *dihydriodide* is prepared by adding sodium iodide to a solution of tetrahydrobrucine in dilute hydrochloric acid. The green colour of the solution disappears, and a yellow gum separates which slowly crystallises on rubbing. When recrystallised from ethyl alcohol, it forms colourless plates, which darken at 220° and melt at 225° (decomp.).

The *methiodide* is readily obtained by warming a solution of the base and an excess of methyl iodide in methyl alcohol for a few moments until crystallisation begins. After cooling, the colourless needles of the methiodide are collected, washed, and dried in a vacuum desiccator; they then melt at 290° (decomp.) (loss at 100°, 5·3. 1MeOH requires loss, 5·5%. Found in material dried at 100°: C, 53·5; H, 6·3. $C_{23}H_{30}O_4N_2,MeI$ requires C, 53·3; H, 6·1%).

The nitrosoamine. Sodium nitrite (0·5 g.) in a little water is added gradually to a cooled solution of tetrahydrobrucine (2 g.) in hydrochloric acid (20 c.c. of 2*N*). The yellow crystals are collected, washed with dilute hydrochloric acid, and recrystallised from ethyl alcohol. *Tetrahydrobrucine nitrosoamine hydrochloride* forms buff-coloured needles, which, after drying in a desiccator, darken and shrink at 190°, have become black at 250°, and melt at 288° (decomp.) (loss at 100°, 8·5. 1EtOH requires loss, 9·0%. Found in material dried at 100°: Cl, 7·5. $C_{23}H_{29}O_5N_3,HCl$ requires Cl, 7·6%).

When sodium carbonate is added to an aqueous solution of the hydrochloride, the *nitrosoamine* separates in needles. It is collected, washed, and recrystallised from dilute ethyl alcohol, separating in lemon-yellow needles which shrink at 205° and melt at 213—214° (decomp.) (Found: C, 64·2; H, 6·7. $C_{23}H_{29}O_5N_3$ requires C, 64·6; H, 6·8%). It is readily soluble in ethyl alcohol, and gives Liebermann's nitroso-reaction.

The Conversion of Tetrahydrobrucine into Brucidine.

A mixture of tetrahydrobrucine (5 g.) and phosphorus oxychloride (50 g.) is warmed on the water-bath for about 30 minutes; hydrogen chloride is evolved, whilst the base becomes gummy, partly dissolves, and soon changes to a mass of crystals. The excess of phosphorus oxychloride is removed by distillation on the water-bath under reduced pressure, and the residue is dissolved in water (25 c.c.), much heat being produced. After cooling and addition of ice, the solution is mixed with potassium hydroxide, and the semi-solid precipitate is collected on a glass rod, drained as thoroughly as possible, and boiled with a little methyl alcohol. The product becomes crystalline, and after cooling it is collected, washed with methyl alcohol, and dried at 100° (yield 3·6 g.; 75% of that theoretically possible). The crystals melt at 203—203·5° either alone or when mixed with a specimen of brucidine.

The Electrolytic Reduction of Methylbrucine. Brucidine Methohydroxide and Metho-salts.

Methylbrucine.—The conversion of brucine methosulphate into methylbrucine does not take place under conditions similar to those under which strychnine methosulphate yields methylstrychnine (this vol., p. 1624), because the methosulphate is precipitated unchanged by the alkali. If, however, a higher temperature and more concentrated potassium hydroxide are used, the liquid sets to a gelatinous mass, which certainly contains methylbrucine, but which can be neither crystallised nor purified. Methylbrucine was therefore prepared by a modification of the method of Leuchs and Anderson (*loc. cit.*, p. 3047), who used less concentrated alkali. Hot, dilute sodium hydroxide solution (200 c.c. of 2·5*N*) is added in one batch to a hot solution of brucine methosulphate (10 g.) in water (50 c.c.), and the mixture is heated on the water-bath for 5 minutes. On cooling, the yellow solution does not gelatinise (compare Leuchs and Anderson); sodium hydroxide (20 c.c. of 30%) is now added, and the mixture set aside. Next day, the needles, which fill the liquid, are collected, and are sufficiently pure for the purpose of the reduction described below. When purified by the addition of acetone to a concentrated aqueous solution, and dried at 100°, methylbrucine forms colourless needles, m. p. 300° (decomp.) when heated quickly. Leuchs and Anderson give the melting point as 300° (decomp.).

The reduction. A solution of methylbrucine (20 g.) in sulphuric acid (100 c.c. of 60%) is reduced in the usual apparatus for 6 hours with a current of 5 amps., while the temperature is kept at 18° by cooling in running water. The liquid is diluted with an equal volume of water, heated on the water-bath, and neutralised by an excess of barium carbonate. The deep red filtrate, mixed with the washings of the barium precipitate, is evaporated to dryness under reduced pressure on the water-bath. The dark red, glassy residue dissolves readily in water or methyl or ethyl alcohol, and shows very little tendency to crystallise. A small specimen, however, was obtained in a crystalline condition from methyl alcohol by cooling in ice. It was recrystallised once from that solvent in colourless nodules of needles, m. p. 265° (decomp.) after drying in a vacuum desiccator, and appears from analysis to be *brucidine methohydrogencarbonate* containing two molecules of water (Found: C, 60·3; H, 7·1. $C_{25}H_{32}O_6N_2,2H_2O$ requires C, 61·0; H, 7·3%). This view is confirmed by the conversion of this substance into brucidine methiodide and methohydroxide (see below), and also by its interaction with dilute hydrochloric acid. Carbon dioxide is evolved, and the substance dissolves to a green solution; the addition of ferric chloride intensifies this colour, and gives it the pink tinge in thin layers which is characteristic of brucidine and its derivatives.

When sodium iodide is added to an aqueous solution of the methohydrogencarbonate, brucidine methiodide is formed. It separates from water in colourless needles, m. p. 322° (decomp.), and is identical with a specimen prepared from brucidine (p. 1638).

Brucidine methohydroxide is obtained by grinding the crude methohydrogencarbonate with 30% potassium hydroxide solution. The resulting crystalline paste is filtered, and the solid recrystallised twice from water, in which it dissolves very readily. Brucidine methohydroxide forms colourless, hair-fine needles, m. p. 268° (decomp.), which retain two molecules of water after drying in a vacuum desiccator (Found: C, 64·1; H, 7·6. $C_{23}H_{28}O_3N_2,MeOH,2H_2O$ requires C, 64·3; H, 8·0%). The same substance was prepared for comparison from brucidine methiodide. An aqueous solution of the methiodide was shaken with an excess of silver carbonate, and the dark red filtrate evaporated to dryness under reduced pressure on the water-bath. The residual dark red glass (not purified) was dissolved in water, and mixed with 50% potassium hydroxide solution; brucidine methohydroxide then separated in crystalline form, and was recrystallised from a little water in colourless needles, m. p. 268° (decomp.).

The specimen obtained from the reduction of methylbrucine was converted into brucidine methiodide either (i) by adding sodium iodide to a solution in dilute hydrochloric acid, or (ii) when a solution of the methohydroxide (4 g.) and methyl iodide (10 c.c.) in ethyl alcohol (30 c.c.) was boiled for 10 minutes, and then cooled. In either case, the crystalline precipitate which separated was recrystallised from water, and formed colourless needles, m. p. 322° (decomp.) (Found: C, 55·1; H, 6·1. $C_{23}H_{28}O_3N_2,MeI$ requires C, 55·2; H, 5·9%). The identity of this substance with brucidine methiodide was confirmed by converting it into methoxymethyldihydrobrucidine (see below), which is formed by heating brucidine metho-salts with methyl-alcoholic potassium hydroxide. Brucidine methochloride (not purified), prepared by shaking with an excess of silver chloride an aqueous solution of the methiodide obtained above, and evaporating the filtrate to dryness under reduced pressure on the water-bath, was heated with a large excess of 25% methyl-alcoholic potassium hydroxide for 30 minutes, cooled, mixed with water, and the precipitate collected. Crystallisation from ethyl alcohol yielded colourless needles, m. p. 115° either alone or mixed with an authentic specimen of methoxymethyldihydrobrucidine.

