CXCVII.—*The Constitution of Aconitine.*

By OSCAR LISLE BRADY.

THERE has been considerable controversy over the empirical formula of aconitine, but that proposed by Freund and Beck (*Ber.*, 1894, **27**, 433) is now most generally accepted, namely, $C_{34}H_{47}O_{11}N$, although Schulze (*Apoth. Zeit.*, 1904, **18**, 783; 1905, **20**, 368) has recently proposed $C_{34}H_{45}O_{11}N$. There seems, however, no reason at present for departing from the formula of Freund and Beck, at least for aconitine of German origin; Dunstan (T., 1905, **87**, 1653), however, maintains that the alkaloid from English sources has a different composition. The aconitine used in this investigation was procured in Germany, and corresponds in properties with the substance described by Freund and Beck; consequently the formula suggested by these authors is used throughout this paper.

Aconitine has been shown to possess four methoxyl groups, three hydroxyl groups, one *N*-methyl, one acetyl, and one benzoyl group, but of the constitution of the rest of the molecule little is known, although Ehrenberg and Purfürst (*J. pr. Chem.*, 1892, [ii], **45**, 605), by the distillation of aconine (the product of the hydrolysis of aconitine) with barium hydroxide, obtained what they believed to be quinoline or tetrahydroquinoline, indicating that aconitine belonged to the quinoline group of alkaloids. Carr (T., 1912, **101**, 2241) has described a compound, to which he has given the name oxonitin, obtained by the decomposition of aconitine permanganate with dilute sulphuric acid at 40°. The present author (compare P., 1912, **28**, 289) obtained this compound independently, in small yield, by warming to 80° a solution of aconitine in excess of dilute sulphuric acid with potassium permanganate. When aconitine itself is acted on by a neutral solution of potassium permanganate there is obtained a compound very similar to oxonitin, and on account of its general resemblance to that compound (particularly with regard to their melting points) it was at first regarded

by the author as identical with oxonitin. As considerably better yields of this compound were obtained it was employed in the greater portion of the author's earlier work, and the analytical figures published (*loc. cit.*), with the exception of the percentages of carbon and hydrogen, were obtained from this substance. It now appears, however, that the compound obtained by the oxidation of aconitine with neutral permanganate is not identical with oxonitin, but contains a larger percentage of carbon, as can be seen from the following table of analytical results:

	Mean of figures given by Carr (<i>loc. cit.</i>).	Preparation of oxonitin by author using Carr's method.	Author's original preparation of oxonitin in acid solution.	Oxidation with neutral permanganate crystallised from methyl alcohol and chloroform.	Last substance after a further crystallisation.
C	59·3	59·6	59·5	60·7	60·6
H	6·5	6·3	6·4	6·5	6·7
N	3·2	—	—	3·2	—
OMe ...	19·3	—	—	18·2	—

This new compound has been assigned the formula $C_{24}H_{26}O_9N$. It still retains the acetyl and benzoyl groups of aconitine; it is insoluble in most organic solvents, but dissolves more readily in chloroform than does oxonitin; it is also soluble in concentrated hydrochloric acid, being precipitated on dilution. When placed in the bath at 250° it melts and decomposes at 274° , and does not appreciably depress the melting point of oxonitin. As, however, the melting points of both these compounds depend largely on the rate of heating and are attended with decomposition, in the opinion of the author no justifiable conclusion can be drawn from their mixed melting point. The compound is a neutral substance combining with neither acids or alkalis; its solution in concentrated hydrochloric acid gives no precipitate with platinic chloride, whilst phenylhydrazine, semicarbazide, and hydroxylamine are without action on it.

By the action of nitric acid on aconitine an orange-yellow, crystalline substance melting at 205° has been obtained, to which it is proposed to assign the formula $C_{22}H_{26}O_{11}N_2$. This compound is a carboxylic acid dissolving readily in alkalis, and forming an amorphous silver salt. On warming an alkaline solution a small quantity of dimethylamine is evolved, the liquid darkens in colour, and mineral acids no longer give a precipitate with the solution; alkaline permanganate apparently decomposes the compound completely, dimethylamine is evolved, and acetic and benzoic acids are the only substances recoverable from the mixture.

