400. *Strychnine and Brucine. Part XXXV. Hofmann Degradation of Dihydrobrucidine.*

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IN the introduction to Part XVII (Achmatowicz, Perkin, and Robinson, J., 1932, 775) it was remarked that, although methyl-ψ-dihydrostrychnidine (Clemo, Perkin, and Robinson, J., 1927, 1589) is identical with dihydrostrychnidine-A (Oxford, Perkin, and Robinson, J., 1927, 2389), and methyl-ψ-brucidine is really *neo*brucidine, yet methyl-ψ-dihydrobrucidine is not identical with dihydrobrucidine (Part V; Gulland, Perkin, and Robinson, J., 1927, 1627).

Further examination of the Hofmann degradation of dihydrobrucidine along the lines of Part XXVI (Achmatowicz and Robinson, J., 1934, 581—Hofmann degradation of dihydrostrychnidine-A) has shown that methyl-ψ-dihydrobrucidine is a true methyl-*des*-base of dihydrobrucidine, and nomenclature on this basis is now preferred in view of the deletion of the expressions methyl-ψ-strychnidine and methyl-ψ-brucidine from the literature.

The most favourable yields of decomposition products were obtained on heating *dimethyldihydrobrucidinium dicarbonate*, and these consisted of (a) dihydrobrucidine, (b) a substance, $C_{24}H_{34}O_4N_2$, m. p. 169°, recognised as *hydroxymethyltetrahydrobrucidine*, (c) a *des*-base, $C_{24}H_{32}O_3N_2$, m. p. 221°, identical with methyl-ψ-dihydrobrucidine and now termed N(b)-*methyl*-des-*dihydrobrucidine-a*, and (d) a *des*-base, $C_{24}H_{32}O_3N_2$, m. p. 133°, termed N(b)-*methyl*-des-*dihydrobrucidine-b*. This base was isolated in the form of a methiodide and later obtained by decomposition of the methochloride. However, it was shown that the cycle of processes could be repeated.

Hydroxymethyltetrahydrobrucidine, m. p. 169°, furnishes an O-*acetyl* derivative which, on thermal decomposition, affords methyl acetate and dihydrobrucidine. On treatment with methyl sulphate and aqueous potassium hydroxide the base, m. p. 169°, yields a methosulphate, and the related methiodide decomposes on heating with formation of methyl iodide and methoxymethyltetrahydrobrucidine (Part V, *loc. cit.*). Furthermore, methyldihydrobrucidinium hydrogen sulphate is obtained on boiling a solution of the base, m. p. 169°, in 25% sulphuric acid. These facts establish the nature of this product, which corresponds to hydroxymethyltetrahydrostrychnidine (Part XXVI, *loc. cit.*).

N(*b*)-Methyl-*des*-dihydrobrucidine-a, m. p. 221°, undergoes similar transformations to those characteristic of the *des*-base-D * from dihydrostrychnidine-A, and it is unquestionably analogous in constitution. Its formation in moderate yield from *N*(*b*)-methyldihydrobrucidinium salts on heating with methyl-alcoholic sodium methoxide proves that the elimination concerns N(b).

The base contains ⁝NMe, but ⁝CMe groups are absent; it is unchanged on attempted electrolytic reduction or on attempted catalytic reduction in neutral solutions (benzene). Catalytic reduction (palladised charcoal) in acid solution affords, however, two isomeric quaternary salts and, after conversion into the iodides, neither salt was identical with methyldihydrobrucidinium iodide.

The analogy with the behaviour of the *des*-base-D from dihydrostrychnidine-A is evident, although the latter substance afforded only one quaternary salt on attempted catalytic reduction.†

As in the case of the *des*-base-D, the process is accompanied by the absorption of almost a molecular proportion of hydrogen, but this does not appear in the composition of the products. The best proof of the correctness of our views on this aspect of the reaction is the reconversion of the quaternary salt (only one of them in the brucine series) into the *des*-base that constituted the starting point.

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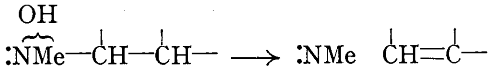
* The capital letters (A, B, C, D, E) used to distinguish isomeric series among the dihydrostrychnidines are not transferred to the dihydrobrucidine series, because they are used to denote isolated isomeric dihydrostrychnidines and the isomeric dihydrobrucidines have not yet been isolated. It is thought that the use of the same distinguishing letters in the dihydrostrychnidine and dihydrobrucidine series might imply relationships not fully proved to exist.

† A search for an isomeride will be made.

Attention has already been drawn in Part XXVI to the unique nature of this reversed Hofmann or Emde reaction under the influence of a catalyst, and the present example gives further support to the hypothesis advanced in Part XXVI.

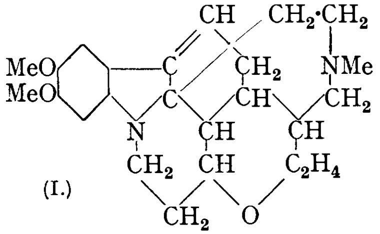
If the Hofmann scission had been of the form



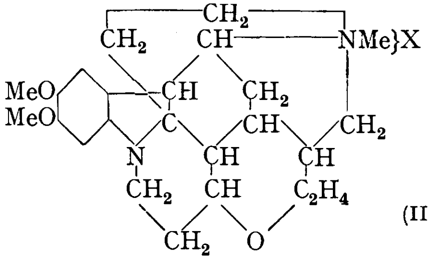
$$\overset{OH}{:\!NMe}\!-\!\overset{|}{C}H\!-\!\overset{|}{C}H\!- \longrightarrow :\!NMe\ \ \overset{|}{C}H\!=\!\overset{|}{C}\!-$$

the reconstitution of the quaternary ammonium system should have reproduced the starting point, in the form of one of the isomerides, and this was not the case. On the other hand, the groups :NMe and :C:C: in some other position can clearly give rise to structurally isomeric quaternary salts. The point will be clarified by reference to actual formulæ.