Methoxymethyldihydrobrucidine.—A mixture of brucidine methosulphate (30 g.) and methyl-alcoholic potassium hydroxide (150 c.c. of 25%) is heated on the water-bath for 30 minutes in an open flask so that the methyl alcohol partly evaporates. The initial yellow solution gradually clouds and deposits a solid precipitate which increases on cooling in running water. Water (500 c.c.) is added, and the precipitate is collected after 1 hour, washed with water, and dried roughly on porous tile. The crude product is crystallised from ethyl alcohol, from which about 20 g. of pure material separate, and the addition of water to the mother-liquor yields a further quantity of practically pure substance (total yield, *ca.* 90%). *Methoxymethyldihydrobrucidine* forms colourless needles, m. p. 115° without decomp. after drying in a vacuum [Found: C, 70·2; H, 7·8; OMe, 21·9. $C_{25}H_{34}O_4N_2$ requires C, 70·4; H, 8·0; $(OMe)_3$, 21·8%]. It distils without decomposition at 265—267°/1·5 mm., and is rather readily soluble in the usual solvents except light petroleum. A solution in glacial acetic acid is not precipitated on addition of water. The base and its solutions become red on keeping, especially if exposed to laboratory fumes.

The dihydriodide. The addition of sodium iodide to a solution of methoxymethyldihydrobrucidine in dilute sulphuric acid produces a red, uncrystallisable oil, which rapidly oxidises, but when concentrated sodium iodide solution is added slowly with constant stirring to a solution of the base (5 g.) in 2*N*-sulphuric acid (20 c.c.), saturated with sulphur dioxide, an additive compound separates as a brick-red oil which soon crystallises on rubbing. This is collected (approximately 8 g.), and boiled with water until the orange colour of the solution and the smell of sulphur dioxide have disappeared; the dihydriodide then crystallises on cooling in colourless leaflets, m. p. 217—218° (decomp.) (loss at 100°, 3·5. $1\frac{1}{2}H_2O$ require loss, 3·8%. Found in material dried at 100°: C, 43·8; H, 5·3. $C_{25}H_{34}O_4N_2,2HI$ requires C, 44·0; H, 5·3%). The crystals become yellow on keeping, on exposure, or on drying, and when heated char and evolve hydrogen iodide.

The methiodide (*A*). This substance is obtained under the following conditions. (i) Methoxymethyldihydrobrucidine (10 g.) and pure methyl iodide (15 c.c.) are heated together at 100° in a sealed tube for 5 minutes. The solution becomes purple and fills with crystals, which are collected after cooling, washed with methyl iodide, and dried in a vacuum (12 g.). The mother-liquors deposit a further amount (1 g.) on standing over-night. The yield is about 98%. (ii) A mixture of methoxymethyldihydrobrucidine (15 g.) and methyl iodide (15 c.c.) is boiled under reflux for 15 minutes, and next day 13—15 g. of crude product are collected. The methiodide obtained by either method separates from methyl alcohol in creamy tablets which become chalky when dried in a vacuum; m. p. 190° (loss at 100°, 2·6. 0·5MeOH requires loss, 2·8%. Found in material dried at 100°: C, 55·1; H, 6·5; N, 4·9. $C_{25}H_{34}O_4N_2$,MeI requires C, 55·0; H, 6·5; N, 4·9%). It crystallises from water in stout prisms, m. p. 190°, or from ethyl alcohol in rectangular plates, m. p. 179°, which contain alcohol of crystallisation (loss at 100°, 3·6. 0·5EtOH requires loss, 3·9%. Found in dried material: C, 55·2; H, 6·7%). It yields the methochloride (A) when treated with silver chloride (see below).

The methyl-alcoholic mother-liquors gradually deposit a very small amount of crystalline material which does not contain iodine. This is recrystallised by dissolving it in much methyl alcohol and concentrating the solution; *oxymethoxymethyldihydrobrucidine* then separates in pink bipyramids, which shrink at 270° and melt at 277° (decomp.) (Found: C, 67·3; H, 7·6. $C_{25}H_{34}O_5N_2$ requires C, 67·9; H, 7·7%). The same substance may be obtained in greater quantity by a simpler method. When a solution of methoxymethyldihydrobrucidine in ethyl alcohol containing a few crystals of iodine is exposed to the air for some days, the solution becomes deep crimson, and gradually deposits oxymethoxymethyldihydrobrucidine as pale pink, perfectly formed prisms, which soften at 270°, melt at 277°, and are analytically pure (Found: C, 67·6; H, 7·8; N, 6·1. $C_{25}H_{34}O_5N_2$ requires N, 6·3%). It is very sparingly soluble in ethyl alcohol or acetone, but dissolves in warm benzene, and is readily soluble in chloroform. It is insoluble in boiling water or sodium hydroxide, but dissolves readily in dilute hydrochloric acid. When it is boiled with methyl alcohol (charcoal) and the filtered solution is concentrated, a slightly more soluble base separates in irregular, boat-shaped crystals, m. p. 270° (decomp.), which appear from the analysis to be *dioxymethoxymethyldihydrobrucidine* (X) (compare pp. 1647, 1648) (Found: C, 65·5; H, 7·4. $C_{25}H_{34}O_6N_2$ requires C, 65·5; H, 7·4%).

When methoxymethyldihydrobrucidine and methyl iodide interact in methyl-alcoholic solution the reaction follows a course very similar to that, described above, in the absence of methyl alcohol, and the chief product is the monomethiodide (A), accompanied by small quantities of oxymethoxymethyldihydrobrucidine (compare Part IV, this vol., p. 1607). In addition to these substances, an intermediate *base*, m. p. about 210—218°, appears to be formed. This does not contain iodine, and changes into oxymethoxymethyldihydrobrucidine in boiling methyl alcohol or acetone, in which solvents it is sparingly soluble. This substance was not obtained sufficiently pure for analysis, and the change evidently takes place so readily that the intermediate product did not appear in some experiments, but had been completely converted into oxymethoxymethyldihydrobrucidine. The following is an account of an experiment in which the intermediate base was formed. A mixture of methoxymethyldihydrobrucidine (5 g.) and methyl iodide (5 c.c.) in methyl alcohol (25 c.c.) was boiled under reflux for 3 hours, and then concentrated to half its volume. The residue was cooled for several hours in ice and salt, and the crystals which had separated were collected, washed with methyl alcohol, and dried (3 g.). The mother-liquors were examined separately (see below). The crude crystals were extracted with boiling methyl alcohol (20 c.c.), and the insoluble portion was collected, washed thoroughly with methyl alcohol, and dried (0·2 g.). It consisted of indefinite crystals, m. p. 210°, which did not contain iodine. The methyl-alcoholic extract contained practically pure methiodide (A).

The methyl-alcoholic mother-liquors (see above) were mixed with water, and the solid was collected and extracted with boiling methyl alcohol. The insoluble portion (0·1 g.) formed indefinite crystals, m. p. 218°, which did not contain iodine. Oxymethoxymethyldihydrobrucidine separated in the characteristic bipyramids, m. p. 277°, when a solution of the mixed fractions, m. p. 210° and 218°, in much boiling methyl alcohol was concentrated and cooled.

The Action of Methyl-alcoholic Potassium Hydroxide on the Methiodide (*A*) *and the Methochloride* (*A*).—The reaction follows the same course in both cases, but takes place more readily with the methochloride. This is prepared from the methiodide by heating an aqueous solution with excess of silver chloride for 1 hour, and evaporating the filtrate to dryness on the water-bath under reduced pressure. The gummy *methochloride* crystallises in colourless needles on standing for some days. The methochloride (7 g.) and methyl-alcoholic potassium hydroxide (60 c.c. of 25%) are heated in an open flask on the water-bath for 40 minutes, and after cooling and addition of water, the precipitate is collected and dried in a desiccator (5 g.). Recrystallisation of this crude material from ethyl alcohol yields colourless needles; m. p. 115°, either alone or mixed with a specimen of methoxymethyldihydrobrucidine (Found: C, 70·6; H, 7·8; OMe, 21·4%). A careful examination of the mother-liquors yields no other product.

