CXC.—iso*Quinoline Derivatives. Part VI.*
neoOxyberberine.

By FRANK LEE PYMAN.

THE main features of the constitution of berberine were determined by Perkin (Trans., 1889, **55**, 63; 1890, **57**, 992) by a study of its oxidation products. Later, Gadamer (*Arch. Pharm.*, 1905, **243**, 42) and Perkin and Robinson (Trans., 1910, **97**, 321) proposed certain alterations in Perkin's original formula, and the constitution of this alkaloid is now recognised as that given below:

Berberine.

Perkin found that the careful oxidation of berberine, even in small quantities and with a limited amount of permanganate (in the presence of potassium carbonate), led to the formation of a mixture of a large number of products. This fact is readily explained by the above formula, by which the molecule is shown to contain two double linkings, at either or both of which oxidation would be expected to take place.

Now it seemed of interest to study the oxidation of a derivative of berberine in which one of these points of attack was protected, for in that case a more uniform oxidation product or a less complicated mixture of products should result. With this object in view the oxidation of berberineacetone was undertaken. This compound was first described by Gaze (*Zeit. Naturwiss. Halle*, 1890, **62**, 399)

as a molecular compound before the nature of berberine was fully understood, but Gadamer (*loc. cit.*) recognised it later as a condensation product of the same type as anhydrocotarnineacetone, and suggested for it the formula (I), which satisfactorily explains its properties:

Reference to the formula will show that this compound only contains one double linking. By hydrolysing it with dilute acids, however, the acetone can be removed and the second double linking replaced with the formation of berberine hydrochloride; this reaction is common to all similarly constituted *isoquinoline* derivatives, such as anhydrocotarnineacetone.

On oxidising berberineacetone, $C_{23}H_{23}O_5N$, in acetone solution with aqueous permanganate, a new colourless compound, $C_{23}H_{23}O_6N$, containing one more atom of oxygen, resulted. This substance, which was isolated in a yield of about 45 per cent. of the theoretical, has been designated *neooxyberberineacetone*. Oxidation of berberineacetone would naturally be expected to take place at the double linking, and *neooxyberberineacetone* would then have the formula (II) or the tautomeric form (III). The first of these, however, is eliminated by the insolubility of the compound in aqueous sodium hydroxide, but formula (III) satisfactorily accounts for its behaviour and that of its derivatives:

On hydrolysing *neooxyberberineacetone* with dilute mineral acids, acetone is split off, and the salt of a quaternary base is produced, as is the case with all similarly constituted acetone-condensation products. The base obtained on treating this salt with alkali, however, is not the corresponding quaternary base, $C_{20}H_{19}O_6N$ (IV),

but a substance, $C_{20}H_{17}O_5N$, derived from it by the elimination of the elements of water. This compound is isomeric with oxyberberine and the *isooxyberberine* recently described by Bland, Perkin, and Robinson (Proc., 1911, **27**, 59), and has been designated *neooxyberberine* (V). Its formation from the enolic form of the quaternary base may be represented as follows:

This formula depicts *neooxyberberine* as a phenolbetaine, and this is justified by its behaviour, for it has the usual characteristics of such compounds (compare Decker and Dunant, *Annalen*, 1908, **358**, 296). Thus, it is golden-brown in colour, crystallises with a molecule of either alcohol or chloroform of crystallisation, and is liberated from its salts by means of sodium carbonate. Its salts with acids are of a much less intense colour than the base, and are derived from formula IV or the corresponding ketonic form by substitution. Definite proof of its phenolbetaine nature, however, is afforded by the fact that it yields with methyl iodide the iodide of a quaternary base containing three methoxyl groups, that is, one more than the parent compound. This substance, *methoxyberberinium iodide*, has the formula (VI) given below, and its

quaternary nature is shown by the fact that the corresponding base is not liberated by means of sodium carbonate, sodium hydroxide being requisite for this purpose.

neoOxyberberine also shows the behaviour, associated with phenolbetaines, of forming salts containing two molecules of the base to one of acid (compare Trans., 1910, **97**, 269); thus the hydrochloride has the formula $HO\cdot R:N\cdot O\cdot R:NCl$, although the hydriodide has the normal constitution $HO\cdot R:N\cdot I$.

