XVIII.—*Contributions to our Knowledge of the Aconite Alkaloids.* Part IX. *The Effect of Heat on Aconitine and some of its Derivatives. Formation of Pyraconitine.*

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IN Part I of these contributions, the observation was recorded that when aconitine is heated at its melting point, 188—189°, a volatile compound escapes, the alkaloid losing about 10 per cent. in weight. At first it was conjectured that this might be due to the loss of benzoic anhydride and the formation of aconine. Further investigation has shown, however, that the decomposition is of a wholly

different kind, and that a new alkaloid is produced which, having regard to its mode of origin, we propose to name *pyraconitine*.

By heating in a paraffin bath a weighed quantity of pure aconitine at its melting point ($189-190^{\circ}$), the alkaloid being contained in a small bulb-tube, having a small U-tube sealed on so as to act as a condenser, it was ascertained that *acetic acid* distilled over. By conducting the last stage of this operation in a slow current of air, it was proved, by titrating the distillate with standard alkali, that 9.28 per cent. of the acid is given off from the alkaloid; the loss, determined by weighing the residue, is represented by almost the same percentage, namely 9.96; weight of aconitine, 1.5079; weight of residue, 1.3577 = 9.96 per cent. The loss of 1 molecular proportion of acetic acid by 1 molecular proportion of aconitine corresponds with 9.27 per cent., a number which is in close agreement with the experimental results. A minute quantity of benzoic acid also passes over, but the amount is almost inappreciable if the temperature is not allowed to rise during the experiment. The identity of the acetic acid was conclusively proved by converting it into the silver salt and submitting this to analysis. Silver salt, 0.1722 gram; silver, 0.1112 gram = 64.58 per cent. Calculated for silver acetate, 64.66 per cent.

The production of acetic acid from aconitine was not to be inferred from previous knowledge of the properties of this alkaloid. Wright has stated that benzoic acid is the only acid formed when aconitine is hydrolysed. This benzoic acid which so readily separates on hydrolysis is not detached from aconitine when it is heated at its melting point. There is no doubt that aconitine contains one benzoyl group, and that the acetic acid is derived from an acetyl group. Further investigation has shown that aconitine must be regarded as *acetylbenzoylaconine*, and our so-called "isaconitine" as *benzoylaconine*; for we shall prove in our next paper that one molecular proportion of acetic acid separates when the one alkaloid changes into the other, and also when aconitine is hydrolysed.

Composition and Properties of Pyraconitine.

The dark-coloured alkaloidal residue remaining after the distillation was dissolved in dilute sulphuric acid and the solution filtered; dilute ammonia was then added in slight excess, and the liquid extracted several times with ether. The alkaloid was removed from the ethereal solution by shaking it with very dilute hydrobromic acid, and the acid liquid precipitated in fractions by the addition of dilute ammonia in order to remove the brown colouring matter, which

accumulated in the first and second precipitates; excess of ammonia was then added to the colourless solution, and the alkaloïd extracted with ether. When the dry ethereal solution was spontaneously evaporated, it left a varnish-like residue of base which refused to crystallise; it was therefore dissolved in dilute hydrobromic acid, and the neutral liquid slowly evaporated in a desiccator. No crystalline salt separated. The dry residue was next dissolved in absolute alcohol, and the clear solution mixed with anhydrous ether until it became slightly turbid. The small, white crystals of the hydrobromide which separated from this mixture melted at 280° , and still melted at the same temperature after recrystallisation. On adding soda in slight excess to the solution of the pure salt, and extracting with ether, white slender needles (m. p. 167.5° corr.) of the base were obtained by the slow evaporation of the ethereal solution. The crystals are sparingly soluble in water, but readily in alcohol, chloroform, and ether. The aqueous solution is slightly bitter, but with a somewhat burning after-taste. The solution in anhydrous alcohol is without action on polarised light; although some specimens examined, probably not quite pure, exerted a feeble dextrorotation, and others a feeble lævorotation. The base readily dissolves in acids, forming salts which are difficult to obtain well crystallised from an aqueous solution, but separate in well-defined crystals from solution in a mixture of anhydrous alcohol and ether.

Pyraconitine hydrobromide $C_{31}H_{41}NO_{10} \cdot HBr$ separates in anhydrous crystals from a mixture of alcohol and ether, and melts at 280° (corr.). It is soluble in water and in alcohol.

0.2289 of salt gave 0.0624 $AgBr$. $Br = 11.6$.

$C_{31}H_{41}NO_{10} \cdot HBr$ requires $Br = 11.97$ per cent.

On some occasions crystals of this salt, possibly hydrate have been obtained, melting at 204° . When burned in a stream of oxygen, the salt furnished the following data.