Methoxymethyldihydrobrucidine methochloride (*B*) cannot be obtained directly from methoxymethyldihydrobrucidine, but it is formed when methoxymethyldihydrobrucidine dimethochloride (B) (compare p. 1647) (15 g.) is heated in boiling nitrobenzene (30 c.c.) until all has dissolved and the evolution of gas appears to have ceased—10 to 15 minutes. After standing over-night, the crystals which have separated are collected, washed with light petroleum, dried in a desiccator (10 g.), and crystallised from acetone, being thus obtained in colourless prisms, m. p. 164° (decomp.) (Found: C, 64·9; H, 7·4. $C_{25}H_{34}O_4N_2$,MeCl requires C, 65·5; H, 7·8%). This substance yields methyl-ψ-brucidine when heated gently in a test-tube over a free flame (compare p. 1651). The nitrobenzene mother-liquors contain both methyl-ψ-brucidine and methyl-ψ-brucidine methochloride; their examination is described on p. 1652.

The *methiodide* (*B*) is prepared from the methochloride with sodium iodide, but has not been obtained in any other way. It crystallises from water in colourless, coarse prisms, m. p. 291° (decomp.), and is less soluble in water and methyl or ethyl alcohol than the isomeric methiodide (A).

The *dimethiodide* (*A*) is obtained when methoxymethyldihydrobrucidine (5 g.) and pure methyl iodide (10 c.c.) are heated in a sealed tube in an oil bath at 135—140° for 7½ hours. After removal of the methyl iodide by distillation, the brown, sandy powder (8·5 g.) is crystallised from methyl alcohol (charcoal), from which the dimethiodide (4·5 g.) separates in pink leaflets which become colourless at 110°, form a pasty mass at 215°, and evolve gas freely at 230° (loss at 110°, 8·6. 2MeOH requires loss, 8·3%. Found in material dried at 110°: C, 45·3; H, 5·5. $C_{25}H_{34}O_4N_2$,2MeI requires C, 45·6; H, 5·6%).

The *methosulphate* (*A*) is formed when a solution of methoxymethyldihydrobrucidine (3 g.) and pure methyl sulphate (10 c.c.) in dry benzene (70 c.c.) is boiled under reflux for 4 hours and allowed to remain over-night. A mixture of stellar aggregates of coarse crystals and a purple gum separates, and the crystals of the monomethosulphate are easily detached and pressed on porous tile (1·7 g.). The gum consists essentially of the dimethosulphate (B) (see below). The methosulphate is crystallised from ethyl alcohol, in which it is rather readily soluble, and forms colourless, rectangular plates, m. p. 231—232° (decomp.) (Found: S, 6·0. $C_{25}H_{34}O_4N_2$,Me_2SO_4 requires S, 5·8%). This substance is very soluble in water and is converted by sodium iodide into the methiodide (A), m. p. 190°.

The Dimethosulphate (*B*) *and the Dimethiodide* (*B*).—A solution of carefully dried methoxymethyldihydrobrucidine (60 g.) and pure methyl sulphate (150 c.c.) in dry benzene (500 c.c.) is boiled for 9 hours under reflux, carefully protected from moisture. It rapidly becomes purple, and after some time a brown gum forms slowly and increases steadily with diminution of the purple colour. After the benzene has been decanted, the gum is washed with benzene, and freed from excess of the solvent by a current of air. It undoubtedly consists essentially of the *dimethosulphate* (*B*), although traces of benzene and methyl sulphate are still present, but all attempts to crystallise it are unsuccessful, and it is therefore converted into the corresponding dimethiodide by sodium iodide. Sodium iodide (100 g.) in warm water (40 c.c.) is added to the dimethosulphate in warm water (100 c.c.) and, after cooling, the mixture is scratched and set aside over-night. The crystalline precipitate is collected, washed with water, dried in a vacuum desiccator (84 g.), and recrystallised from water. The *dimethiodide* (*B*) forms colourless columns, m. p. 290° (decomp.), with darkening below this, and is sparingly soluble in alcohol (loss at 105°, 1·0. $\frac{1}{2}H_2O$ requires loss, 1·2%. Found in dried material : C, 45·0; H, 5·5. $C_{25}H_{34}O_4N_2,2MeI$ requires C, 45·6; H, 5·6%).

The mother-liquors from the precipitation with sodium iodide are mixed with 50% potassium hydroxide solution; the caseous precipitate then soon hardens. It is washed roughly with water, and boiled with alcohol, which causes it to crystallise without passing into solution. After cooling, the crystals are collected (13 g.), and recrystallised from water, being obtained in colourless columns, m. p. 290° (decomp.), identical with those obtained by direct precipitation from the solution of the dimethosulphate with sodium iodide (loss at 105°, 1·1%. Found in dried material: C, 45·5; H, 5·4%). The total yield is 97 g., or 96% of that theoretically possible.

The dimethiodide is stable to 25% methyl-alcoholic potassium hydroxide at 120°, but reaction takes place with the corresponding dimethohydrogensulphate obtained by means of silver sulphate. The dimethiodide (10 g.) in water (75 c.c.) is heated on the water-bath for 1 hour with excess of silver sulphate, the filtrate is evaporated to dryness under reduced pressure on the water-bath, the residue taken up in methyl alcohol to eliminate silver sulphate, and the solution again evaporated to dryness. The gummy dimethohydrogensulphate thus obtained (not isolated) is mixed with methyl-alcoholic potassium hydroxide (100 c.c. of 25%) and heated in an oil-bath for 45 minutes while the temperature is gradually raised from 110° to 130°. After cooling and addition of water, the roughly dried, sandy powder is crystallised from ethyl alcohol, and shown to be identical with methoxymethyldihydrobrucidine by mixed m. p., and by conversion into the methiodide (A), m. p. 190°.

The *dimethochloride* (*B*), prepared in the usual way from the dimethiodide by silver chloride, is a colourless glass which could not be crystallised.

Nitromethoxymethyldihydrobrucidine.—A solution of methoxymethyldihydrobrucidine (3 g.) in water (75 c.c.) and nitric acid (*d* 1·4; 7·5 c.c.) is heated under reflux on the water-bath for 2 hours. From the cooled mixture, ammonia (*d* 0·880) precipitates a negligible quantity of a base, which is discarded, and the addition of 50% potassium hydroxide solution yields a mixture of tar and crystals which is pressed on porous tile, crystallised twice from ethyl alcohol, and dried in a desiccator. *Nitromethoxymethyldihydrobrucidine* forms colourless needles, m. p. 276—278° (decomp.), which contain alcohol of crystallisation (loss at 110°, 9·6. 1EtOH requires loss, 9·8%. Found in material dried at 110°: C, 63·9; H, 7·0; N, 9·2. $C_{25}H_{33}O_6N_3$ requires C, 63·7; H, 7·1; N, 8·9%). It is rather curious that this substance exhibits the brucidine reaction with 60% sulphuric acid and potassium dichromate.

Permanganate Oxidation of Methoxymethyldihydrobrucidine. The Isomeric Dioxymethoxymethyldihydrobrucidines (*Y*) and (*Z*).

A number of experiments showed the necessity of adhering to the conditions described below. Powdered (80-mesh) potassium permanganate (20 g.; 4 atoms of oxygen) is added gradually to a solution of methoxymethyldihydrobrucidine (20 g.) in purified acetone (800 c.c.), stirred mechanically, and cooled in ice and salt so that the internal temperature remains at −10°. The manganese precipitate, collected and washed with acetone, yields with water a solution in which only oxalic acid can be detected.