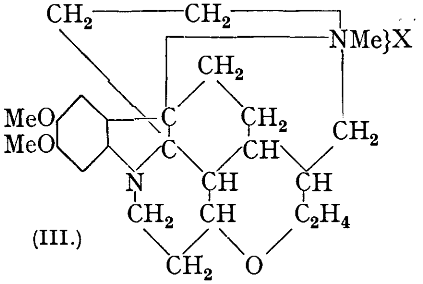
In accordance with our views of the constitution of strychnine and brucine these bases and their derivatives are substituted γ-phenylpropylamines and Hofmann elimination would be expected to give rise to substituted *iso*propenylbenzenes. Thus *N*(*b*)-methyl-*des*-dihydrobrucidine-a may well be (I), in which case the quaternary salts obtained from it by the agency of a hydrogenating catalyst will be represented by (II) and (III).



(I.)



(II.)



(III.)

These substances are designated *N*(*b*)-methyldihydrobrucidinium-c (or -d) salts and they differ markedly in their relative ease of reconversion into the *des*-base (I). From the known behaviour of the α- and β-phenylethylamine derivatives it may be argued that the methyldihydrobrucidinium-d salts have the formula (II) and methyldihydrobrucidinium-c salts correspond to the expression (III). Attempts to decompose these salts with formation of isomeric dihydrobrucidines-c and -d were unsuccessful.

It will now be clear that the formation of methyl-ψ-dihydrobrucidine from methoxymethyltetrahydrobrucidine dimethocarbonate (Part V, *loc. cit.*) involves a stage of ring closure to a methyl (or dimethyl) dihydrobrucidinium carbonate, followed by ring fission in a different direction. Highly interesting observations were made in examining the action of methyl iodide on methyl-*des*-dihydrobrucidine-a. Two isomeric dimethiodides were obtained, namely, the normal *dimethiodide*, m. p. 286°, formed as the result of gentle action, and the allo-*dimethiodide*, m. p. 246°, formed when the base is boiled with methyl iodide or with methyl sulphate in benzene solution for relatively longer periods.

The normal dimethiodide yields a *dimethochloride* which is decomposed by methyl-alcoholic sodium methoxide with formation of methyl-*des*-dihydrobrucidine-a, m. p. 221° (loss of 2Me attached to nitrogen).

The *allo*-dimethiodide is a structural isomeride, because the related *dimethochloride*, treated with methyl-alcoholic sodium methoxide, furnishes a new des-*base*, $C_{25}H_{34}O_3N_2$, m. p. 154—155°. This base contains ·N(b)Me$_2$ and thus a second stage in the Hofmann degradation has been accomplished. It seems that the dimetho-salts of (I) must undergo a rearrangement of the ring system or ethylene linking or both, and with formation of the *allo*-isomeride, but speculation as to the nature of the change is useless at this stage. Similar results have been obtained on submitting the *des*-base-D from dihydrostrychnidine-A to the prolonged action of methyl sulphate in boiling benzene solution. The resulting dimethosulphate affords a new des-*base*, $C_{23}H_{30}ON_2$, m. p. 157—159°, on treatment with methyl-alcoholic sodium methoxide. The description of this substance and of the behaviour of the *des*-bases towards oxidising agents and further Hofmann degradations is reserved for future communication.

The second *des*-base, m. p. 133°, namely *N*(*b*)-methyl-*des*-dihydrobrucidine-b, does not appear to contain the group ⁝CMe and so it is improbably the brucine analogue of *N*(*b*)-methyl*chano*dihydro*neo*strychnidine. The most acceptable view in this case is that the *des*-base is the outcome of a normal Hofmann elimination unaccompanied by migration phenomena. The position of the ethylene linkage remains an open question and oxidation experiments are in progress.

EXPERIMENTAL.

Derivatives of Dihydrobrucidine.—Dihydrobrucidine was prepared in quantity by hydrogenation of brucidine in the presence of palladised charcoal (cf. J., 1930, 1771). When brucidine was reduced at 65—70° in portions larger than 3—5 g., the volume of hydrogen absorbed was invariably greater than that required for saturation of one ethylene linkage and the yield of dihydrobrucidine was considerably diminished (from 86% to 40—45%). This must be attributed to the hydrogenation of the aromatic nucleus (compare Leuchs, *Ber.*, 1935, **68**, 91) and we have isolated some by-products which seem to be perhydro-bases and are under examination.

N(b)-*Methyldihydrobrucidinium carbonate* was prepared by heating an aqueous suspension of *N*(*b*)-methyldihydrobrucidinium iodide (20 g.) on the steam-bath with a 20% excess of pure, freshly precipitated silver carbonate for 2 hours. After concentration of the reddish-brown filtrate from the silver salts under diminished pressure, the quaternary carbonate remained as an amorphous, deep red, hygroscopic solid; it was freely soluble in water or methyl alcohol and exhibited no tendency to crystallise (Found in material dried at 110° in a vacuum: C, 68·5; H, 8·0. $C_{48}H_{66}O_6N_4,CO_3$ requires C, 68·9; H, 7·7%). On treatment with hydriodic acid carbon dioxide was evolved and *N*(*b*)-methyldihydrobrucidinium iodide, m. p. 298°, obtained.

N(a)N(b)-*Dimethyldihydrobrucidinium dicarbonate* was similarly prepared from the corresponding di-iodide and silver carbonate. The salt is crystallisable with difficulty and it was used for the experiments described below after being dried at 105—110° in a vacuum. When a concentrated aqueous solution of this dicarbonate is kept for several weeks in an open vessel, a pasty mass of minute greenish needles is gradually formed; this polyhydrate, m. p. 75—80°, loses a part of the water of crystallisation over sulphuric acid, affording a hygroscopic hydrate, m. p. 190—192° (decomp.), containing $16H_2O$ (Found in material dried over sulphuric acid: C, 50·3; H, 8·7; loss at 105—110° in a vacuum, 23·1, 23·3. $C_{50}H_{72}O_6N_4,2CO_3,16H_2O$ requires C, 50·7; H, 8·4; $16H_2O$, 23·4%. Found in anhydrous material: C, 65·8; H, 7·9. $C_{50}H_{72}O_6N_4,2CO_3$ requires C, 66·1; H, 7·6%). On addition of hydriodic acid it evolves carbon dioxide and furnishes *N*(*a*)*N*(*b*)-dimethyldihydrobrucidinium di-iodide, m. p. 286—288° alone or when mixed with an authentic specimen.