*neo*Oxyberberine readily furnishes tetrahydroberberine (VII) in good yield when reduced by means of tin and hydrochloric acid:

The most remarkable property of this compound, however, is the facility with which it undergoes spontaneous oxidation when exposed to the air in chloroform solution. So large a quantity as 25 grams of *neo*oxyberberine (containing 1EtOH) appeared to be completely decomposed after exposure to the air for eighteen days, and the reaction product gave 1-keto-6:7-methylenedioxytetrahydroisoquinoline (VIII) in a yield amounting to 53 per cent. of the theoretical, together with a quantity of one of the ethyl hydrogen hemipinates, probably the 1-ester (IX). Small quantities of other crystalline products, and a considerable amount of amorphous material, were produced at the same time. The formation of the two compounds isolated may be represented as follows:

1-Keto-6:7-methylenedioxytetrahydroisoquinoline was, of course, one of the oxidation products of berberine isolated by Perkin (*loc. cit.*).

The degradation of *neo*oxyberberine in this manner recalls the analogous cleavage of the somewhat similarly constituted *N*-alkylisopapaverines (X) into veratraldehyde (XI) and dimethoxy-

N-alkylisoquinolones (XII), which Decker and Klauser (*Ber.*, 1904, 37, 520) effected by drawing air through dilute alkaline solutions:

EXPERIMENTAL.

The berberineacetone used in this investigation was prepared from commercial berberine sulphate by the method described by Gaze (*loc. cit.*). It melted and decomposed at 175° (corr.). (Found, C=70.0; H=5.9. Calc., C=70.2; H=5.9 per cent.)

Oxidation of Berberineacetone. Formation of neoOxyberberineacetone.

The oxidation of berberineacetone, $C_{23}H_{23}O_5N$, to neoxyberberineacetone, $C_{23}H_{23}O_6N$, involves the addition of one atom of oxygen. It has, however, been found advantageous to employ a quantity of permanganate corresponding with two atoms for the oxidation, and the following conditions have been found to give a satisfactory result.

Five and a-half grams of potassium permanganate were dissolved in 500 c.c. of water, and the solution was poured into a solution of 10 grams of berberineacetone in 500 c.c. of acetone at the laboratory temperature. The mixture was kept for fifteen minutes, then filtered from the separated manganese hydroxide, and the liquor somewhat evaporated on the water-bath. During the removal of the acetone, a quantity of crystals mixed with some resinous matter separated, and after nearly all the acetone had evaporated, the solid was collected, and ground with a little ethyl acetate, when 4.0 to 4.9 grams of neoxyberberineacetone, melting at 228—229° (corr.), were obtained. This product has a more or less marked buff colour, but is otherwise pure. It may be decolorised by crystallisation from alcohol, using animal charcoal.

neoOxyberberineacetone, $C_{23}H_{23}O_6N$ (III, p. 1691).

This base crystallises from absolute alcohol in colourless, transparent, hexagonal and trigonal plates, which melt and decompose at 228—229° (corr.), forming a dark red liquid. It is insoluble in water, and sparingly or very sparingly soluble in the usual organic

solvents, with the exception of warm chloroform, in which it is moderately easily soluble:

0.1527 gave 0.3773 CO_2 and 0.0786 H_2O . $\text{C}=67.4$; $\text{H}=5.8$.

0.1900 „ 5.8 c.c. N_2 at 24° and 770 mm. $\text{N}=3.6$.

$\text{C}_{23}\text{H}_{23}\text{O}_6\text{N}$ requires $\text{C}=67.5$; $\text{H}=5.7$; $\text{N}=3.4$ per cent.

This base dissolves to some extent in cold dilute hydrochloric acid, but soon crystallises out as a very sparingly soluble, colourless *hydrochloride*. When warmed with dilute hydrochloric acid, the base yields a yellow solution, and eventually yellow, silky needles consisting of *neoxyberberine semihydrochloride*. *neoOxyberberine-acetone* is not attacked by hot aqueous sodium hydroxide, in which it is insoluble.

neoOxyberberine, $\text{C}_{20}\text{H}_{17}\text{O}_5\text{N}$ (V, p. 1692).