0.1452 gave 0.2975 CO_2 and 0.08349 H_2O . $C = 55.87$; $H = 6.38$.

0.1314 „ 0.2685 „ „ 0.0731 „ $C = 55.72$; $H = 6.18$.

Calculated for $C_{31}H_{41}NO_{10} \cdot HBr$. $C = 55.69$; $H = 6.28$ per cent.

„ „ $C_{31}H_{39}NO_{10} \cdot HBr$. $C = 55.85$; $H = 6.0$ „

Of the two probable formulæ for aconitine (Part I), namely, $C_{33}H_{43}NO_{12}$ and $C_{33}H_{45}NO_{12}$, these analyses agree better, perhaps, with the formula for pyraconitine derived from $C_{31}H_{39}NO_{10}$. However, until more decisive evidence has been obtained on this point we shall retain the formula $C_{31}H_{41}NO_{10}$.

The equation representing the production of pyraconitine from aconitine is therefore

Pyracnitine hydrobromide is lævorotatory. A determination of this specific rotation in aqueous solution gave the following result.

$$\alpha[15^\circ] = -2^\circ; l = 2 \text{ dm.}; c = 2.1364,$$

$$\text{whence } \frac{2 \times 100}{2 \times 2.1368} = [\alpha]_D = -46.8^\circ.$$

Pyracnitine hydrochloride, $\text{C}_{31}\text{H}_{41}\text{NO}_{10}\text{HCl}$, crystallises in rosettes from a mixture of alcohol and ether. It melts at 248.75° (corr.).

Pyracnitine hydriodide, $\text{C}_{31}\text{H}_{41}\text{NO}_{10}\text{HI}$, also crystallises from a mixture of alcohol and ether in colourless rosettes, which are apt to become yellowish on standing. They melt sharply at 220.5° (corr.), and can be crystallised (in prisms) from aqueous solution more readily than the hydrochloride or hydrobromide.

The salts of pyracnitine are somewhat bitter, and are apparently not toxic in small doses. The exact physiological action of this alkaloid is being investigated by Professor Cash, F.R.S.

Pyracnitine aurichloride, $\text{C}_{31}\text{H}_{41}\text{NO}_{10}\text{HAuCl}_4$, is thrown down as a pale yellow precipitate, when auric chloride is added to a solution of the hydrochloride; all attempts to crystallise this salt have hitherto failed. Experiments have been made with the view of preparing an aurichlor-derivative from it similar to that producible in the case of isaconitine, but the pyracnitine compound exhibits no tendency to form such a derivative.

Hydrolysis of Pyracnitine.

Pyracnitine and its salts readily undergo hydrolysis when heated with water and acids, or when allowed to remain in contact with fixed alkalis. When soda is added to an aqueous solution of a salt of pyracnitine, the alkaloid is thrown down in white flocks, which gradually dissolve if excess of alkali is added, owing to the rapidity with which hydrolysis occurs; nothing is obtained from the solution on distillation, but ether extracts from it an alkaloid *pyracnine*, which remains as an uncrystallisable varnish when the ether is evaporated. The residual alkaline solution furnishes *benzoic acid* when acidified, but no other acid product; by estimating this, it has been found that the benzoic acid produced amounts to 17.91 per cent. of the pyracnitine. The amount calculated from the equation

is 18.26 per cent. It therefore appears that the benzoyl group of aconitine is present in pyracnitine, which, like aconitine, undergoes

hydrolysis, losing its benzoyl group as benzoic acid, and furnishing a new base which it will be convenient, following the analogy of aconitine, to name pyraconine.

Composition and Properties of Pyraconine.

Pyraconine is an amorphous base resembling aconine in its properties. It is readily soluble in water and also in ether: in the latter respect it differs from aconine. The aqueous solution has a somewhat sweet taste, and is lævorotatory. A determination of the specific rotation gave the following data.

$$\alpha[15^\circ] = -2.04^\circ; l = 2 \text{ dm.}; c = 1.121,$$

whence
$$\frac{2.04 \times 100}{1.121 \times 2} = [\alpha]_D = -90.99^\circ.$$

Pyraconine combines with acids, forming salts which are very soluble in water. They crystallise more or less readily from their aqueous solutions, but are more easily obtained in well-defined crystals from a mixture of alcohol and ether.

Pyraconine hydrochloride, $C_{24}H_{37}NO_9 \cdot HCl$, crystallises in cubes with $1H_2O$, which is lost at 100° . They melt at 154° (corr.), and are very soluble both in alcohol and in water. The aqueous solution is lævorotatory. In determining the specific rotation the following results were obtained.

$$\alpha[15^\circ] = -4.4^\circ; l = 2 \text{ dm.}; c = 1.9595,$$

whence
$$\frac{100 \times 4.4}{1.9595 \times 2} = [\alpha]_D = -102.07.$$

Unlike aconitine, isaconitine, and aconine, the specific rotation of pyraconine and its salts have the same sign, both are lævorotatory.