Both quaternary carbonates were thermally decomposed, but *N*(*a*)*N*(*b*)-dimethyldihydrobrucidinium dicarbonate gave the more satisfactory results. The action of heat on *N*(*b*)-methyldihydrobrucidinium carbonate gives rise to deep red, gummy products along with small quantities of dihydrobrucidine, m. p. 172—173° (yield, 15%) and *N*(*b*)-methyl-*des*-dihydrobrucidine-A, m. p. 221—222° (yield, 5%).

The Thermal Decomposition of N(a)N(b)-*Dimethyldihydrobrucidinium Dicarbonate.*—The salt (200 g.), dried at 110° under diminished pressure and finely powdered, was cautiously heated over a free flame in wide test-tubes in batches of 1—2 g. until the effervescence ceased and the product became liquid. The volatile decomposition products were recognised as carbon dioxide, methyl alcohol, and water. After many tedious experiments, and when the properties of the decomposition products had been ascertained, the following method for the separation of the constituents of the crude mixture was found to be convenient. The brown glassy product was rubbed with the minimum quantity of cold methyl alcohol (3—5 c.c. for each tube); crystallisation began almost immediately and crop (1) was collected after 12 hours. The combined methyl-alcoholic filtrates were evaporated to dryness under diminished pressure; the residue rapidly crystallised in contact with acetone (200 c.c.) and furnished crop (2). The acetone filtrate was concentrated to half its volume and, on cooling, crop (3) gradually separated; the mother-liquor was evaporated to dryness (vacuum), the brown solid residue dissolved in warm methyl alcohol (150 c.c.), and freshly distilled methyl iodide (10 c.c.) added. This operation afforded crop (4). The methyl-alcoholic filtrate was concentrated to half its volume, cooled, and seeded with a crystal from crop (4); after being left over-night, it yielded crop (5). The filtrate was mixed with small pieces of porous porcelain (150 g.) and evaporated to dryness under diminished pressure; the dark brown residue was extracted several times with boiling petroleum (3000 c.c. of b. p. 90—110°), and thus resolved into fraction (A), soluble in petroleum, and fraction (B), which remained undissolved.

The petroleum extract containing fraction (A) was concentrated to half its volume under diminished pressure and then kept for 2 days in the ice-chest; the solution gradually deposited a brownish precipitate (crop 6) containing halogen. The liquid was further concentrated, cooled, and filtered from the halogen-containing precipitate, and this operation was repeated until a solution free from halogen was obtained. This was evaporated to dryness (vacuum) and the pale yellow, residual gum was dissolved in the minimum quantity of boiling light petroleum (250 c.c. of b. p. 70—90°); on slow cooling, crop (7) gradually separated as tufts of needles. Further concentration of the mother-liquor yielded during 3—4 weeks crops (8) and (9). The final mother-liquor was evaporated to dryness (vacuum) and the residue (11 g.) was distilled without decomposition at 250—310°/1·5 mm. None of the four fractions collected could be induced to crystallise, and they were not further examined.

The fraction (B) (insoluble in petroleum) was freely soluble in many organic solvents, but not in ethyl acetate, and advantage was taken of this property. The crude product (5 g.) was dissolved in the minimum quantity of boiling methyl alcohol (10 c.c.) and mixed with hot chloroform (15 c.c.), the filtered solution heated to boiling, and boiling ethyl acetate added until a turbidity appeared; on slow cooling, crop (10) gradually separated in large yellowish columns. A further small quantity of the same substance was obtained when the mother-liquor was evaporated to dryness (vacuum) and the residual gum was crystallised as described above. The final mother-liquor, on evaporation to dryness, afforded a gum (fraction 11), from which no further pure product could be isolated by direct crystallisation.

Crop (1) consisted of almost pure *N*(*b*)-methyl-*des*-dihydrobrucidine-a; the pale-coloured crude product had m. p. 217—220°, raised to 221—222° after two recrystallisations from methyl alcohol (norit) (yield, 45 g.).

Crops (2) and (3) were separately recrystallised from acetone, and in both cases pure dihydrobrucidine (34 g.) was obtained. It was identified by m. p., by mixed m. p. (172—173° in both cases), by the power to retain acetone of crystallisation, by conversion into the methiodide, m. p. 298°, and by analysis (Found in air-dried material: C, 70·7; H, 8·4; loss at 130° in a vacuum, 13·5. Calc. for $C_{23}H_{30}O_3N_2,C_3H_6O$: C, 70·9; H, 8·2; C_3H_6O, 13·2. Found in material dried at 130° in a vacuum : C, 72·5; H, 7·9. Calc. for $C_{23}H_{30}O_3N_2$: C, 72·3; H, 7·9%).

Crops (4), (5), and (6) consisted of *N*(*b*)-methyldihydrobrucidinium iodide (yield, 19 g.). Purified by recrystallisation from methyl alcohol (norit) and subsequently from water, it formed colourless prisms, m. p. 298° (alone or when mixed with a specimen prepared directly from the components) (Found in material dried at 104° : C, 55·1; H, 6·6. Calc. for $C_{23}H_{30}O_3N_2,CH_3I$: C, 55·0; H, 6·3%).

Crops (7), (8), and (9) were repeatedly crystallised from light petroleum (b. p. 70—90°) and gave a substance, m. p. 169—171°, which was recognised as hydroxymethyltetrahydrobrucidine (yield, 17 g.).

Crop (10) was recognised as pure *N*(*b*)-methyl-*des*-dihydrobrucidine-b methiodide containing a molecule of chloroform of crystallisation (yield, 28 g.).

