17. *Aconitine. Part I. Oxonitin and the Oxidation of Aconitine with Nitric Acid and Chromic Acid.*

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OXONITIN, one of the only two previously described oxidation products of aconitine, has now been known for 25 years, but its formula is still undecided. The original C_{23} formula of Carr (J., 1912, **101**, 2241) and those of Brady (J., 1913, **103**, 1821), Barger and Field (J., 1915, **107**, 231), and Majima and Suginome (*Ber.*, 1925, **58**, 2047) were recognised by Späth and Galinovsky (*Ber.*, 1930, **63**, 2994) and Henry and Sharp (J., 1931, 581) to be too small. Whilst, however, Späth and Galinovsky proposed $C_{32}H_{43}O_{12}N$, Henry and Sharp preferred $C_{31}H_{39}O_{12}N$, and were supported in this by further observations of Majima and co-workers (*Ber.*, 1932, **65**, 595), the question turning on whether the molecule did or did not contain a methylimide group.

Späth and Galinovsky (*Ber.*, 1931, **64**, 2201) pointed out that failure to obtain the theoretical quantity of silver iodide in the methylimide determination might not indicate the absence of such a group and instanced other similar cases. They pointed out that, on the C_{32} formula, the liberation of acetaldehyde in this oxidation noted by Carr would imply that the methylimide group remained unaffected.

The analytical results now presented, obtained with oxonitin prepared in this laboratory, are in agreement with the formula of Späth and Galinovsky. No more than traces of silver iodide, however, could be obtained in the methylimide determination. It would appear, therefore, that the evidence for the presence of this group is somewhat scanty, and that, in view of the poor yields of oxonitin obtained by Carr, the acetaldehyde need not be a product of the oxonitin oxidation in particular, and should therefore not be admitted as evidence in the question under consideration.

Oxonitin oxidised with nitric acid in acetic acid solution has been shown to yield a crystalline acidic *compound* with the loss of a methoxyl group. To the compound, which gives Liebermann's nitroso-reaction, and probably contains a nitro-group in addition, the formula $C_{31}H_{35}O_{14}N_3$ has been ascribed.

By the action of chromic acid on aconine, Schulze (*Arch. Pharm.*, 1908, **246**, 281) obtained a base, $C_{24}H_{35}O_8N$, and a substance, $C_{24}H_{33}O_9N$, with amphoteric properties. A base, $C_{30}H_{37}O_9N$, for which the name *aconitoline* is proposed, has now been obtained by the action of chromic acid on aconitine dissolved in acetone. It contains one methoxyl and two hydroxyl groups less than the parent alkaloid, and would therefore appear to be derived by the oxidation of some other part of the molecule than that concerned in the oxonitin oxidation. Attempts to acetylate the remaining hydroxyl group were unsuccessful, the initial material being unchanged. The formula of aconitoline may be extended thus:

$$C_{17}H_{16}O(CH_3{\cdot}CO{\cdot}O)(C_6H_5{\cdot}CO{\cdot}O)(N{\cdot}CH_3)(OH)(O{\cdot}CH_3)_3.$$

In view of the difficulty of isolating the hydrolysis product of aconitine on account of its great solubility in water, it was thought desirable to try the action of hydrolysing agents on aconitoline. By the action of sodium ethoxide, benzoic acid was split off, leaving a hygroscopic base, $C_{23}H_{33}O_8N$; this could be readily crystallised as the *hydrochloride*, $C_{23}H_{33}O_8N,HCl,3H_2O$, the water of crystallisation of which was not removable below 150°. Prolonged heating with sodium ethoxide did not further hydrolyse this compound. The base on acetylation yielded a crystalline *diacetyl* derivative, showing the presence of two hydroxyl groups.

By the action of dilute nitric acid on aconitine, a crystalline *acid*, $C_{31}H_{35}O_{13}N_3$, containing a nitroso-group was obtained. The formula may be extended thus: $C_{18}H_{16}N(O{\cdot}CH_3)_3(NO_2)(NO)(C_6H_5{\cdot}CO{\cdot}O)(CH_3{\cdot}CO{\cdot}O)(CO{\cdot}OH)(OH)$. The acid contains three of the four methoxyl and one of the three hydroxyl groups present in the aconitine molecule, the methylimide group also having been lost. In view of the similarity in formula of this compound and the product obtained by the action of nitric acid on oxonitin, the oxonitin oxidation and that of aconitine with nitric acid may be concerned with the same part of the molecule.

By the action of anhydrous hydrogen chloride on a suspension of the nitroso-acid in alcohol, the nitroso-group was removed, yielding a crystalline *hydrochloride* of an amino-acid, $C_{31}H_{36}O_{12}N_2,HCl,2H_2O$.

By the hydrolysis of the nitroso-acid $C_{31}H_{35}O_{13}N_3$ with alcoholic barium hydroxide (compare Majima and Suginome, *loc. cit.*), benzoic and acetic acids were removed, giving the water-soluble *derivative* $C_{22}H_{29}O_{11}N_3$.