This salt was burned for the determination of the carbon and hydrogen, and the water and chlorine were also estimated, with the following results.

0.1266 gave 0.2462 CO_2 and 0.0881 H_2O . $C = 53.03$; $H = 7.73$.

0.1097 „ 0.2154 „ „ 0.078 „ $C = 53.55$; $H = 7.9$.

0.2924 lost 0.0087 of water. $H_2O = 2.97$.

0.2837 gave 0.0756 $AgCl$. $Cl = 6.57$.

$C_{24}H_{37}NO_9 \cdot HCl \cdot H_2O$ requires $C = 53.59$; $H = 7.44$; $H_2O = 3.37$;
 $Cl = 6.58$ per cent.

Pyraconine aurichloride, $C_{24}H_{37}NO_9 \cdot HAuCl_4$, is thrown down as a yellow, amorphous precipitate, which quickly aggregates to a sticky mass, when auric chloride is added to a strong solution of pyraconine hydrochloride. If this salt crystallises at all, it does so only with great difficulty. Crystals have only once been obtained, and then

not in quantity sufficient to enable us to ascertain that they consisted of the aurichloride. As a rule, it separates from solvents as an oil.

From the observations recorded in the foregoing account, it will be seen that pyraconitine bears little resemblance to aconitine, but exhibits some affinities with isaconitine; the salts of pyraconitine, however, melt as a rule at lower temperatures, and show greater rotatory-power, than those of isaconitine. Moreover, pyraconitine does not possess the peculiar property of forming an aurichlor-derivative so characteristic of isaconitine.

Pyraconine, the product of the hydrolysis of pyraconitine, somewhat closely resembles aconine, the hydrolytic product of both aconitine and isaconitine. It differs from aconine, however, in several respects, notably in its rotatory power, and that of its salts, as well as in its solubility in ether.

Action of Heat on Aconitine Salts.—We find that the salts of aconitine, like aconitine itself, lose acetic acid when they are heated at about 190° . The acetate of aconitine requires rather a higher temperature for its decomposition, acetic acid not being evolved until the salt has been heated to a temperature of nearly 198° .

Action of Heat on Isaconitine.—Having fully made out the mode of action of heat on aconitine, it became of considerable interest to ascertain how far isaconitine resembled it in this respect. About 1 gram of the pure colourless amorphous base was gradually heated in a paraffin bath. At 115° , the alkaloid fused to a clear liquid, which underwent nothing more than a darkening in colour on raising the temperature to about 200° ; slightly above this decomposition set in, attended with effervescence, and a colourless liquid distilled, consisting chiefly of water; no acetic acid was obtained, in fact, the distillate was not acid to test-paper. A further important constitutional difference between aconitine and isaconitine is thus brought to light, which is explained by the results recorded in a subsequent paper.

Action of Heat on Aconine.—As the usual formula of aconine, $C_{26}H_{41}NO_{11}$, differs from that of pyraconine, $C_{24}H_{37}NO_9$, by the elements of acetic acid, $C_2H_4O_2$, and, moreover, as, according to Wright, only aconine and benzoic acid are obtained by the hydrolysis of aconitine, aconine when heated should lose acetic acid and furnish pyraconine, for we have shown that aconitine when heated loses acetic acid forming pyraconitine, which, on hydrolysis, loses benzoic acid producing pyraconine. When pure dry aconine is gradually heated in a paraffin bath, it fuses to a clear liquid at 120° ; as soon as the temperature has risen to 190° , the liquid darkens, and at a somewhat higher temperature begins to effervesce, the vapours evolved

condensing in the receiver to a colourless liquid. On examination, this was found to be chiefly water; no acetic acid was present, the liquid not being acid to test-paper. By weighing the dark-coloured residue of alkaloid it was ascertained that the aconine had lost nearly 10 per cent. in weight; this residue, when heated at about 250°, decomposed completely. The fact that aconine does not give acetic acid on heating points to the conclusion that this acid must have been split off in its formation from aconitine. We have shown in previous communications that both aconitine and isaconitine undergo hydrolysis, aconine being the basic product in each case. In a subsequent paper we show that when aconitine passes into isaconitine, it loses acetic acid. Synthetical experiments are being made to test the accuracy of this new view of the constitution of "aconitine" and "isaconitine," which would represent pyraconitine as the anhydro-derivative of the latter alkaloid.

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