The chief constituent of fraction (11) (12 g.) was undoubtedly *N*(*b*)-methyldihydrobrucidinium iodide. The crude product was suspended in water and heated for 3 hours with a large excess of silver chloride; the filtrate from the silver salts was evaporated to dryness, and the dark gummy residue decomposed by sodium methoxide at 135°; this operation gave dihydrobrucidine (2·4 g.), m. p. 172—173°, methoxymethyltetrahydrobrucidine (3·1 g.), m. p. 134—136°, and *N*(*b*)-methyl-*des*-dihydrobrucidine-a (1·7 g.), m. p. 221—222° (compare the action of sodium methoxide on dihydrobrucidine metho-salts, p. 1693).

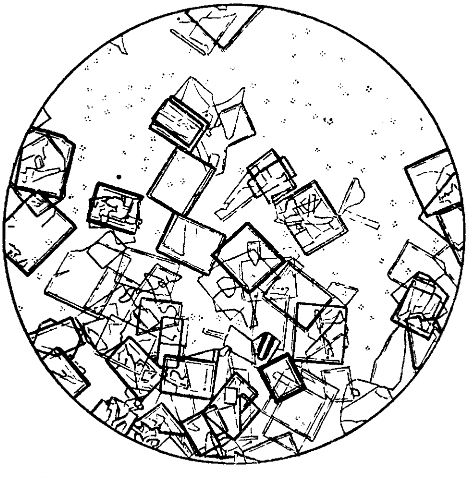
N(b)-*Methyl-*des*-dihydrobrucidine-a* (Methyl-ψ-dihydrobrucidine of Part V).—The base crystallises from the simple alcohols in colourless quadrilateral plates, m. p. 221—222° (Fig. 1)

[Found: C, 72·6, 72·7; H, 8·3, 8·3; N, 7·2, 7·3; MeO, 15·9, 16·0; Me(*N*), 4·1, 4·0. Calc. for $C_{24}H_{32}O_3N_2$: C, 72·7; H, 8·1; N, 7·1; 2MeO, 15·7; Me(*N*), 3·8%]. Estimation of side-chain methyl groups kindly undertaken by Dr. H. Roth of Heidelberg gave negative results. A mixture with methyl-ψ-dihydrobrucidine had m. p. 221° and a careful comparison proved the identity of the specimens. This substance is characterised by its sparing solubility in most organic solvents (in cold ethyl alcohol, 1 : 250; in boiling ethyl alcohol, 1 : 65; in methyl alcohol it is still less readily soluble) except chloroform and benzene; it becomes faintly yellow on keeping in the air, whereas its alcoholic solutions become pink. Solutions of the base in very dilute or in concentrated (30%) hydrochloric acid give, on addition of ferric chloride, a green coloration, which becomes pale yellow on warming or keeping.

The base remained unchanged after attempted electrolytic reduction in the usual apparatus for 12 hours at 95—100°; fruitless attempts were also made to reduce it in benzene solution by means of hydrogen in the presence of palladised charcoal or platinum-black.

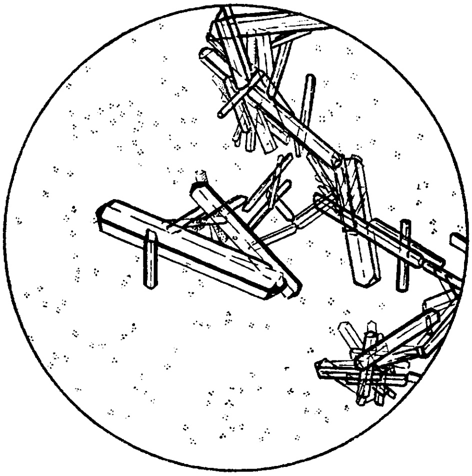
The Action of Methyl Iodide on N(b)-*Methyl*-des-*dihydrobrucidine-a. Formation of Isomeric Dimethiodides.*—*N*(*b*)-Methyl-*des*-dihydrobrucidine-a does not appear to combine with methyl iodide in the cold, but interaction occurs when a mixture of the components (methyl iodide in excess) is heated for a short time at 50—60° and N(b)-*methyl*-des-*dihydrobrucidine-a dimethiodide* is formed in theoretical yield. The derivative crystallises from water in colourless quadrilateral plates of a tetrahydrate, m. p. 284—286° (decomp.); it is sparingly soluble in cold water, moderately soluble in methyl alcohol, and dissolves readily in the hot solvents; it gradually loses $2H_2O$ at 105° and subsequently at 130° in a high vacuum, but the remaining $2H_2O$ are retained tenaciously (Found: loss at 105°, 2·8; loss at 130°, 4·2, 4·6. $C_{24}H_{32}O_3N_2,2MeI,4H_2O$ requires $1H_2O$, 2·4; $2H_2O$, 4·7%. Found in material dried at 130°: C, 43·8, 43·6, 43·7, 43·6; H, 5·7, 5·7, 5·5, 5·8; I, 36·1. $C_{24}H_{32}O_3N_2,2MeI,2H_2O$ requires C, 43·6; H, 5·9; I, 35·4%). This behaviour seems to be common among brucidine and dihydrobrucidine derivatives; it characterises several other substances described in the present communication and was the frequent cause of difficulties in connection with the analyses.

FIG. 1.



N-*Methyl*-des-*dihydrobrucidine-a, m. p.* 221—222° (*from* MeOH).

FIG. 2.



N-*Dimethyl*-des-*brucidine, m. p.* 155—156° (*from* MeOH).

N(*b*)-Methyl-*des*-dihydrobrucidine-a combines readily with methyl sulphate in the cold, yielding a gummy dimethosulphate, which, however, could not be crystallised. It was treated with an excess of aqueous sodium iodide and the above-described dimethiodide, m. p. 284—286°, was obtained in theoretical yield.