The removal of the acetone by distillation yields 12—15 g. of thick, brown oil. When this is dissolved in warm alcohol (15 c.c.), cooled, and scratched, 2·5—2·8 g. of fairly pure crystalline material separate. (The examination of the mother-liquors, called M, is described on p. 1648.) Recrystallisation from ethyl alcohol yields colourless prisms, m. p. 185—186°, which appear from the analyses to be *dioxymethoxymethyldihydrobrucidine* (called Y; compare p. 1643) (loss at 100°, 4·4. $\frac{1}{2}$EtOH requires loss, 4·8%. Found in dried material: C, 65·3; H, 7·6; N, 6·3. $C_{25}H_{34}O_6N_2$ requires C, 65·5; H, 7·4; N, 6·1%). This substance is insoluble in water or alkali, but readily dissolves in dilute hydrochloric acid, giving a green solution;

on addition of ammonia, the base is precipitated and the colour changes to red. The compound is recovered unchanged after boiling for a few minutes with acetic anhydride, and attempts to form a semicarbazone resulted in a dark red, uncrystallisable oil.

The *methiodide* is prepared by heating the base (2 g.) and methyl iodide (3 c.c.) in a sealed tube at 100° for 5 hours. The residue is pressed on porous tile, and separates from ethyl alcohol as a mixture of plates and needles, m. p. 223°. On recrystallisation from ethyl alcohol, both forms separate again, but when the mixture is boiled with insufficient alcohol for complete solution, the needles dissolve more rapidly, and ultimately the undissolved portion consists of plates only. These are collected and recrystallised, by seeding, from ethyl alcohol, separating in colourless plates, m. p. 225—226°, which lose nothing at 110° (Found: C, 52·3; H, 6·4. $C_{25}H_{34}O_6N_2$,MeI requires C, 52·0; H, 6·2%). When the hot alcoholic solution from the separation of plates and needles is cooled and set aside, it begins to deposit needles only, and on scratching, the material separates entirely in that form; but if allowed to remain undisturbed, the mixture of crystals again separates. The needles are recrystallised in the same form, m. p. 223—224°, from ethyl alcohol, and contain 2 molecules of alcohol of crystallisation after drying in a vacuum desiccator (loss at 110°, 12·1. 2EtOH requires loss, 13·3%. Found in material dried at 110°: C, 52·2; H, 6·4%). Both forms are sparingly soluble in ethyl alcohol, and a hot solution of each in that solvent, when cooled and seeded with the other form, deposits only that by which it has been seeded. A mixture of the two pure forms melts at 223°.

The alcoholic mother-liquors (M; p. 1647) are evaporated to dryness, and a filtered, aqueous solution of the residue is made strongly alkaline with potassium hydroxide. The oil thus precipitated is extracted as far as possible with ether, and the extract dried with potassium carbonate. The oil which remains undissolved in the ether yields no crystalline product, and is discarded. The oily residue from the evaporation of the ether is dissolved in ethyl alcohol (5 c.c.), cooled in ice and salt, and scratched frequently; crystals (3·2 g.) then separate slowly. Three recrystallisations from ethyl alcohol yield colourless, square plates, m. p. 110—111° after drying in a vacuum desiccator, which appear from analysis to be a *dioxymethoxymethyldihydrobrucidine* (called Z) (loss at 100°, 4·0. ½EtOH requires loss, 4·8%. Found in material dried at 100°: C, 65·0, 65·1; H, 7·6, 7·5; N, 5·8. $C_{25}H_{34}O_6N_2$ requires C, 65·5; H, 7·4; N, 6·1%). This substance is sparingly soluble in cold water, dissolves readily on heating to give a neutral solution, and on cooling separates in colourless, rectangular prisms. It is readily soluble in the usual organic solvents except light petroleum, from which it crystallises when a hot solution is cooled, and gives the same colour reactions as methoxymethyldihydrobrucidine. It dissolves rapidly in cold dilute hydrochloric acid, but no iodide separates with sodium iodide. The compound is recovered unchanged after heating with excess of methyl iodide in a sealed tube at 100° for 4 hours, and an alcoholic solution does not form a sparingly soluble picrate.

Ethoxymethyldihydrobrucidine.—This substance was prepared in order to ascertain whether alkyloxy-groups other than methoxyl can be introduced into brucidine. The action between brucidine methosulphate and sodium ethoxide follows a similar course to that described on p. 1642 with methyl-alcoholic potassium hydroxide, but the isolation of the product was not successful, and further investigation was abandoned. Brucidine methosulphate (15 g.) and a solution of sodium (10 g.) in ethyl alcohol (150 c.c.) were heated in an open flask for 1 hour on the water-bath and then for 1 hour in an oil-bath at 120°. After cooling and addition of water, the sticky precipitate was pressed on porous tile. Attempts to crystallise the sandy powder (10 g.) thus obtained were fruitless, although it probably consisted of ethoxymethyldihydrobrucidine, and it was converted into the methiodide by boiling with excess of methyl iodide in ethyl alcohol (15 c.c.) for 20 minutes. On cooling, the purple solution set to a mass of crystals, which were washed with alcohol until they became colourless. *Ethoxymethyldihydrobrucidine methiodide*, recrystallised from ethyl alcohol, forms colourless needles, m. p. 176° (decomp.) (Found: C, 55·6; H, 7·1. $C_{26}H_{36}O_4N_2$,MeI requires C, 55·6; H, 6·9%).

*Methyl*neo*brucidinium Salts.*

*Methyl*neo*brucidinium Iodide.*—When a solution of methoxymethyldihydrobrucidine (25 g.) in sulphuric acid (250 c.c. of 10% by weight) is boiled gently under reflux for 2½ hours it becomes red, and methyl alcohol is evolved and can be burnt at the neck of the flask. The solution is cooled, rendered alkaline with ammonia (no precipitate), and just acidified with sulphur dioxide. The careful addition of concentrated sodium iodide precipitates a crystalline *iodide* (22 g.), which separates from water in stout, pink columns, m. p. 298° (decomp.) (Found: C, 55·3; H, 6·0. $C_{24}H_{31}O_3N_2I$ requires C, 55·2; H, 5·9%). When prepared in this way, the salt is always red; it may, however, be obtained practically colourless by crystallisation from aqueous potassium carbonate, or from ethyl alcohol, from which it separates in leaflets, m. p. 298° (decomp.). It is sparingly soluble in cold water, acetone, or methyl or ethyl alcohol, and crystallises unchanged when a boiling solution in 30% potassium hydroxide is cooled.

The mother-liquors from the precipitation by sodium iodide (see above) were investigated in the expectation of isolating an isomeric iodide (compare methyl*neo*strychnidinium iodide, this vol., p. 1612), but only a further quantity of the same methyl*neo*brucidinium iodide was obtained, the total yield being 90% of that theoretically possible. The mother-liquors are concentrated to quite a small volume under reduced pressure on the water-bath, and after cooling, the aqueous layer is decanted from the oil which has separated during the distillation. This oil crystallises on being boiled with a little acetone; part dissolves, crystallisation begins suddenly, and the oil soon changes into a mass of colourless needles. After cooling, these are collected, washed with acetone, and dried (5 g.); m. p. 295° (decomp.). One recrystallisation from water yields the iodide in colourless, prismatic columns, m. p. 298° (decomp.). The identity of this substance with the methyl*neo*brucidinium iodide obtained above was shown by seeding an aqueous solution with a crystal of the authentic material.