Aconitoline, oxidised with nitric acid under the same conditions as aconitine, yielded a corresponding *nitroso-acid*, $C_{29}H_{33}O_{13}N_3$, the methylimide group having been lost. With anhydrous hydrogen chloride the nitroso-group could be removed, giving an *amino-acid* $C_{29}H_{34}O_{12}N_2$, which yielded, on hydrolysis of the benzoyl group with sodium ethoxide, the crystalline *hydrochloride* of an amino-acid $C_{22}H_{30}O_{11}N_2$. The free amino-acid was not obtained crystalline.

By the action of nitrous acid on aconitine dissolved in acetic acid, a crystalline *nitroso*-compound, $C_{31}H_{40}O_{12}N_2$, was obtained in rather poor yield.

The preparation of the derivatives described above facilitates the characterisation of the three oxidation products, oxonitin, aconitoline, and the nitroso-acid. Although no deep-seated decomposition products of the aconitine molecule have been obtained, the formation of the nitro-nitroso-derivative may possibly indicate the presence of a tetrahydroquinoline system in the molecule.

Experimental.

Oxonitin was prepared by Barger and Field's method (*loc. cit.*), except that no acetic acid was used to keep the acetone neutral during the oxidation; the yield from 5 g. of aconitine was 2·4 g., m. p. 278° (decomp.) (Found: C, 60·9, 60·6, 60·8, 61·1; H, 6·85, 6·8, 6·9, 6·7; N, 2·5, 2·3, 2·2, 2·2; OMe, 19·7, 19·8. Calc. for $C_{32}H_{43}O_{12}N$: C, 60·6; H, 6·8; N, 2·2; 4OMe, 19·6%).

Oxidation of Oxonitin with Nitric Acid.—Oxonitin (1 g.), suspended in glacial acetic acid (5 c.c.), dissolved when heated with concentrated nitric acid (5 c.c.) on the steam-bath. After brown fumes ceased to be evolved, the product was poured into water, collected, and crystallised from alcohol–acetone, forming stout, pale yellow prisms, m. p. 263° (decomp.) (Found: C, 55·3, 55·5; H, 5·4, 5·4; N, 6·1, 6·0; OMe, 13·4; NMe, nil. $C_{31}H_{35}O_{14}N_3$ requires C, 55·3; H, 5·2; N, 6·2; 3OMe, 13·8%).

Aconitoline.—Aconitine (5 g.) was dissolved in purified acetone (50 c.c.) and chromic acid (5 g.), dissolved in acetone (50 c.c.), was added. After 3 days the acetone was allowed to evaporate and the residue was dissolved in sulphurous acid. The solution was shaken with ether to remove a neutral substance, made alkaline with sodium carbonate, and extracted with ether; evaporation of the ether left a syrup, which crystallised from alcohol in prisms (2·3 g.), m. p. 220° (Found: C, 64·6, 65·1, 64·5, 65·0; H, 6·8, 6·8, 6·8, 6·8; N, 2·5, 2·5, 2·7, 2·6; OMe, 15·15, 15·4; NMe, 5·0; active H, 0·179, 0·198. $C_{30}H_{37}O_9N$ requires C, 64·9; H, 6·85; N, 2·5; 3OMe, 16·7; NMe, 5·4%; 1 active H, 0·180). *Aconitoline* was much less stable to alkaline potassium permanganate than the parent alkaloid.

Hydrolysis of Aconitoline.—Four times the theoretical amount of sodium ethoxide in ethyl alcohol was added to an alcoholic solution of aconitoline, and the mixture warmed for a few minutes on the water-bath. The solution was neutralised with dilute hydrochloric acid, the sodium chloride removed, the filtrate evaporated under reduced pressure, and the residue dissolved in water and extracted with ether to remove benzoic acid. On evaporation under reduced pressure, the product separated in fine needles, which were recrystallised from aqueous alcohol; m. p. 222° (Found: C, 51·5; H, 7·5; N, 2·4; Cl, 6·4; no loss in a vacuum at 100°. $C_{23}H_{33}O_8N,HCl,3H_2O$ requires C, 50·9; H, 7·4; N, 2·6; Cl, 6·55%). The free base could not be obtained crystalline; it distilled unchanged in a high vacuum. When it was heated with hydrochloric acid, the acetyl group was removed, but no crystalline product could be isolated. The base on treatment with acetic anhydride and sulphuric acid gave a *diacetyl* derivative crystallising in needles, m. p. 239° (Found: C, 60·25; H, 6·9; N, 2·5. $C_{27}H_{37}O_{10}N$ requires C, 60·6; H, 6·9; N, 2·6%).