Twelve grams of *neoxyberberineacetone* were boiled for two hours under a reflux condenser with 1.2 litres of 1 per cent. aqueous hydrochloric acid. The almost insoluble powder gradually dissolved, forming a deep canary-yellow solution, from which a large quantity of curved, silky, yellow needles separated while the boiling was still in progress. The needles, which decomposed at 227° (corr.), consisted of *neoxyberberine semihydrochloride*; they were not, however, collected, but converted into the base by adding 200 c.c. of 10 per cent. aqueous sodium hydroxide to the liquor and boiling it for another twenty minutes. The almost insoluble *neoxyberberine* was then collected, and crystallised from alcohol, when 9.6 grams of the pure base (containing 1EtOH) were obtained; this yield amounts to 84 per cent. of the theoretical.

neoOxyberberine crystallises from alcohol in long, golden-brown, prismatic needles, which contain one molecule of alcohol of crystallisation. It melts and decomposes at 275° (corr.), and is almost insoluble in boiling water, sparingly soluble in cold alcohol and most of the other usual organic solvents, but easily soluble in chloroform or hot alcohol:

0.1562 * lost 0.0176 at 100° . $\text{C}_2\text{H}_6\text{O}=11.3$.

0.1528 * gave 0.3702 CO_2 and 0.0800 H_2O . $\text{C}=66.1$; $\text{H}=5.9$.

$\text{C}_{20}\text{H}_{17}\text{O}_5\text{N}, \text{C}_2\text{H}_6\text{O}$ requires $\text{C}=66.5$; $\text{H}=5.8$; $\text{C}_2\text{H}_6\text{O}=11.6$ per cent.

0.1386 † gave 0.3469 CO_2 and 0.0615 H_2O . $\text{C}=68.3$; $\text{H}=5.0$.

0.1454 † „ 5.0 c.c. N_2 at 20° and 773 mm. $\text{N}=4.1$.

0.2102 † „ , by Zeisel's method, 0.2758 AgI. $\text{MeO}=17.3$.

$\text{C}_{20}\text{H}_{17}\text{O}_5\text{N}$ requires $\text{C}=68.3$; $\text{H}=4.9$; $\text{N}=4.0$;

$2\text{MeO}=17.7$ per cent.

* Air-dried.

† Dried at 100° .

The molecular weight was determined by the ebullioscopic method in glacial acetic acid:

0.2344 † in 16.75 gave Δt 0.11°. M.W. = 322.

0.4988 † „ 16.75 „ Δt 0.20°. M.W. = 377.

$C_{20}H_{17}O_5N$ requires M.W. = 351.

neoOxyberberine yields with acids sparingly soluble salts; it is insoluble in aqueous sodium hydroxide.

The *semihydrochloride* crystallises from water or alcohol in long, deep yellow, curved, silky needles, which decompose at 227° (corr.). It is very sparingly soluble in boiling water, and sparingly so in boiling alcohol. After crystallisation from water, and drying in the air, this salt has the composition $(C_{20}H_{17}O_5N)_2 \cdot HCl, 3H_2O$:

0.1378 * gave 0.3058 CO_2 and 0.0676 H_2O . C = 60.5; H = 5.5.

0.1566 * „ 0.0294 AgCl. Cl = 4.6.

0.1266 * lost 0.0090 at 110°. H_2O = 7.1.

$(C_{20}H_{17}O_5N)_2 \cdot HCl, 3H_2O$ requires C = 60.5; H = 5.2; Cl = 4.5;

H_2O = 6.8 per cent.

The *hydriodide* crystallises from water in deep yellow needles, which decompose at 275° (corr.). It is very sparingly soluble in water, and crystallises with $1H_2O$:

0.2555 * lost 0.0099 at 100°. H_2O = 4.0.

$C_{20}H_{17}O_5N \cdot HI, H_2O$ requires H_2O = 3.7 per cent.

0.2456 † gave 0.4532 CO_2 and 0.0834 H_2O . C = 50.3; H = 3.8.

0.3630 † „ 0.1780 AgI. I = 26.5.

$C_{20}H_{17}O_5N \cdot HI$ requires C = 50.1; H = 3.8; I = 26.5 per cent.

Methoxyberberinium Salts (VI, p. 1692).