*Methyl*neo*brucidinium chloride* is prepared from the iodide in the usual way by silver chloride. When sulphur dioxide is passed into the dark red filtrate after this has been concentrated on the water-bath under reduced pressure, slightly sticky, yellow needles separate; these are triturated with hot acetone, which causes the compound to crystallise in beautiful prisms. Methyl*neo*brucidinium chloride crystallises from absolute alcohol, in which it is rather readily soluble, in colourless, anhydrous needles, m. p. 188°, which absorb moisture on keeping and then melt at about 163°. On addition of ether to an alcohol–acetone solution, the chloride forms pale yellow, waxy prisms, m. p. 163°, which retain a molecule of water of crystallisation after being heated at 100° (Found : C, 63·9; H, 7·5. $C_{24}H_{31}O_3N_2Cl,H_2O$ requires C, 64·2; H, 7·4%). It dissolves readily in water, and is precipitated unchanged as a rapidly-crystallising oil by 50% potassium hydroxide solution. The colour reactions with ferric chloride in hydrochloric acid are identical with those given by methoxymethyldihydrobrucidine, and are also produced by silver nitrate in dilute nitric acid, whilst the addition of a drop of potassium dichromate to a solution in 60% sulphuric acid develops a yellowish-brown colour which does not alter on standing. After the chloride has been heated with 25% methyl-alcoholic potassium hydroxide on the water-bath for 30 minutes in the usual way, the addition of water precipitates a base, which crystallises from ethyl alcohol in colourless needles, m. p. 115°; the base melts at the same temperature in admixture with methoxymethyldihydrobrucidine. The chloride yields methyl-ψ-brucidine when heated (see p. 1652). In order to test the possibility of reducing methyl*neo*brucidinium salts, the sulphuric acid solution obtained directly from methoxymethyldihydrobrucidine was reduced in the usual apparatus for 18 hours with a current of 4·5 amps. The contents of the colourless solution, which began to redden as soon as the current was switched off, were isolated as the iodide in the manner described above. This iodide formed colourless prisms, m. p. 298° (decomp.), which were identical with a very pure specimen of methyl*neo*brucidinium iodide (Found : C, 55·6; H, 6·0%). The fact that reduction had not taken place was confirmed by converting the corresponding chloride, m. p. 188°, into methyl-ψ-brucidine by heating.

Methyl-ψ-brucidine.—This substance is prepared either (i) from methoxymethyldihydrobrucidine dimethochloride (B) or (ii) from methyl*neo*brucidinium chloride.

(i) Methoxymethyldihydrobrucidine dimethochloride (B) (27 g.), free from inorganic material, is heated gently over a flame in test-tubes in batches of 3 g. until the evolution of methyl chloride and inflammable gas ceases. The clear, glassy residue is dissolved in benzene, the solution filtered from a little charred material, and the solvent distilled; the crystalline solid (16·5 g.), m. p. 194°, thus obtained is recrystallised from ethyl alcohol. Pure *methyl-ψ-brucidine* forms colourless tablets, m. p. 198—199° without decomposition [Found : C, 72·8; H, 7·7; N, 7·4; OMe, 15·7; *M*, in camphor, 430. $C_{24}H_{30}O_3N_2$ requires C, 73·1; H, 7·6; N, 7·1; $(OMe)_2$, 14·9%; *M*, 394]. It is, however, often green, melting at about 196°, but in this condition is sufficiently pure for most purposes. It is insoluble in water, readily soluble in benzene, acetone, and dilute acetic acid, and is stable to boiling 20% potassium hydroxide solution. A solution in dilute sulphuric acid instantly decolorises permanganate, forming the characteristic green solution with the pink tinge which is also produced by ferric chloride in dilute hydrochloric acid or ethyl alcohol. The base is recovered unchanged after being electrolysed in 25% sulphuric acid for 9 hours with a current of 4·5 amps. in the usual apparatus, or after being shaken in cold dilute acetic acid solution in an atmosphere of hydrogen in presence of reduced palladous chloride and gum arabic.

The *dihydriodide*, prepared by adding sodium iodide to a solution of the base in dilute hydrochloric acid, crystallises from water in leaflets, m. p. 259° (decomp.) (Found in material dried at 100° : C, 44·1; H, 4·9. $C_{24}H_{30}O_3N_2,2HI$ requires C, 44·3; H, 4·9%).

The *methiodide* is formed (*a*) directly from methyl-ψ-brucidine, or (*b*) from methoxymethyldihydrobrucidine dimethochloride (B).

(*a*) Powdered methyl-ψ-brucidine (1 g.) and methyl iodide (3 c.c.) react at once in the cold to form a jelly which rapidly crystallises. The methiodide, obtained thus in theoretical yield, separates from methyl alcohol in colourless plates, m. p. 297° (decomp.) (Found : C, 55·8 ; H, 6·1. $C_{24}H_{30}O_3N_2$,MeI requires C, 55·9 ; H, 6·1%). Occasionally it crystallises in needles, m. p. 297°, which change slowly into plates in presence of methyl alcohol.

(*b*) The nitrobenzene mother-liquors from the action of boiling nitrobenzene on methoxymethyldihydrobrucidine dimethochloride (B) (compare p. 1645) contain a small quantity of methyl-ψ-brucidine methochloride and also a little methyl-ψ-brucidine, and these are removed separately by extraction first with water and then with dilute hydrochloric acid. The methochloride was not isolated from the aqueous extract, but was converted by sodium iodide into the methiodide. The crystalline solid thus formed crystallised from ethyl alcohol in colourless needles, m. p. 297° (decomp.) (Found : C, 56·1 ; H, 6·2%).

The identity of these two specimens of the methiodide was shown by causing a solution of (*b*) in methyl alcohol to deposit plates on seeding with (*a*), and also by seeding an ethyl-alcoholic solution of (*a*) with (*b*), when the methiodide separated in needles.

The Formation of a By-product by the Action of Heat on Methoxymethyldihydrobrucidine Dimethochloride (*B*).—When the dimethochloride is contaminated by inorganic matter, *e.g.*, sodium chloride if the silver chloride used in its formation has been prepared from sodium chloride, the yield of methyl-ψ-brucidine is lowered, pyridine bases are formed during the heating, and a *by-product* is obtained. For example, the dimethochloride (30 g.), containing some sodium chloride, yielded a benzene extract containing pure methyl-ψ-brucidine (10 g.) together with a residue insoluble in benzene (4 g.). The investigation of this substance is at present in progress and the results already obtained show that we have encountered here an important degradation by fission of the brucine molecule.

Methyl-ψ-brucidine (ii). This base is also obtained by heating methyl*neo*brucidinium chloride in an oil-bath at 200—210° until effervescence ceases. The dark brown glass is dissolved in dilute acid, and the base is precipitated by potassium hydroxide and crystallised from ethyl alcohol. It forms tablets, melting, either alone or mixed with an authentic specimen of methyl-ψ-brucidine, at 198°.

Permanganate Oxidation of Methyl-ψ-brucidine.

Brucidone Semicarbazone.—Powdered potassium permanganate (6·8 g. : 5 atoms of oxygen) is added gradually to methyl-ψ-brucidine (5 g.) in ice-cold, mechanically-stirred acetone (500 c.c.) ; the colour of the permanganate disappears slowly, and oxidation seems to be complete at the end of the addition. The manganese precipitate is filtered off, but yields no solid product. Removal of the acetone leaves a pale yellow, gummy residue (4 g.), which has not been obtained crystalline, and which yields only oily products when heated with methyl-alcoholic potassium hydroxide, or when dissolved in concentrated sulphuric acid (compare strychnidone, this vol., p. 1615). It is therefore converted into the semicarbazone by boiling a solution of the gum, semicarbazide hydrochloride (3·4 g.), and potassium acetate (3·4 g.) in aqueous alcohol under reflux for 1½ hours. Water is added, the alcohol distilled off under reduced pressure, and the crystalline precipitate, which forms during the distillation, is recrystallised from ethyl alcohol, being obtained in colourless needles which shrink at 210° and evolve gas at 226°, without complete fusion (loss at 100°, 13·1. 1½EtOH requires loss, 12·8%. Found in dried material: C, 60·8; H, 7·0; N, 15·1. $C_{24}H_{31}O_5N_5$ requires C, 61·4; H, 6·6; N, 14·9%). This *semicarbazone* is very sparingly soluble in cold methyl or ethyl alcohol. From the analyses, it appears to be the monosemicarbazone of a ketone derived from methyl-ψ-brucidine by the loss of CH_2 and its replacement by O, and the further introduction of one oxygen atom.

