100. *Strychnine and Brucine. Part XVII.* neo*Brucine and* neo*Brucidine.*

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IN the two preceding parts of this series it is shown that the methyl-ψ-strychnidine of Part IV (Clemo, Perkin, and Robinson, J., 1927, 1589) is in reality an isomeride of strychnidine to be termed *neo*strychnidine and is related to *neo*strychnine, which has also been prepared and investigated.

Similarly, methyl-ψ-dihydrostrychnidine is identical with dihydrostrychnidine (A), a fact which was already noted in Part VI (Oxford, Perkin, and Robinson, J., 1927, 2389).

Part V (Gulland, Perkin, and Robinson, J., 1927, 1627) was concerned with brucine derivatives and " methyl-ψ-brucidine " and " methyl-ψ-dihydrobrucidine " were amongst the substances described. We now find that " methyl-ψ-brucidine " is actually neo*brucidine*, an isomeride of brucidine, but " methyl-ψ-dihydrobrucidine " is *not* identical with dihydrobrucidine.

The contrast with the strychnine series is noteworthy at this point and it may mean either that methyl-ψ-dihydrobrucidine is correctly named or that isomerism of the type exemplified by the dihydrostrychnidines (A), (B), and (C) has been encountered; furthermore, demethylation of a methoxyl group is a possibility. " Methyl-ψ-dihydrobrucidine " will be re-examined and we need not consider further the explanation of the anomaly at the present stage.

We have also obtained neo*brucine*, and the whole series of derivatives is parallel with the *neo*strychnine series described in Parts XV and XVI.

Benzylbrucidinium chloride and methyl-alcoholic sodium methoxide afford a crystalline *methoxybenzyldihydro*neo*brucidine*,

$(MeO)_2C_{17}H_{20}O[N(a)\cdot CH_2][N(b)C_7H_7](:C\cdot OMe)(C:C)$ (I),

and this is converted by boiling dilute sulphuric acid into benzyl*neo*brucidinium sulphate; the related chloride,

$(MeO)_2C_{17}H_{20}O[N(a)\cdot CH_2][N(b)C_7H_7\cdot C\vdots](C:C)\}Cl$ (II),

decomposed, when heated, with formation of benzyl chloride and neo*brucidine*, $(MeO)_2C_{17}H_{20}O[N(a)\cdot CH_2][N(b)\cdot C\vdots](C:C)$ (III). Catalytic or electrolytic reduction of *neo*brucidine furnished the base already obtained by hydrogenation of brucidine in the presence of palladium (Part XI; Achmatowicz, Fawcett, Perkin, and Robinson, J., 1930, 1769).

Again, methylbrucine and alcoholic sodium methoxide yield *methoxymethyldihydro*neo*brucine*,

$(MeO)_2C_{17}H_{20}O[N(a)\cdot CO][N(b)Me](MeO\cdot C:)(C:C)$ (IV),

from which methyl*neo*brucinium salts and *neo*brucine are derived in the usual manner. *neo*Brucine is catalytically reduced to dihydrobrucine.

EXPERIMENTAL.

Benzylbrucidinium Chloride.—When equivalent quantities of brucidine and benzyl chloride were stirred together, combination occurred rapidly; the crude product was washed with benzene. The salt is readily soluble in water and separates from a concentrated solution (1 g. in 5 c.c.) as a thick paste of colourless crystals which, dried at 100°, have m. p. 305—307° (decomp.) (Found: C, 70·7; H, 7·2; Cl, 7·1. $C_{30}H_{35}O_3N_2Cl$ requires C, 71·1; H, 6·9; Cl, 6·9%).

*Methoxybenzyldihydro*neo*brucidine* (I).—When benzylbrucidinium chloride (20 g.) was treated with methyl-alcoholic potash (100 c.c. of 25%) under the conditions employed for the preparation of methoxybenzyldihydro*neo*strychnidine (this vol., p. 490), methoxybenzyldihydro*neo*brucidine (70%) and *neo*brucidine (15—20%) were obtained: they were separated by fractional crystallisation from ethyl alcohol or acetone.

*Methoxybenzyldihydro*neo*brucidine* separates from ethyl alcohol or acetone in well-developed colourless prisms, m. p. 159—160°, which become rose-coloured when exposed to the air (Found: C, 73·8; H, 7·3. $C_{31}H_{38}O_4N_2$ requires C, 74·1; H, 7·6%). When ferric chloride is added to its solution in dilute hydrochloric acid, a green coloration is developed. The base combines with methyl iodide at 100° with the formation of an *iodide*, m. p. 249—250° (Found : C, 60·0 ; H, 6·2. $C_{32}H_{41}O_4N_2I$ requires C, 59·6 ; H, 6·4%) ; this salt may be the methiodide or possibly slightly impure benzyl*neo*brucidinium iodide.