Oxidation of Aconitine with Nitric Acid.—A mixture of nitric acid (50 c.c., *d* 1·2) and aconitine (5 g.) was heated under reflux on the steam-bath till brown fumes ceased to be evolved and the substance which separated had become crystalline (2 hours). Water (200 c.c.) was then added, and the product (3·4 g.) collected; it crystallised from alcohol–acetone in pale yellow prisms, m. p. 268° (decomp.) (Found: C, 56·4, 56·35; H, 5·4, 5·4; N, 6·45, 6·3; OMe, 13·0; NMe, nil. $C_{31}H_{35}O_{13}N_3$ requires C, 56·6; H, 5·4; N, 6·4; 3OMe, 14·15%). The *acid* gave the Liebermann nitroso-reaction, dissolved in alkali to give a brown solution, and was precipitated again by acid.

Hydrolysis of the Acid $C_{31}H_{35}O_{13}N_3$.—The acid (1 g.) was suspended in alcohol (25 c.c.), 0·25*N*-barium hydroxide (40 c.c.) added, and the mixture warmed for 30 minutes. Carbon dioxide was then passed through the clear solution to precipitate barium and the alcohol was removed by distillation under reduced pressure. Barium carbonate was removed and the filtrate was neutralised with dilute sulphuric acid, filtered, extracted with ether to remove benzoic acid, and evaporated almost to dryness on the water-bath under reduced pressure. On further concentration in a desiccator, the solution deposited crystals which, on recrystallisation from alcohol, gave very pale yellow prisms, m. p. 201° after softening at 186° (Found: C, 51·9, 51·2; H, 6·05, 5·8; N, 7·9; OMe, 19·5, 18·6; CO_2H, 8·2, 8·4. $C_{22}H_{29}O_{11}N_3$ requires C, 51·7; H, 5·7; N, 8·2; 3OMe, 18·2; CO_2H, 8·8%).

Action of Hydrogen Chloride on the Acid $C_{31}H_{35}O_{13}N_3$.—When anhydrous hydrogen chloride was bubbled through a suspension of the nitroso-acid (0·5 g.) in absolute alcohol (10 c.c.), the latter dissolved and a product separated which on recrystallisation from aqueous alcohol

formed yellow prisms, m. p. 218° (decomp.). The *substance* was soluble in water and gave the test for chloride, but not the Liebermann nitroso-reaction (Found : C, 52·8; H, 6·0; N, 3·7; Cl, 4·9. $C_{31}H_{36}O_{12}N_2,HCl,2H_2O$ requires C, 53·1; H, 5·85; N, 4·0; Cl, 5·1%). The free amino-acid, precipitated from an aqueous solution of the substance by sodium acetate, crystallised with some difficulty from alcohol in pale yellow rosettes, m. p. 207° (decomp.).

Action of Nitric Acid on Aconitoline.—When nitric acid (*d* 1·2) reacted with aconitoline under the conditions used for the corresponding oxidation of aconitine, a *nitroso-acid* separated, and on recrystallisation from alcohol–acetone, pale yellow prisms were obtained, m. p. 186° (decomp.) (Found : C, 55·7, 55·4; H, 5·4, 5·6; N, 6·2, 6·3; NMe, nil. $C_{29}H_{33}O_{13}N_3$ requires C, 55·15; H, 5·2; N, 6·65%).

By the action of anhydrous hydrogen chloride on this compound suspended in absolute alcohol, the nitroso-group was removed, and an amino-acid hydrochloride, m. p. 214° (decomp.), was isolated. The action of sodium acetate on this gave the *amino-acid*, which crystallised from aqueous alcohol in yellow prisms, m. p. 250° (decomp.) (Found : C, 58·9; H, 5·8; N, 4·8. $C_{29}H_{34}O_{12}N_2$ requires C, 57·8; H, 5·65; N, 4·65%).

Hydrolysis of the Amino-acid $C_{29}H_{34}O_{12}N_2$.—The acid was suspended in alcohol and warmed with four times the theoretical quantity of sodium ethoxide. When worked up in the manner previously described, the *hydrochloride* of the hydrolysed amino-acid was obtained in colourless felted needles from aqueous alcohol, m. p. 218° (decomp., after softening at 180°) (Found : C, 47·8; H, 6·2; N, 4·8; Cl, 6·3. $C_{22}H_{30}O_{11}N_2,HCl,H_2O$ requires C, 47·7; H, 6·0; N, 5·1; Cl, 6·4%).

Oxidation of Aconitine with Nitrous Acid.—A solution of aconitine (1 g.) in aqueous acetic acid (50 c.c.) was heated on the water-bath, and saturated aqueous sodium nitrite slowly added till no more solid separated. The product, recrystallised from boiling acetic acid, formed small colourless prisms, m. p. 276° (decomp.), very sparingly soluble in the usual solvents. The *substance* gave the nitroso-reaction, but it was not found possible to remove this group with hydrogen chloride as in previous cases (Found : C, 58·8, 59·2, 58·5, 59·3; H, 6·35, 6·5, 6·3, 6·7; N, 4·2, 4·6, 4·4, 4·6. $C_{31}H_{40}O_{12}N_2$ requires C, 58·9; H, 6·3; N, 4·4%). The action of nitric acid on it produced the same nitroso-acid as was obtained by the oxidation of aconitine with nitric acid.

The micro-analyses were carried out by Roth, Heidelberg, and Schoeller, Berlin.

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