The unsharp melting point suggested that this material might be a mixture, and fruitless efforts were made to obtain pure components by repeated crystallisation from methyl or ethyl alcohol. The melting point remained unaltered. Purification was also attempted by extracting the substance with boiling methyl alcohol in sufficient quantity to dissolve only half, filtering the hot solution from the residue *A*, allowing it to deposit a second fraction *B* on cooling, and obtaining a third fraction *C* when the mother-liquor had remained over-night. *A* was recrystallised, and the mother-liquor yielded a very small fraction, *D*, on standing over-night. These fractions all formed colourless needles, which were dried in a vacuum desiccator, and the analyses agreed well with the formula already suggested (see below). On the other hand, the specimens differ in melting point and contain different amounts of solvent of crystallisation. (*A*) shrinks at 200°, melts at 220—225° (decomp.), and is not changed by recrystallisation (loss at 100°, 2·3. ½MeOH requires loss, 3·3%. Found in material dried at 100°: C, 62·0; H, 6·5%). (*B*) shrinks at 245°, melts at 257° (decomp.), and is not changed by recrystallisation (loss at 100°, 11·4. 2MeOH requires loss, 12·0%. Found in dried material: C, 61·6; H, 6·6%). (*C*) shrinks at 200° and melts at 235° (decomp.); there was not enough for recrystallisation (loss at 100°, 7·5. 1MeOH requires loss, 6·4%. Found in dried material: C, 61·4; H, 6·7%). (*D*), only

0·0327 g., shrinks at 195° and melts at 245° (decomp.) (loss at 100°, 10·4%. Found in dried material: C, 59·7; H, 6·5%).

It is possible that brucidone is a mixture of isomerides or that the semicarbazone group introduces geometrical isomerism.

Methoxymethyltetrahydrobrucidine.—A solution of methoxymethyldihydrobrucidine (20 g.) in sulphuric acid (200 c.c. of 20%) is reduced in the usual apparatus for 16 hours with a current of 5 amps., the temperature being kept at 18° by cooling in water. The methoxymethyldihydrobrucidine may be used in the crude condition in which it is obtained when water is added to the product of the interaction of brucidine methosulphate and methyl-alcoholic potassium hydroxide. After the reduction, excess of ammonia (*d* 0·880) is added while the liquid is stirred and cooled in ice; the product is thus obtained as a finely divided solid, whereas precipitation without cooling yields a caseous mass which solidifies to a single hard lump. The precipitate is collected, washed, dried (18 g.), and crystallised from methyl alcohol, from which it separates in colourless needles (Found: C, 70·2; H, 8·3. $C_{25}H_{36}O_4N_2$ requires C, 70·0; H, 8·4%).

Methoxymethyltetrahydrobrucidine melts at 133—135° and distils without decomposition at 253°/2 mm. It is somewhat soluble in the usual solvents and crystallises in beautiful needles from light petroleum (b. p. 60—80°). It dissolves readily in dilute acetic or mineral acid, and does not redden on exposure nearly so quickly as methoxymethyldihydrobrucidine. Acetic anhydride seems to be without action; after the mixture has been boiled for a few minutes and water and excess of ammonia have been added, the base is recovered unchanged.

The *dihydriodide* is prepared by adding concentrated sodium iodide solution to a solution of the base in 2*N*-sulphuric acid. On scratching, the dihydriodide separates in practically quantitative yield; it crystallises from water in colourless needles, which melt at 212° to a yellow froth (Found: I, 37·3. $C_{25}H_{36}O_4N_2,2HI$ requires I, 37·1%). It is sparingly soluble in ethyl alcohol, and becomes yellow on keeping.

When a hot aqueous solution of the dihydriodide is treated with excess of silver chloride, and the filtrate is evaporated to dryness under reduced pressure on the water-bath, the *dihydrochloride* is obtained as a colourless glass, which crystallises when ether is added carefully to a solution in alcohol–acetone. It forms rectangular plates, which are very soluble in water and evolve gas at 150° without melting completely. The residue is probably methyl*neo*dihydrobrucidinium chloride, which is produced when the dihydrochloride is decomposed in boiling mesitylene (b. p. 165°) (see p. 1659).

The *methiodide* (*A*) is prepared by heating the base (4 g.) and methyl iodide (5 c.c.) under reflux on the water-bath for 20 minutes; a crystalline precipitate is soon formed. The methyl iodide is distilled away, and the residue separates from ethyl alcohol in colourless leaflets (Found: C, 54·9; H, 7·2. $C_{25}H_{36}O_4N_2$,MeI requires C, 54·7; H, 6·8%). The methiodide dissolves rather readily in water. It melts at 166—167°, losing methyl iodide quantitatively (loss in an oil-bath at 165—170°, 24·9. $C_{25}H_{36}O_4N_2$,MeI requires loss, 24·9%), and regenerating the base, m. p. 134°, which was identified by the mixed melting-point method.

The *methochloride* (*A*), prepared in the usual way from the methiodide and silver chloride, forms a glassy mass. When it was heated with an excess of methyl-alcoholic potassium hydroxide at 120° for 1 hour, and water was added, methoxymethyltetrahydrobrucidine was regenerated, and identified by the mixed melting-point method.

The *methiodide* (*B*) is obtained by heating either (i) the dimethiodide (A) (p. 1658) or (ii) the dimethiodide (B) (p. 1656).

(i) When methoxymethyltetrahydrobrucidine dimethiodide (A) is heated in an oil-bath at 230°, it melts and evolves methyl iodide quantitatively. The glassy residue crystallises from ethyl alcohol in flattened needles or leaflets, m. p. 298° (decomp.) (Found: C, 54·9; H, 6·7. $C_{25}H_{36}O_4N_2$,MeI requires C, 54·7; H, 6·8%). This substance is sparingly soluble in ethyl alcohol and in water and crystallises from the latter in characteristic prisms, m. p. 298° (decomp.), which become chalky when dried in a vacuum desiccator.

(ii) Methoxymethyltetrahydrobrucidine dimethiodide (B) (1 g.) is heated gently in a test-tube over a flame until the evolution of methyl iodide ceases. If the heating becomes too vigorous, deep-seated decomposition takes place, and gases are evolved which burn with a luminous flame, partly condense on the cold part of the tube, and smell strongly of pyridine bases. The residue is crystallised from ethyl alcohol, and this purification is repeated if necessary until leaflets, m. p. 298° (decomp.), are obtained. This *methiodide* (*B*) separates from water in colourless, characteristic prisms, m. p. 298° (decomp.) (Found: C, 55·1; H, 6·9; I, 22·4. $C_{25}H_{36}O_4N_2$,MeI requires I, 22·3%). The identity of the specimens of the methiodide (B) obtained from the dimethiodides (A) and (B) was shown by seeding an aqueous solution prepared in one way with a crystal prepared in the other way.

The *methochloride* (*B*), prepared in the usual way from the methiodide and silver chloride, forms a colourless glass. When this is heated in a test-tube over a flame, it decomposes before methyl chloride is split off, and no methyldihydrobrucidine can be isolated from the charred residue. When exposed to water vapour in a bell-jar, the glassy methochloride crystallises in sticky needles, which after being pressed on porous tile and dried in a vacuum desiccator, decompose without melting at about 210.°

Methoxymethyltetrahydrobrucidine Dimetho-salts.

The Dimethosulphates (*A*) *and* (*B*).—Methoxymethyltetrahydrobrucidine reacts with methyl sulphate even more slowly than does methoxymethyldihydrobrucidine. In this case no monomethosulphate has been isolated. A solution of dried methoxymethyltetrahydrobrucidine (46 g.) and pure methyl sulphate (100 c.c.) in dry benzene (300 c.c.) is boiled on the water-bath under reflux for 24 hours, carefully protected from moisture. The hot benzene is decanted, but the residual mixture of brown gum and needles (90 g.) still retains some methyl sulphate and a little solvent, even after being washed as thoroughly as possible with benzene, which is then blown away in a current of air. This mixture must contain two dimethosulphates, (A) and (B), since it is converted into two dimethiodides, but attempts to isolate the dimethosulphates have been fruitless, and the mixture is therefore converted into the dimethiodides (A) and (B) by sodium iodide.