The *dimethochloride*, prepared from the dimethiodide by means of silver chloride, is freely soluble in water and dissolves readily in methyl alcohol. It separates from a concentrated methyl-alcoholic solution in colourless prismatic needles containing $3H_2O$. This trihydrate shrinks at 60—65° and on further heating melts and decomposes at 296—298°. When it is dried at 105° or over sulphuric acid, it is converted into the monohydrate; the anhydrous salt, formed only at a much higher temperature, is very hygroscopic and gives unsatisfactory analytical results (Found in air-dried material : C, 56·3 ; H, 7·9 ; loss at 105° or over sulphuric acid, 6·6, 6·3. $C_{24}H_{32}O_3N_2,2MeCl,3H_2O$ requires C, 56·6 ; H, 8·0 ; $2H_2O$, 6·5%. Found in material dried at 105° : C, 60·2 ; H, 8·1. $C_{24}H_{32}O_3N_2,2MeCl,H_2O$ requires C, 60·6 ; H, 7·8%).

When the salt was digested with an excess of 20% methyl-alcoholic sodium methoxide, as described in similar cases, *N*(*b*)-methyl-*des*-dihydrobrucidine-a, m. p. 221—222° alone or after admixture with an authentic specimen, was recovered in almost theoretical yield. The dimethochloride remained unchanged after being agitated for 2 hours at 18° in hydrogen in the presence of palladised charcoal.

allo-N(b)-*Methyl*-des-*dihydrobrucidine-a dimethiodide* is obtained when the reaction is effected at higher temperatures. A mixture of *N*(*b*)-methyl-*des*-dihydrobrucidine-a (5 g.) and methyl iodide (30 c.c.) was heated under reflux on the steam-bath ; a colourless precipitate was gradually formed. After 3 hours the excess of methyl iodide was distilled, and the solid residue dissolved in boiling methyl alcohol (50 c.c.) ; on cooling, *allo*-*N*(*b*)-methyl-*des*-dihydrobrucidine-a dimethiodide separated as an oil, which solidified on being rubbed (yield, 8·5 g.). The same substance was obtained when the base, dissolved in benzene, was refluxed for 3 hours with an excess of methyl sulphate and the gummy dimethosulphate which was then formed was treated with aqueous sodium iodide. The derivative is sparingly soluble in water or methyl alcohol and has a tendency to separate from the latter as an oil. When, however, a methyl-alcoholic solution is allowed to cool slowly, the salt crystallises in aggregates of colourless needles, m. p. 245—246° (decomp.). Unlike its isomeride, it forms a trihydrate which loses all its solvent of crystallisation at 105° (Found : loss at 105°, 7·2. $C_{24}H_{32}O_3N_2,2MeI,3H_2O$ requires $3H_2O$, 7·3%. Found in anhydrous material : C, 45·9 ; H, 5·6 ; I, 36·9. $C_{24}H_{32}O_3N_2,2MeI$ requires C, 45·9 ; H, 5·6 ; I, 37·4%).

The *dimethochloride*, prepared by the usual method, separated from a concentrated methyl-alcoholic solution in colourless leaflets, m. p. 202—204° (decomp.), freely soluble in water and in methyl alcohol ; it seems to be capable of retaining simultaneously methyl alcohol and water of crystallisation, which are lost at 110° in a vacuum. The anhydrous salt is very hygroscopic and has not been analysed (Found : loss at 110° in a vacuum, 25·8.

$$C_{24}H_{32}O_3N_2,2MeCl,4H_2O,3MeOH$$

requires $4H_2O,3MeOH$, 25·4%. Found in material dried over sulphuric acid : C, 52·2 ; H, 8·3. $C_{24}H_{32}O_3N_2,2MeCl,4H_2O,3MeOH$ requires C, 52·3 ; H, 8·7%). When the salt was heated in the hope of obtaining *allo*-*N*(*b*)-methyldihydrobrucidine, a gum was produced, from which no crystalline product could be isolated ; fruitless attempts were also made to reduce the salt by means of hydrogen in the presence of palladium.

The Action of Sodium Methoxide on allo-N(b)-*Methyl*-des-*dihydrobrucidine-a Dimethochloride. Formation of* N(b)N(b)-*Dimethyl*-des-*brucidine*.—*allo*-*N*(*b*)-Methyl-*des*-dihydrobrucidine-a dimethochloride (5 g.) was mixed with a methyl-alcoholic solution of sodium methoxide (30 c.c. of 20%) and heated for 2 hours in an open flask in a rapidly boiling water-bath. The cooled mixture, on dilution with ice-water, gave a caseous precipitate, which was washed with water, dried, and thrice crystallised from methyl alcohol. *Dimethyl*-des-*brucidine* (yield, 90%) forms colourless needles, m. p. 155—156° (Fig. 2) [Found in air-dried material : C, 73·1 ; H, 8·3 ; MeO, 14·6 ; Me(*N*), 7·5. $C_{25}H_{34}O_3N_2$ requires C, 73·2 ; H, 8·3 ; 2MeO, 15·1 ; 2Me(*N*), 7·3%]. The base is moderately readily soluble in the simple alcohols, sparingly soluble in ethyl acetate or petroleum, but dissolves readily in chloroform or benzene. The ferric reaction of the base in dilute aqueous acid solution is of brucidine type, but the green coloration is not so intense as in the case of brucidine and it changes to pale yellow on warming.

The Action of Hydrogen on N(b)-*Methyl*-des-*dihydrobrucidine-a in Acid Solution in the Presence of Palladised Charcoal. Formation of Isomeric Quaternary Iodides.*—The base (4 g.) was dissolved in 50% acetic acid (30 c.c.) and hydrogenated at 15—17° in the presence of palladised charcoal (0·4 g. of palladous chloride, 4 g. of charcoal previously heated to redness, and 50 c.c. of water). Absorption of the gas was rapid and ceased after 90 minutes, 245 c.c. (at N.T.P.) having been absorbed (calc. for 2H, 224). The filtered solution containing the readily soluble quaternary acetates was basified with ammonia (no precipitate) and mixed with sodium iodide (3 g.) ; N(b)-*methyldihydrobrucidinium-d iodide* was deposited as a heavy greyish precipitate, whereas N(b)-*methyldihydrobrucidinium-c iodide* remained in the solution, which exhibited a green fluorescence.