Methoxyberberinium iodide was prepared in almost theoretical yield by heating *neooxyberberine* with methyl iodide in a sealed tube at 100° for two hours. It crystallises from boiling water, in which it is somewhat sparingly soluble, in golden-brown, prismatic plates, which melt to a black liquid at 256° (corr.), after sintering a few degrees earlier. It is anhydrous:

0.1651 gave 0.3086 CO_2 and 0.0634 H_2O . C = 51.0; H = 4.3.

0.1510 „ 0.0722 AgI. I = 25.8.

0.2158 „ , by Zeisel's method, 0.2989 AgI. MeO = 18.3.

$C_{21}H_{20}O_5NI$ requires C = 51.1; H = 4.1; I = 25.7;

3MeO = 18.9 per cent.

Methoxyberberinium chloride was prepared from the iodide by double decomposition with silver chloride. It is very readily soluble in water, and crystallises from this solvent in long, yellow needles, which contain 3 molecules of water of crystallisation, and

† Dried at 100°.

* Air-dried.

melt at about 117° (corr.). It suffers decomposition when heated at 100° :

0.4000 * lost 0.0470 in a vacuum over H_2SO_4 . $\text{H}_2\text{O} = 11.7$.

0.1982 * gave, by Zeisel's method, 0.2971 AgI. $\text{MeO} = 19.8$.

$\text{C}_{21}\text{H}_{20}\text{O}_5\text{NCl} \cdot 3\text{H}_2\text{O}$ requires $\text{H}_2\text{O} = 11.9$; $3\text{MeO} = 20.4$ per cent.

After being dried in a vacuum over sulphuric acid:

0.1331 gave 0.3040 CO_2 and 0.0619 H_2O . $\text{C} = 62.3$; $\text{H} = 5.2$.

$\text{C}_{21}\text{H}_{20}\text{O}_5\text{NCl}$ requires $\text{C} = 62.7$; $\text{H} = 5.0$ per cent.

Aqueous solutions of this salt remain clear on the addition of sodium carbonate, but give with sodium hydroxide a yellow, amorphous precipitate, which is readily extracted by ether.

*Reduction of neoOxyberberine. Formation of
Tetrahydroberberine.*

Ten grams of neoOxyberberine were reduced by boiling with granulated tin and a large excess of hydrochloric acid in alcoholic solution until the originally yellow liquid had become nearly colourless. The liquor was then decanted from the tin, sufficiently evaporated to remove most of the alcohol, and diluted with about twice its volume of water, when a tin double salt separated, which was at first amorphous, but quickly became crystalline. This was collected, dissolved in about a litre of boiling water, treated with hydrogen sulphide, filtered from tin sulphide, and precipitated with aqueous sodium carbonate, when an oil separated which became partly crystalline on scratching. When this product was boiled with a little alcohol, 6.0 grams of tetrahydroberberine remained as a nearly colourless, chalky solid, which melted at $168\text{--}169^{\circ}$ (corr.). The melting point of the base was unchanged by crystallising it from alcohol, and suffered no depression when the base was mixed with tetrahydroberberine prepared by the reduction of berberine. The identity of the base was further established by analysis (Found, $\text{C} = 70.7$; $\text{H} = 6.3$. Calc., $\text{C} = 70.8$; $\text{H} = 6.2$ per cent.), and also by the analysis of its hydrochloride, which crystallised from water in lozenge-shaped plates, melting and decomposing at $248\text{--}250^{\circ}$ (corr.). (Found, $\text{C} = 63.6$; $\text{H} = 6.0$; $\text{Cl} = 9.4$. Calc., $\text{C} = 63.9$; $\text{H} = 5.9$; $\text{Cl} = 9.4$ per cent.)

Spontaneous Oxidation of neoOxyberberine.

Twenty-five grams of neoOxyberberine (containing 1EtOH) were dissolved in 300 c.c. of chloroform, and kept for five weeks in a nearly full closed bottle in the dark. A considerable quantity of large, yellowish-brown plates gradually crystallised out, and proved to be neoOxyberberine containing a molecule of chloroform of crystal-

* Air-dried.

lisation. After being dried in the air overnight, the crystals were found to have slightly effluoresced, and on warming them, chloroform was readily given off:

0.2015 * lost 0.0487 at 100°. Loss = 24.2.