The *dimethiodide* (*B*) is prepared by adding sodium iodide (100 g.) in warm water (40 c.c.) to a warm solution of the above mixture of dimethosulphates in water (60 c.c.). On cooling and scratching, crystallisation begins, and after 24 hours the solid is collected, washed with water, and dried in a vacuum (31 g.). (The mother-liquors contain the dimethiodide A together with a small quantity of the dimethiodide B, and their investigation is described on p. 1658.) One recrystallisation from water (filter : see below) is usually sufficient for the purification of this product, although on a few occasions it had an unpleasant smell, which was first removed by grinding with cold ethyl alcohol. The dimethiodide (B) crystallises from water in prismatic needles, m. p. 287° (decomp.) (Found : C, 45·3, 45·4; H, 5·5, 5·7. $C_{25}H_{36}O_4N_2$,2MeI requires C, 45·5; H, 5·9%). It is sparingly soluble in cold water or methyl or ethyl alcohol, but dissolves readily in hot water. When an aqueous solution is saturated with sulphur dioxide, a yellow oil is formed which crystallises on standing. This additive product, which contains sulphur dioxide, is very sparingly soluble in cold water, but readily forms an orange solution on warming, which evolves sulphur dioxide when boiled and then becomes colourless. When the colourless solution is cooled, the dimethiodide separates in a pure condition. The dimethiodide is very stable to alkali, and was recovered in good yield after being heated with a large excess of 25% methyl-alcoholic potassium hydroxide at 140° for 30 minutes.

The crude precipitate of the dimethiodide is usually mixed with a small quantity of an ochreous, amorphous substance, which remains undissolved on recrystallisation of the precipitate from water. The amount of this by-product increases to about one-tenth of the weight of the dimethiodide if the solutions of the dimethosulphates and sodium iodide are boiling when mixed. The insoluble solid from the recrystallisation of the dimethiodide (see above) is crystallised fom methyl alcohol, in which it is very sparingly soluble, by dissolving it in much boiling solvent (charcoal), concentrating the solution until crystallisation begins, and allowing it to cool. The substance thus obtained in purple-red, glistening prisms melts at 230° (decomp.) and is a *periodide* of the dimethiodide (B) (Found: I, 55·6. $C_{25}H_{36}O_4N_2,2MeI,I_2$ requires I, 52·6%). This periodide is slowly decomposed by boiling water; it is stable to cold dilute nitric acid, but is instantly decomposed on boiling, iodine being liberated. When sulphur dioxide is passed into an aqueous suspension, the crystals change into a red gum, which is collected, and boiled with water until the solution becomes colourless and the smell of sulphur dioxide is no longer perceptible; on cooling, the dimethiodide (B) separates in colourless prisms, m. p. 287°.

The *dimethochloride* (*B*) is prepared by heating an aqueous solution of the dimethiodide (B) with excess of silver iodide, and evaporatating the filtrate to dryness on the water-bath under reduced pressure. The colourless, crystalline mass thus obtained separates from ethyl alcohol in plates which melt to a froth and lose solvent at 138°, after drying in a vacuum desiccator. On further heating, the froth hardens and melts at 214°. After drying at 100°, the dimethochloride has m. p. 214° (decomp.) (loss at 100°, 8·5. 1EtOH requires loss, 8·0%. Found in dried material: Cl, 13·7. $C_{25}H_{36}O_4N_2,2MeCl$ requires Cl, 13·4%).

The dimethochloride loses a molecule of methyl chloride when it melts at 214°, forming methoxymethyltetrahydrobrucidine methochloride (B). After heating at 245° in an oil-bath until the evolution of methyl chloride ceased, the residual glass, consisting of the methochloride (B), was converted into the methiodide by adding sodium iodide to an aqueous solution, and crystallising the precipitate from water. The methiodide (B) separated in the characteristic prisms, m. p. 298° (decomp.), which became chalky on drying (Found: C, 54·5; H, 6·8%).

When the dimethochloride was heated in a test-tube at 300°, further decomposition took place. No methyl-ψ-dihydrobrucidine could be isolated from the residue, which consisted only of charred material if the heating was sufficiently prolonged to allow complete elimination of the methyl chloride.

The *dimethiodide* (*A*) is obtained either (i) from the mother-liquors of the preparation of the dimethiodide (B), or (ii) by the direct combination of the base and methyl iodide.

(i) The mother-liquors from the preparation of the dimethiodide (B) (p. 1656) are mixed with 50% potassium hydroxide solution; a caseous mass then separates, and soon hardens sufficiently to be pressed between porous tiles in order to remove as much alkali as possible. On boiling with a little ethyl alcohol, it becomes colourless and completely crystalline, without passing into solution to any great extent. The crystals are collected after several hours, washed with alcohol, and dried in a vacuum desiccator (33 g.). This product is essentially the dimethiodide (A), but contains also a little of the dimethiodide (B). In the first experiment, these were separated by fractional crystallisation from methyl alcohol, but later, when the properties of the dimethiodide (A) became known, the following process was found to be much more satisfactory. The mixture is dissolved in a little boiling water, and the solution is cooled, seeded with the dimethiodide (B), and set aside over-night. The remainder of the dimethiodide (B) separates in a practically pure state, and is collected, washed, and dried (5 g.). The filtrate now contains the dimethiodide (A), which is very soluble in water. It is saturated with sulphur dioxide while stirred continuously, and the yellow, crystalline additive compound which is formed is collected, washed with a little sulphurous acid, and dissolved in boiling methyl alcohol. After boiling for about 15 minutes, the solution becomes colourless, and is then concentrated to about 100 c.c. On cooling, the *dimethiodide* (*A*) crystallises in an almost pure condition, m. p. 230° (25 g.). (The yield of the combined dimethiodides A and B is about 81% of that theoretically possible.) One recrystallisation from methyl alcohol gives the pure product in stout prisms, which melt at 230—232° to a colourless froth (see below) (Found: C, 45·1; H, 5·8. $C_{25}H_{36}O_4N_2$,2MeI requires C, 45·5; H, 5·9%). It dissolves readily in cold water, but only very sparingly in methyl or ethyl alcohol. When it is heated at its melting point, a molecule of methyl iodide is liberated smoothly; the glassy residue crystallises from water in the characteristic prisms of the methiodide (B) (see p. 1655).

(ii) A preliminary experiment showed that methoxymethyltetrahydrobrucidine combines with only one molecule of methyl iodide at 100°, even when heated for long periods. When, however, the base (5 g.) and methyl iodide (10 c.c.) are heated in a sealed tube at 140° for 24 hours, and the methyl iodide is distilled off, the residual solid is the *dimethiodide* (*A*). After two recrystallisations from methyl alcohol, it forms stout prisms, m. p. 230°, which are identical in every way with the substance described above (Found : C, 45·6; H, 6·0; I, 35·4. $C_{25}H_{36}O_4N_2,2MeI$ requires I, 35·7%).

The *dimethochloride* (*A*), prepared from the dimethiodide in the usual way by silver chloride, forms a colourless glass which cannot be crystallised. When it is heated gently in a test-tube over a flame, methyl chloride is evolved smoothly; the colourless residue, crystallised from methyl alcohol, forms needles, melting, either alone or when mixed with a specimen of methoxymethyltetrahydrobrucidine, at 133°.

*Methyl*neo*dihydrobrucidinium Salts.*

Methoxymethyltetrahydrobrucidine is not attacked by boiling 10% sulphuric acid under the conditions in which methoxymethyldihydrobrucidine yields methyl*neo*brucidinium sulphate. After the acid solution had been boiled for 2½ hours, ammonia precipitated 98% of the base used. Nor were successful results obtained when methoxymethyltetrahydrobrucidine dihydriodide or dihydrochloride was heated in a test-tube, since a much wider decomposition evidently took place. Ultimately, however, it was found possible to obtain the iodide in the following way.

The iodide. A suspension of methoxymethyltetrahydrobrucidine dihydrochloride (5 g.) in mesitylene (40 c.c.) is heated in an oil-bath at 180°. The solid becomes gummy and evolves hydrogen chloride, which is blown away from time to time in a current of air. After 20 minutes, the light brown gum hardens and is broken up, and the heating is continued for 10 minutes more in order to ensure complete decomposition. Ether is added to the cooled product, and the glassy solid is collected and dried at 100° (3·9 g.). Attempts to crystallise this chloride were unsuccessful (compare below), and it was therefore converted into the iodide. A solution of the chloride in water (25 c.c.) is saturated with sulphur dioxide, and concentrated sodium iodide is added drop by drop until no more oil separates. This additive product solidifies after a short time, and the orange mass thus obtained is boiled with water until the smell of sulphur dioxide has disappeared. On cooling, *methyl*neo*dihydrobrucidinium iodide* (3 g.) separates; it crystallises from water in colourless bipyramids, m. p. 283° (decomp.) (Found : C, 54·9; H, 6·4. $C_{24}H_{33}O_3N_2I$ requires C, 55·0; H, 6·3%). It is rather sparingly soluble in cold water or ethyl alcohol and crystallises in plates from the latter. An aqueous solution is not precipitated by ammonia or dilute alkali solution; concentrated potassium hydroxide solution precipitates the iodide unchanged.