Crude *N*(*b*)-methyldihydrobrucidinium-d iodide, washed with warm water, dried, and twice recrystallised from water, forms colourless plates, m. p. 317—318° (decomp.) ; on keeping in the air, it gradually becomes rose-coloured. It separates from methyl alcohol as a jelly which soon becomes crystalline ; it is unusually sparingly soluble in cold or boiling water and in most organic solvents; it is also characterised by the property of retaining water of crystallisation, which is not lost even at 270°/1 mm. Crystallised from water or methyl alcohol and subsequently dried in the air, it seems to form a dihydrate, which changes into a monohydrate on being dried at 105—110° under atmospheric pressure or in a high vacuum, or after being recrystallised from boiling butyl alcohol; dried at 270° in a high vacuum, it sublimes to a small extent, but does not lose all the solvent of crystallisation (Found: loss at 105°, 2·7, 2·5. $C_{24}H_{33}O_3N_2I,2H_2O$ requires $1H_2O$, 3·2%. Found in material dried at 105° in a vacuum: C, 53·2, 53·3; H, 6·4, 6·7; I, 23·8, 23·4. Found in material dried at 170° in a high vacuum: C, 53·3; H, 6·5. Found in material crystallised from butyl alcohol: C, 53·1; H, 6·5. $C_{24}H_{33}O_3N_2I,H_2O$ requires C, 53·1; H, 6·5; I, 23·4%. Found in material dried at 270° in a high vacuum: C, 53·6, 54·1; H, 6·9, 6·8. $C_{24}H_{33}O_3N_2I,0{\cdot}5H_2O$ requires C, 54·1; H, 6·4%).

The *chloride*, prepared from this iodide by means of silver chloride, forms a deep red powder, m. p. 304—306° (decomp.); it is readily soluble in water and dissolves moderately in methyl alcohol. Like the corresponding iodide, it forms a trihydrate, which loses $2H_2O$ at 105° but retains $1H_2O$ tenaciously (Found: loss at 105°, 7·7. $C_{24}H_{33}O_3N_2Cl,3H_2O$ requires $2H_2O$, 7·4%. Found in material dried at 105° in a high vacuum: C, 64·2; H, 8·0. $C_{24}H_{33}O_3N_2Cl,H_2O$ requires C, 63·9; H, 7·8%).

When the chloride was digested for an hour with an excess of methyl-alcoholic sodium methoxide (20%) in an open flask on the steam-bath and the crude product was treated with water, *N*(*b*)-methyl-*des*-dihydrobrucidine-a was recovered in almost theoretical yield, m. p. and mixed m. p. 221—222° after recrystallisation from methyl alcohol.

Fruitless attempts were made to obtain the hypothetical dihydrobrucidine-d by thermal decomposition of the chloride; heated in a test-tube over a flame, this salt decomposed before any methyl chloride was split off and yielded a dark oily product and much charred material.

N(b)-*Methyldihydrobrucidinium-c iodide* was isolated from the alkaline filtrate (see p. 1690) by the addition of much solid anhydrous potassium carbonate; crystallised from water and then twice from methyl alcohol, it formed colourless, elongated, quadrilateral plates, m. p. 304—306° (decomp.), moderately readily soluble in water or the simple alcohols. Unlike *N*(*b*)-methyldihydrobrucidinium-d iodide, it does not discolour in the air. It also has the power to retain solvent of crystallisation at 230° in a high vacuum (Found: loss at 105° in a high vacuum, 4·5. $C_{24}H_{33}O_3N_2I,2{\cdot}5H_2O$ requires $1{\cdot}5H_2O$, 4·9%. Found in material dried at 105° in a high vacuum: C, 53·3, 53·6; H, 6·6, 6·6; I, 22·6. $C_{24}H_{33}O_3N_2I,H_2O$ requires C, 53·1; H, 6·5; I, 23·4%).

The *chloride* produced from this iodide by the usual method separated from a concentrated aqueous solution as a pink powder (Found: loss at 230° in a high vacuum, 8·9. $C_{24}H_{33}O_3N_2Cl,3H_2O$ requires $2{\cdot}5H_2O$, 9·2%. Found in material dried at 230° in a high vacuum: C, 65·6; H, 7·8. $C_{24}H_{33}O_3N_2Cl,0{\cdot}5H_2O$ requires C, 65·2; H, 7·7%). The salt is readily soluble in water or methyl alcohol and melts at 233—235° without decomposition. When heated above its m. p. in a tube over a free flame, extensive decomposition occurred and dihydrobrucidine-c was not formed.

In contrast to *N*(*b*)-methyldihydrobrucidinium-d chloride, *N*(*b*)-methyldihydrobrucidinium-c chloride is resistant towards boiling methyl-alcoholic sodium methoxide and it was recovered unchanged after being digested with this reagent for 2 hours. The decomposition was, however, effected by heating the salt with the sodium methoxide solution for ½ hour at 120—125°, and a good yield of *N*(*b*)-methyl-*des*-dihydrobrucidine-a, m. p. 221—222° (alone or after admixture with a pure specimen), was obtained.

Hydroxymethyltetrahydrobrucidine.—The base crystallises from petroleum (b. p. 70—90°) in tufts of pale yellow, arrow-shaped needles (Fig. 3), m. p. 169—171° [Found: C, 69·1, 69·3; H, 8·3, 8·4; N, 7·0; MeO, 14·9; Me(*N*), 3·9. $C_{24}H_{34}O_4N_2$ requires C, 69·5; H, 8·2; N, 6·8; 2MeO, 15·1; Me(*N*), 3·6%]. It is appreciably soluble in water, very readily soluble in most organic solvents, except light petroleum, and it exhibits brucidine-type colour reactions. The base was recovered unchanged after prolonged refluxing with methyl iodide; it was also indifferent towards benzaldehyde in methyl-alcoholic solution in the presence of sodium methoxide.