$C_{20}H_{17}O_5N$.CHCl₃ requires CHCl₃ = 25.4 per cent.

The crystals decomposed at 275° (corr.) when heated either alone or mixed with the base containing alcohol of crystallisation. The chloroform mother liquor left on evaporation a crystalline mass of *neo*oxyberberine in an almost pure condition (m. p. 260°). *neo*Oxyberberine is therefore not attacked by chloroform in the absence of air.

Twenty-five grams of *neo*oxyberberine (containing 1EtOH) were then dissolved in 300 c.c. of chloroform, and exposed to the air in a wide-mouthed glass bottle in a dark cupboard. After keeping for two days a drop of the solution readily gave a crystalline residue, but after five days only an amorphous residue was obtained in this way. The solution was exposed to the air for eighteen days in all, the chloroform lost on evaporation being replaced from time to time, and the original intense yellowish-brown colour gave place to a brown port-wine shade. The liquid was then filtered from a trace of yellow insoluble matter, extracted several times with dilute aqueous sodium carbonate to remove the acidic constituents, and the extract (*E*) set aside. The chloroform solution was then dried with anhydrous potassium carbonate, and evaporated nearly to dryness, when the residue became partly crystalline. It was mixed with a little benzene, filtered, and the residual pink, chalky, crystalline mass washed with benzene. From the filtrate only very small quantities of crystalline compounds were isolated, the chief constituent being a reddish-brown, amorphous substance. The air-dried, crystalline mass amounted to 8.3 grams, and melted at about 155°; on recrystallisation from benzene it gave first 4.8 grams of 1-keto-6:7-methylenedioxytetrahydroisoquinoline, melting at 185—186° (corr.). Perkin (*loc. cit.*) gives 181—182°. (Found, C = 62.4; H = 4.9. Calc., C = 62.8; H = 4.8 per cent.)

The benzene mother liquors gave on evaporation several small crops of crystals, melting at about 140°. On recrystallising these from water, however, a further 1.6 grams of 1-keto-6:7-methylenedioxytetrahydroisoquinoline separated, making in all 6.4 grams, that is, 53 per cent. of the theoretical; the aqueous mother liquors contained hemipinic acid.

The sodium carbonate extract (*E*) was acidified with hydrochloric acid, and completely extracted with ether. The ethereal extract was dried, and evaporated to low bulk, when 2.9 grams of 1-ethyl

* Air-dried.

hydrogen hemipinate separated in large, clear, colourless prisms, which melted at $148-149^{\circ}$ (corr.), after drying at 100° . The ethereal filtrate on evaporation to dryness gave 3.1 grams of a slightly sticky, pink, crystalline mass, and on recrystallising this from water, using animal charcoal, a further 1.3 grams of 1-ethyl hydrogen hemipinate were obtained in long, colourless needles, which contained $1\text{H}_2\text{O}$, and melted at $148-149^{\circ}$ (corr.), after drying at 100° . (Found, $\text{C}=56.5$; $\text{H}=5.6$. Calc., $\text{C}=56.7$; $\text{H}=5.6$ per cent.)

On saponifying this acid with 10 per cent. aqueous sodium hydroxide, acidifying, and extracting with ether, pure hemipinic acid was obtained. This melted and effervesced at $184-185^{\circ}$ (corr.), solidified again on cooling, and then melted at about 165° . (Found, $\text{C}=52.9$; $\text{H}=4.8$. Calc., $\text{C}=53.1$; $\text{H}=4.5$ per cent.)

The ethyl hydrogen hemipinate thus obtained gave no coloration with ferric chloride in aqueous solution. It is therefore described as the 1-ester, since Wegscheider (*Monatsh.*, 1895, **16**, 38) states that the 1- and 2-ethyl hydrogen hemipinates are distinguished by the fact that the 2-ester gives with ferric chloride in aqueous solution a yellow coloration and turbidity, whilst the 1-ester does not. The ethyl hydrogen hemipinate from *neooxyberberine* also agrees better in melting point with the 1-ester (m. p. $146.5-148.3^{\circ}$) than with the 2-ester (m. p. $144.5-145^{\circ}$). Wegscheider's 1-ester, however, contained no water of crystallisation, whilst the 2-ester crystallised from water in long needles containing $1\text{H}_2\text{O}$.

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