The *chloride*, prepared by heating an aqueous solution of the iodide with silver chloride and evaporating the filtrate under reduced pressure on the water-bath, is a colourless glass which does not crystallise. An aqueous solution is not precipitated by ammonia or dilute alkali solution. On heating in a test-tube over a flame, charring occurs very readily; the residue dissolves in water to a red solution, which becomes deep red on addition of ammonia, and then bright green on addition of a few drops of potassium hydroxide; much concentrated potassium hydroxide solution precipitates a green oil, which has not been examined. No methyl-ψ-dihydrobrucidine is formed.

Methoxymethyltetrahydrobrucidine Dimethohydrogencarbonates (A) and (B) and their Decomposition by Heat. Methyl-ψ-dihydrobrucidine.

The Dimethohydrogencarbonate (*A*).—This substance is prepared by shaking a hot aqueous solution of methoxymethyltetrahydrobrucidine dimethiodide (A) with an excess of either silver hydroxide or silver carbonate. In either case, the alkaline filtrate is evaporated as far as possible in an open basin on the water-bath, and then left in a vacuum desiccator over-night. The gummy residue crystallises on being rubbed with acetone containing a little ethyl alcohol, and is recrystallised by the cautious addition of ether to an ethyl-alcoholic solution. The *dimethohydrogencarbonate* (*A*) forms almost colourless, hygroscopic crystals, m. p. 92—94°, or 103—104° when heated in a sealed capillary tube (Found in material dried in a vacuum desiccator: C, 52·5; H, 8·3. $C_{25}H_{36}O_4N_2,2MeHCO_3,5H_2O$ requires C, 51·9; H, 8·1%). It is very soluble in water or ethyl alcohol, and evolves carbon dioxide on treatment with dilute hydrochloric acid. When a small quantity is heated gently in a test-tube over a flame, carbon dioxide is eliminated; the light brown, glassy residue crystallises from methyl alcohol in colourless needles, which, either alone or when mixed with methoxymethyltetrahydrobrucidine, melt at 134°.

The *dimethohydrogencarbonate* (*B*) is prepared from the dimethiodide (B) exactly in the manner described above in the case of the isomeride (A). It is crystallised by the careful addition of ether to a filtered solution in ethyl alcohol, and forms colourless prisms, which are hygroscopic and melt at 109° after drying in a vacuum desiccator (Found: C, 50·3; H, 8·3. $C_{25}H_{36}O_4N_2,2MeHCO_3,6H_2O$ requires C, 50·6; H, 8·1%). It is very soluble in water or ethyl alcohol, and evolves carbon dioxide on treatment with acids.

When it is heated at 135° in an oil-bath, carbon dioxide is evolved. The heating is continued for 30 minutes until the frothing has ceased, and the clear, glassy residue is dissolved in water. As the solution gives no precipitate with ammonia and evolves carbon dioxide on treatment with acids, it must contain a methohydrogencarbonate. Sodium iodide is therefore added; the precipitate formed crystallises from water in colourless prisms, m. p. 298°, and is identical with methoxymethyltetrahydrobrucidine methiodide (B). The product of the decomposition is therefore the *methohydrogencarbonate* (*B*).

Methyl-ψ-dihydrobrucidine. The dimethohydrogencarbonate (B) (1 g.) is heated gently in a test-tube over a flame. It melts to a froth while gradually losing carbon dioxide, and the methyl alcohol which is evolved may be burnt at the mouth of the tube; when the effervescence has ceased, the light brown residue is quite mobile. After cooling, the tubes are broken and the contents extracted with boiling ethyl alcohol. The filtrate is concentrated to small volume; *methyl-ψ-dihydrobrucidine*, which then separates in moderate yield, recrystallises from ethyl alcohol in colourless tablets, m. p. 220—221° [Found: C, 72·5; H, 8·2; OMe, 15·8. $C_{24}H_{32}O_3N_2$ requires C, 72·7; H, 8·1; $(OMe)_2$, 15·6%]. This substance is soluble in dilute hydrochloric or acetic acid; it is sparingly soluble in ethyl alcohol, moderately easily soluble in acetone, and dissolves readily in benzene. It is extremely stable to oxidation by permanganate in acetone.

The *dihydriodide*, prepared by the addition of sodium iodide to a solution of the base in dilute hydrochloric acid, crystallises from water in small, wart-like granules, which melt at 215—217° to a yellow froth (Found in material dried at 100°: C, 44·0; H, 5·2. $C_{24}H_{32}O_3N_2,2HI$ requires C, 44·2; H, 5·2%). It separates from ethyl alcohol in stout prisms, and is sparingly soluble in this solvent and in water.

Colour Reactions of the Brucidine Derivatives.

The most useful reaction is that with ferric chloride in dilute hydrochloric acid, and a positive result is a deep green or bluish-green coloration, pink in thin layers, becoming red on boiling; when the reaction is negative, no colour is produced even on heating. The following substances give the reaction: brucidine, brucidine methosulphate, tetrahydrobrucine and its methochloride, methoxymethyldihydrobrucidine and its methochloride (B), methoxymethyltetrahydrobrucidine and its methochloride (B), methyl-ψ-brucidine and its methochloride prepared by either method, methyl*neo*brucidinium chloride, methyl-ψ-dihydrobrucidine, and methyl*neo*dihydrobrucidinium chloride. The substances which do not give the reaction are: methoxymethyldihydrobrucidine methosulphate (A) and methochloride (A), methoxymethyltetrahydrobrucidine methochloride (A), methoxymethyldihydrobrucidine dimethochlorides (A) and (B), methoxymethyltetrahydrobrucidine dimethochlorides (A) and (B), dioxymethoxymethyldihydrobrucidine (Y) methochloride, and, as already mentioned, brucine itself.* Since both strychnidine and brucidine give characteristic but entirely different ferric chloride reactions, the latter must be concerned with the only part of the molecule which is not identical in the two substances, namely, the aromatic nucleus, and this view is confirmed in the case of strychnidine by the observation that those derivatives which give a negative or feeble ferric chloride reaction are the only strychnidine derivatives which do not couple with diazonium salts. It then becomes apparent that the occurrence of the reaction in a particular case is dependent on the condition of the nitrogen atom bound to the aromatic nucleus. When this is salt-forming, the reaction is positive, whilst a negative reaction is due to its inclusion in the group –N–CO– as in brucine, or in a quaternary ammonium salt grouping as in the various dimethochlorides (and dihydrochlorides) described in this and the preceding communications. These views are in complete harmony with experience of simpler aromatic amine derivatives; thus dimethylaniline couples with diazonium salts, whereas *N*-methylacetanilide and phenyltrimethylammonium chloride do not. It is on this basis that we have allocated formulæ to the methochlorides (A) and (B) of methoxymethyldihydrobrucidine and methoxymethyltetrahydrobrucidine respectively (see pp. 1630 and 1633) and have drawn the important inference that the conversion of brucidine into methoxymethyldihydrobrucidine is accompanied by a transposition of the function of the nitrogen atoms in respect of their basic character.

The dichromate test in 60% sulphuric acid is of inferior diagnostic value. It is given by all the brucidine derivatives, but the green colour appears much more slowly in the cases where the ferric chloride reaction is negative.

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* The brucidine derivatives do not exhibit the reaction in concentrated hydrochloric acid solution. In the cases when the reaction is positive, however, the colour appears on dilution, and this behaviour is clearly due to the formation and hydrolysis of dihydrochlorides.