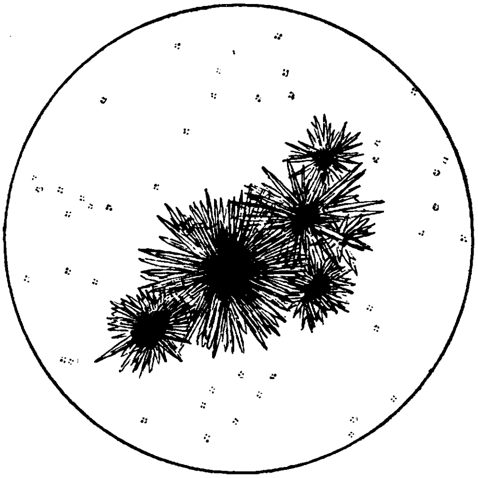
Acetoxymethyltetrahydrobrucidine was prepared by the addition of anhydrous sodium acetate (1 g.) to a cold solution of hydroxymethyltetrahydrobrucidine (3 g.) in acetic anhydride (5 c.c.); reaction occurred immediately with evolution of heat and the derivative crystallised. When the mixture was heated for a few minutes, the yield was considerably diminished and on prolonged heating at 100° no acetyl derivative was produced. The crude product was washed with aqueous sodium hydrogen carbonate, dried, and thrice crystallised from light petroleum (yield, 3 g.), separating therefrom in colourless leaflets, m. p. 258—260° (decomp.) (Found: C, 68·2, 68·3; H, 8·1, 8·0. $C_{26}H_{36}O_5N_2$ requires C, 68·4; H, 7·9%), very readily soluble in the simple alcohols or in chloroform, moderately readily soluble in ethyl acetate, and sparingly in light petroleum.

This acetyl derivative (2 g.) was heated with methyl-alcoholic sodium methoxide (15 c.c. of 10%) for an hour on the steam-bath. The cold product was diluted with water and extracted with chloroform, and the dried extract evaporated to dryness. The residue crystallised from light petroleum in needles (1·2 g.), m. p. 169—171° alone or mixed with hydroxymethyltetrahydrobrucidine.

When the acetyl derivative (0·5 g.) was gently heated in a tube over a flame, a vigorous effervescence took place and the odour of methyl acetate was noted. The pale-coloured, cold, glassy residue crystallised immediately on addition of acetone and after being recrystallised from this solvent had m. p. 172—173°, undepressed after admixture with dihydrobrucidine (yield, 0·3 g.).

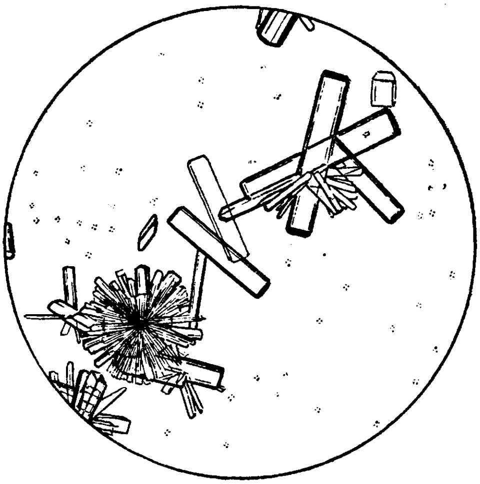
Methylation of Hydroxymethyltetrahydrobrucidine. Formation of Methoxymethyltetrahydrobrucidine Methosulphate.—The base (3 g.) was triturated with aqueous sodium hydroxide (20 c.c. of 40%), and methyl sulphate (10 c.c.) gradually added; the mixture was heated on the steam-bath until the excess of methyl sulphate was decomposed, and the cold liquid was saturated with solid anhydrous potassium carbonate. The yellowish semi-solid product, evidently methoxymethyltetrahydrobrucidine methosulphate, was collected, dissolved in the minimum quantity of water, and mixed with sodium iodide (4 g.). Methoxymethyltetrahydrobrucidine methiodide which was then formed crystallised from ethyl alcohol in colourless leaflets, m. p. 166—167°, undepressed on admixture with a specimen prepared directly from the components (Part V; *loc. cit.*, p. 1655) (Found in material dried at 105° : C, 54·5; H, 7·1. Calc. for $C_{26}H_{39}O_4N_2I$: C, 54·7; H, 6·8%). When the salt was heated in a tube over a free flame, methyl iodide was evolved; the glassy product crystallised from methyl alcohol in colourless needles, m. p. 134—135° (yield, theoretical), identified with methoxymethyltetrahydrobrucidine by m. p. and mixed m. p. 134—135°, and by a close comparison of properties.

FIG. 3.



Hydroxymethyltetrahydrobrucidine, m. p. 169—171° (*from light petroleum*).

FIG. 4.



N-*Methyl*-des-*dihydrobrucidine-b, m. p.* 133—137° (*from light petroleum, rapid crystallisation*).

The Action of Hot Dilute Sulphuric Acid on Hydroxymethyltetrahydrobrucidine.—Hydroxymethyltetrahydrobrucidine is not attacked in 3 hours by boiling 10% (vol.) sulphuric acid, but, when a solution of the substance (2 g.) in 25% sulphuric acid (15 c.c.) was refluxed for 3 hours, about 10% of the base was converted into methyldihydrobrucidinium hydrogen sulphate. (With more concentrated acid no methyldihydrobrucidinium hydrogen sulphate could be isolated from the dark brown solution, which became dark blue on being made alkaline with ammonia.) The cold liquid was basified with ammonia, the unchanged base (1·7 g.; m. p. 169—171° after crystallisation from light petroleum) separated, and the filtrate mixed with sodium iodide (0·5 g.). Methyldihydrobrucidinium iodide separated as a greenish gum, which crystallised when mixed with a little methyl alcohol and seeded with a crystal of the pure salts. It was recrystallised from water (norit) and identified by m. p., by mixed m. p. (296—298° in both cases), and by analysis (Found in material dried at 105°: C, 55·2; H, 6·7. Calc. for $C_{23}H_{30}O_3N_2$,MeI: C, 55·0; H, 6·3%).