The compound contains two methoxyl groups, and gives Liebermann's characteristic nitroso-reaction; hydrolysis with alkalis

yields acetic and benzoic acids, so that the acetyl and benzoyl groups of aconitine are still present. Titration with *N*/10-alkali indicates the presence of two carboxyl groups, two equivalents of the base being neutralised.

In consideration of the above facts, and presuming that the *N*-methyl group of the aconitine has not been affected, the formula may be written:

This compound is of a comparatively simple nature, and the structure of the remaining part of the molecule should not be difficult to determine.

The position of the nitroso-group is at present uncertain, although it is possible that the compound is a nitrosoamine produced by the rupture of a nitrogenous ring and addition of the nitroso-group by the nitrous acid formed in quantity during the oxidation, thus:

The marked colour change, however (see p. 1825), observed during the preparation of this compound may be due to the formation of a nitrosoamine, and subsequent wandering of the nitroso-group into a nucleus.

It is noteworthy that the benzoyl group is not readily removed from this compound, and by boiling with 50 per cent. sulphuric acid for some hours under reflux and subsequent oxidation with hydrogen peroxide a compound melting at 269° has been obtained, which still contains the benzoyl group. This is being further investigated. The action of other oxidising agents on aconitine has also been tried, but so far without satisfactory results.

Alkaline ferricyanide, Caro's acid, hydrogen peroxide, or chromic acid in glacial acetic acid yielded nothing definite, whilst sodium hypobromite acted so vigorously, even in the cold, that the aconitine was completely decomposed.

When an aqueous solution of chromic acid is added to a solution of aconitine in dilute sulphuric acid a yellow precipitate of the dichromate, $\text{C}_{34}\text{H}_{47}\text{O}_{11}\text{N}_2\text{H}_2\text{Cr}_2\text{O}_7$, is obtained, which on gentle warming in the solution forms a viscid mass. From the further investigation of this dichromate a small quantity of a crystalline substance resembling oxonitin has been obtained, but the amount

was too small for identification; beyond this, only benzoic and acetic acids have been separated.

EXPERIMENTAL.

Oxidation of Aconitine with Acid Permanganate.—The aconitine was dissolved in excess of dilute sulphuric acid, warmed to 80° , and potassium permanganate added from time to time until there was a slight effervescence. The crystalline precipitate was collected, suspended in water, and saturated with sulphur dioxide to remove traces of manganese oxides, collected, and recrystallised from a mixture of methyl alcohol and chloroform. This substance proved to be the oxonitin described by Carr (*loc. cit.*). (Found, $C=59.5$; $H=6.4$. $C_{23}H_{29}O_9N$ requires $C=59.6$; $H=6.2$ per cent.)

The yields obtained were very poor, being usually not more than 3 per cent. of the aconitine taken.

Oxidation of Aconitine with Neutral Permanganate.—Ten grams of aconitine were suspended in water, 2 grams of finely-powdered potassium permanganate added, and the mixture was gently warmed on a water-bath, when a vigorous action took place almost at once, acetaldehyde being evolved and a copious precipitate of brown oxides of manganese being formed. The liquid was filtered and the precipitate suspended in water, and the whole saturated with sulphur dioxide to dissolve the oxides of manganese. There remained suspended in the liquid a fine, crystalline substance, which was collected and recrystallised from chloroform and methyl alcohol:

0.1010 gave 0.2250 CO_2 and 0.0591 H_2O . $C=60.7$; $H=6.5$.

After again recrystallising:

0.1146 gave 0.2548 CO_2 and 0.0691 H_2O . $C=60.6$; $H=6.6$.

0.3580 „ 10 c.c. N_2 at 21° and 753 mm. $N=3.2$.

0.3266 „ 0.4508 AgI. $OMe=18.2$.