A close comparison of the properties of *neo*brucidine formed in the above process with those of "methyl-ψ-brucidine" described in Part V showed that the substances are identical.

*neo*Brucidine (III) is readily soluble in benzene and chloroform and moderately readily soluble in acetone and methyl alcohol ; it is stable towards boiling dilute sulphuric acid, but instantly decolorises permanganate. The base melts at 197—199°, alone or mixed with a pure specimen of "methyl-ψ-brucidine" (Found : C, 72·2 ; H, 7·4. Calc. for $C_{23}H_{28}O_3N_2$: C, 72·6 ; H, 7·4%).

Methoxybenzyltetrahydrobrucidine was obtained by the electrolytic reduction of the dihydro-derivative. It is sparingly soluble in methyl or ethyl alcohol and separates therefrom in large colourless prisms, m. p. 107—108° (Found : C, 73·8 ; H, 8·2. $C_{31}H_{40}O_4N_2$ requires C, 73·8 ; H, 7·9%). The base is stable towards permanganate and is not affected by boiling dilute sulphuric acid.

*The Benzyl*neo*brucidinium Salts.—The iodide* (as II). When methoxybenzyldihydro*neo*brucidine (20 g.) was subjected to the action of dilute sulphuric acid (250 c.c. of 20%) under the conditions already described in similar cases (this vol., p. 491), methyl alcohol was evolved and the quaternary benzyl*neo*brucidinium sulphate was produced. This was converted (by addition of aqueous sodium iodide to the basified solution) into *benzyl*neo*brucidinium iodide* (yield, 80%), which is practically insoluble in cold or boiling methyl alcohol and is very sparingly soluble in cold or boiling water. It was recrystallised from the latter (3 g. in 1000 c.c.) and separated in microscopic needles, m. p. 260—261° (decomp.) (Found : C, 60·1 ; H, 5·9. $C_{30}H_{35}O_3N_2I$ requires C, 60·0 ; H, 5·9%).

The chloride was prepared in the usual manner by heating the iodide with water and silver chloride. It was very soluble in water and on evaporation of the solvent remained as an amorphous deep red mass which could not be obtained in the crystalline form.

*The Action of Heat on Benzyl*neo*brucidinium Chloride.*—When the quaternary salt in quantities of 1 g. was heated in a test-tube over a free flame, benzyl chloride was evolved and *neo*brucidine was formed. The decomposition, however, was followed by the formation of tar and the yield of *neo*brucidine was small (30%) in comparison with the yield of *neo*strychnidine obtained in the analogous process (this vol., p. 492). The crude product was extracted with ethyl alcohol (charcoal) and after several recrystallisations almost colourless plates, m. p. 196—198°, were obtained. The melting point was unchanged after admixture with a specimen of *neo*brucidine which had given satisfactory results on analysis.

Formation of Dihydrobrucidine by Reduction of neo*Brucidine.*—(A) A solution of *neo*brucidine (5 g.) in acetic acid (75 c.c. of 20%) was added to the catalyst (0·3 g. of palladous chloride, 1 g. of norite, and about 300 c.c. of water) and agitated in hydrogen. Absorption at the ordinary temperature was very slow and the required volume of hydrogen (284 c.c.) was absorbed in 14 hours. The ice-cold filtered solution was basified with ammonia (no precipitate) and saturated with potassium carbonate and the gummy product which was then deposited was extracted with chloroform. The extract was dried over calcium chloride and filtered, and the solvent evaporated. The greenish-brown residue crystallised immediately when cooled and rubbed with a few drops of acetone. The base (4·3 g.) was recrystallised from acetone, in which it was sparingly soluble, separating in prisms, m. p. 172—173°, which retain a molecule of acetone of crystallisation at 115° (Found in material dried at 115° : C, 70·6; H, 7·6. Calc. for $C_{23}H_{30}O_3N_2,C_3H_6O$: C, 70·9; H, 8·0%. Found in material dried at 130° : C, 72·1; H, 7·8. Calc. for $C_{23}H_{30}O_3N_2$: C, 72·3; H, 7·8%). The specimen was identified with the product of the catalytic reduction of brucidine by direct comparison, and a mixture of the two specimens had m. p. 171—172°.

(B) The electrolytic reduction of *neo*brucidine at room temperature could not be effected and even after 30 hours 80% of the base was recovered unchanged: the remaining fraction was recognised as dihydrobrucidine (m. p. 169—171°). When, however, the reduction was carried out at 100° (5 g. of the base in 100 c.c. of 20% sulphuric acid), the hydrogenation was complete at the end of 12 hours, as shown by the fact that a few drops of the liquid then gave no precipitate or cloudiness on the addition of ammonia. The solution was worked up as described above and finally pure dihydrobrucidine (4·1 g.) was obtained. It was identified with the specimen prepared in the previous experiment (m. p. 171—172° and mixed m. p. 171—172°).