N(b)-*Methyl-*des-*dihydrobrucidine-b.*—As stated on p. 1688, the *methiodide* of this substance constitutes crop (10), and the salt was also obtained by direct union of the free base with methyl iodide. When allowed to crystallise slowly from methyl alcohol–ethyl acetate–chloroform (see p. 1688), it separated in large, transparent, yellowish columns, containing $1CHCl_3$. In this form it melts and decomposes at 242—244° to a purple liquid; it is very readily soluble in the simple alcohols, moderately readily soluble in water or chloroform, and practically insoluble in ethyl acetate or light petroleum. It loses chloroform of crystallisation on being powdered, but removal of the whole of the solvent has proved difficult as in other similar cases. When a sufficient quantity of this substance was heated with water on the steam-bath, the liquid boiled and chloroform was found in the distillate. On crystallisation from methyl alcohol, the chloroform is replaced by 2MeOH and this modification is sparingly soluble in methyl alcohol; it forms faint rose-coloured, thick, quadrilateral plates which melt at 80—82° and decompose at 242—244° to the characteristic purple liquid (Found: loss at 80° in material crystallised from methyl alcohol–ethyl acetate–chloroform, 16·2. $C_{24}H_{32}O_3N_2$,MeI,$CHCl_3$ requires $CHCl_3$, 18·2%. Found: loss at 110° in material crystallised from methyl alcohol, 9·7. $C_{24}H_{32}O_3N_2$,MeI,2MeOH requires 2MeOH, 10·6%. Found in material dried at 110° in a vacuum: C, 55·1, 55·1; H, 6·3, 6·2. Found in material dried at 170° in a high vacuum: C, 55·7; H, 6·2. $C_{24}H_{32}O_3N_2$,MeI requires C, 55·8; H, 6·5%).

The *methochloride* was prepared from the methiodide (10 g.), which was mixed with water (75 c.c.) and heated on the steam-bath in an open flask until the whole of the chloroform had evaporated; freshly precipitated pure silver chloride was then added in excess, and the mixture heated for 2 hours with frequent shaking. The filtrate from the silver salts was evaporated to dryness in a vacuum, and the residue dried over sulphuric acid. The methochloride formed a reddish-brown hygroscopic powder, freely soluble in water and in the simple alcohols; when heated in a capillary tube, it melted at 165—170°, was discoloured, and crystallised again at 175—180°; on further heating, it melted and decomposed at 245—248°. The methochloride was heated gently over a flame in glass tubes (batches of 0·5 g.) until the evolution of methyl chloride (recognised) ceased and the product liquefied. The pale blue, glassy residue was extracted with the minimum quantity of boiling light petroleum (b. p. 70—90°), and the extract evaporated to a small bulk; on slow cooling, *N*(*b*)-methyl-*des*-dihydrobrucidine-b crystallised in stout, quadrilateral, yellowish plates, m. p. 126—129° (Fig. 4). It was twice recrystallised from light petroleum and the m. p. was raised to 133—134°, and remained unchanged on further crystallisation (yield, 90%).

The base is appreciably soluble in water and, in contrast to *N*(*b*)-methyl-*des*-dihydrobrucidine-a, is characterised by being unusually readily soluble in organic solvents, except light petroleum, in which it dissolves moderately readily. A solution of the base in dilute hydrochloric acid gives on addition of a drop of ferric chloride a green coloration, which becomes pink on warming [Found in air-dried material: C, 73·0; H, 8·0; MeO, 15·3; Me(*N*), 3·5. $C_{24}H_{32}O_3N_2$ requires C, 72·7; H, 8·1; 2MeO, 15·6; Me(*N*), 3·8%. Estimations of CMe groups (Dr. H. Roth): yield of $C_2H_4O_2$, 10·0, 11·0%].

The base combined readily with methyl iodide in the cold; the product, crystallised from methyl alcohol–ethyl acetate–chloroform, was identical with the methiodide described on p. 1688. The identity was established by m. p., by mixed m. p. (242—244° in both cases), and by analysis (Found: loss at 80°, 16·6. Found in material dried at 170° in a high vacuum: C, 55·4; H, 6·6%).

When a solution of the base (1 g.) in 50% acetic acid (20 c.c.) was agitated in hydrogen in the presence of palladised charcoal (0·1 g. of palladous chloride, 1 g. of charcoal, and 30 c.c. of water), a rapid absorption of gas took place; after 50 minutes the reaction ceased, 65 c.c. (at N.T.P.) having been taken up (calc. for 2H, 56 c.c.). The filtered solution was rendered alkaline by ammonia, mixed with much solid potassium carbonate, and extracted with chloroform. The pale brown residue, after the solvent had been evaporated in a vacuum, proved to be even more readily soluble than the base before hydrogenation, and it could not be crystallised.

The Decomposition of Dihydrobrucidine Metho-salts by Means of Sodium Methoxide.—Dihydrobrucidine methiodide, methochloride, and methosulphate are not attacked by boiling 20% methyl-alcoholic sodium methoxide. But when a mixture of the methochloride (20 g.) or the methosulphate (but not the methiodide) with methyl-alcoholic sodium methoxide (200 c.c.

of 20%) was heated in an open flask, first on the steam-bath and subsequently on a sand-bath until the temperature of the liquid reached 135°, and the cold product was diluted with ice-water, a grey caseous precipitate was formed. This consisted of dihydrobrucidine (2 g.), methoxymethyltetrahydrobrucidine (10 g.), and *N*(*b*)-methyl-*des*-dihydrobrucidine-a (1·7 g.). This mixture was resolved into its components by fractional crystallisation from methyl alcohol, benzene, and acetone. The named bases were identified by the usual methods and by those described in this memoir.

We are indebted to Dr. K. Lindenfeld of Warsaw for preparing the micro-photographs here reproduced from drawings and for carrying out the micro-analyses.

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[*Received, July 25th*, 1935.]