$C_{24}H_{29}O_9N$ requires $C=60.6$; $H=6.1$; $N=2.9$;

$3OMe=19.5$ per cent.

The molecular weight was determined by the ebullioscopic method in chloroform:

0.1530 in 19.7954 gave $E=0.065^{\circ}$. $M.W.=431$.

The substance melted at 272° if placed in the bath previously heated to 250° . The yield was not very satisfactory, being but 10–15 per cent. of the aconitine used.

Small quantities of a number of other substances have been obtained from the mother liquors of the acid and neutral oxidation of aconitine. One was insoluble and contained no nitrogen, and appeared to be an aldehyde; analysis of an impure specimen gave

C=63·2; H=5·9 per cent.; insufficient was, however, obtained for a more complete investigation. Another product was very soluble in water, and gave with bromine water a yellow precipitate of a bromo-derivative, which on collection dried to a sticky varnish, and was not further examined.

Action of Nitric Acid on Aconitine.—Fifteen grams of aconitine were dissolved in 100 c.c. of nitric acid (D 1·43) and heated on the water-bath. There was a copious evolution of brown nitrous gases, and at the end of an hour the mixture was poured into water. A copious, white precipitate was formed, which changed after a few minutes to a bright orange-yellow. The precipitate was collected, thoroughly washed with water, and crystallised from alcohol, when it formed an orange-yellow, crystalline powder, melting at 205°:

0·1602 gave 0·1966 CO₂ and 0·0517 H₂O. C=53·5; H=5·7.

0·1032 „ 0·2039 CO₂ „ 0·0516 H₂O. C=53·8; H=5·5.

0·1792 „ 8·8 c.c. N₂ at 20° and 773 mm. N=5·8.

0·1646 „ 0·1536 AgI. OMe=12·4.

C₂₂H₂₆O₁₁N₂ requires C=53·4; H=5·2; N=5·6;
2OMe=12·5 per cent.

The substance gave an abnormal depression of the freezing point in phenol, but 0·2722 in 8·569 of naphthalene gave $\Delta t = -0·445^\circ$. M.W.=494.

0·2700, dissolved in the cold in 50 c.c. of *N*/10-sodium hydroxide, required 39·7 c.c. *N*/10-sulphuric acid to neutralise the excess of sodium hydroxide, showing 10·3 c.c. used. Theory for 2CO₂H=10·8 c.c.

By adding silver nitrate to a solution of the substance in ammonia a yellow, amorphous precipitate of a silver salt was obtained, which deflagrated on heating:

0·1160 gave 0·0358 Ag. Ag=30·8.

C₂₂H₂₄O₁₁N₂Ag₂ requires Ag=30·5 per cent.

This substance when heated with alkaline permanganate evolved dimethylamine, but only acetic and benzoic acids could be recovered from the solution. The dimethylamine was identified by absorption in hydrochloric acid and preparation and analysis of its platinichloride. (Found, Pt=39·3. Calc., Pt=39·0 per cent.)

The compound dissolved readily in alkalis to form a yellow solution, which on warming darkened in colour, a small quantity of dimethylamine being evolved, and the substance could no longer be recovered unchanged from the liquid. After boiling for some time under reflux, acidifying, and distilling in a current of steam, benzoic and acetic acids were identified in the distillate, but ether extracted only a small quantity of a tarry matter from the solution.

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Aconitine Dichromate.—An aqueous solution of chromic acid was added to a solution of aconitine in dilute sulphuric acid, and the yellow precipitate formed was rapidly filtered and dried in a vacuum. Analysis indicated that this substance was aconitine dichromate contaminated with inorganic matter.

Found: C=44·8; H=5·0; Cr₂O₃=18·7.

C₃₄H₄₇O₁₁N, H₂Cr₂O₇ requires C=47·2; H=5·6;

Cr₂O₃=17·6 per cent.

It was found impossible to purify this substance owing to its instability; on gentle warming it gives a dark viscid substance, from which no further results could be obtained.

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