Benzylbrucinium Chloride.—Brucine was triturated with benzyl chloride (3—5% excess) and the resulting solid was powdered, washed with benzene, dissolved in boiling methyl alcohol, and precipitated by the addition of ether. The viscous mass crystallised on keeping and the salt separated from hot water in well-defined colourless prisms, m. p. 275—280° (decomp.) (Found : loss at 104°, 8·2. Found in material dried at 104° : C, 69·1; H, 6·5; Cl, 6·8. $C_{30}H_{33}O_4N_2Cl,2\frac{1}{2}H_2O$ requires H_2O, 8·0%. $C_{30}H_{33}O_4N_2Cl$ requires C, 69·2; H, 6·4; Cl, 6·8%).

Benzylbrucine.—When a hot aqueous solution of benzylbrucinium chloride was mixed with 50% aqueous potassium hydroxide, a mass of colourless microscopic needles separated in good yield. The *base* crystallised from water, in which it was moderately readily soluble, in needles, m. p. 195—196° after being dried at 100° (Found in material dried at 104° : C, 68·0; H, 7·1; N, 5·3. $C_{30}H_{34}O_5N_2,1\frac{1}{2}H_2O$ requires C, 68·0; H, 7·0; N, 5·3%).

*Methoxymethyldihydro*neo*brucine* (IV).—Unfortunately the yield of this substance by the analogous method is greatly inferior to that of the corresponding strychnine derivative and under the following conditions, which are the best we have been able to find, it amounts to barely 15%.

A mixture of methylbrucine (10 g.) and methyl-alcoholic sodium methoxide (3 g. of sodium in 75 c.c.) was heated in an open narrow-necked flask on the steam-bath until the solvent had evaporated. The product was dissolved in water, acidified with acetic acid in slight excess, and heated on the steam-bath for 2 hours. On cooling, crystals were deposited and these were thrice recrystallised from methyl alcohol, giving pale brownish, silky needles, m. p. 204—205° (Found: C, 68·2; H, 7·3. $C_{25}H_{32}O_5N_2$ requires 68·4; H, 7·3%). The *base* is readily soluble in chloroform and sparingly soluble in methyl alcohol. The acid filtrate from these crystals was basified, but no definite product could be isolated from the dark gummy mass which was precipitated.

*The Methyl*neo*brucinium Salts.*—When methoxymethyldihydro-*neo*brucine was heated with 20% sulphuric acid, a quaternary sulphate was formed (yield, 80%); after neutralisation of the solution with ammonia, the iodide was precipitated by the addition of sodium iodide.

*Methyl*neo*brucinium iodide* is almost insoluble in water and is sparingly soluble in methyl alcohol, separating from hot solutions as a pale brown, sandy, crystalline powder, m. p. 302—306° (decomp.) (Found in material dried at 105°: C, 52·7; H, 5·8. $C_{24}H_{29}O_4N_2I,CH_4O$ requires C, 52·8; H, 5·8%).

The related chloride, obtained by double decomposition with silver chloride, is very readily soluble in water and crystallises in colourless microscopic needles, m. p. 255—260° (decomp.).

neo*Brucine.*—The quaternary chloride (0·3 g.) was cautiously heated in a test-tube over a free flame; methyl chloride was evolved. The glassy residue crystallised in contact with methyl alcohol and separated from a hot solution in this solvent in long, colourless, silky needles, m. p. 225—226° (Found: C, 70·3; H, 6·5. $C_{23}H_{26}O_4N_2$ requires C, 70·1; H, 6·6%) (yield, 85—90%).

neo*Brucine* is almost insoluble in ether and sparingly soluble in ethyl acetate; it is moderately readily soluble in the simple alcohols and acetone and is readily soluble in benzene or chloroform. The colour reactions of the base closely resemble those of brucine.

The Catalytic Reduction of neo*Brucine. Formation of Dihydrobrucine.*—A solution of *neo*brucine (1·2 g.) in aqueous acetic acid (75 c.c. of 10%) was mixed with the catalyst (0·2 g. of palladous chloride, 2 g. of norite, and about 200 c.c. of water) and stirred in hydrogen. The theoretical volume of hydrogen was absorbed during 6 hours and the filtered liquid was then cooled in melting ice, basified with ammonia, mixed with potassium carbonate, and extracted with chloroform. The residue, after removal of the solvent, was crystallised from aqueous methyl alcohol and the product was identified with a specimen obtained from brucine (Part XI; *loc. cit.*) by m. p., by mixed m. p. (179—181° in both cases), and by analysis (Found: loss at 100°, 15·5. Found in material dried at 130°: C, 69·6; H, 7·2. Calc. for $C_{23}H_{28}O_4N_2,4H_2O$: H_2O, 15·4%. Calc. for $C_{23}H_{28}O_4N_2$: C, 69·7; H, 7·2%).

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