344. *Aconitine. Part II. The Relationship between Aconitine and Atisine and Some Degradation Products of the Latter.*

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The formula $C_{22}H_{31}O_2N$ for atisine proposed by Wright and by Jowett is not in agreement with the analytical results now reported. The formula $C_{22}H_{33}O_2N$ is preferred.

Atisine has been shown to possess a methylenedioxy- and a methylimido-group, and to form a dihydro-derivative by catalytic hydrogenation, thus being derived from the fully hydrogenated nucleus $C_{20}H_{33}N$. This would indicate that the carbon skeleton has a pentacyclic structure. This being so, the relationship of atisine to aconitine is not obvious, for on the basis of Freudenberg's work (*Ber.*, 1936, **69**, 1962) aconine, of which aconitine is the benzoyl acetyl derivative, should have a hexacyclic nucleus. Atisine appears, however, to be more closely related to lucidisculine (from *A. lucidisculum*), $C_{24}H_{37}O_4N$ (Majima and Morio, *Ber.*, 1932, **65**, 599).

Some degradation products of atisine are described, a hydrocarbon $C_{17}H_{16}$ and a base $C_{17}H_{17}N$ representing the most far-reaching degradations yet attained.

THE rhizomes of the Indian plant *Aconitum heterophyllum* (Wall.), used in native medicine under the name of atis root, contain an alkaloid atisine, for which the formula $C_{22}H_{31}O_2N$ was proposed by Wright ("Year Book of Pharmacy," 1879, 442). A number of its salts were prepared by Jowett (J., 1896, **69**, 1518), but little investigation of its constitution has till now been attempted. The preliminary examination of the alkaloid and several degradation products are now described; none of the latter have yet been identified.

The material was obtained through the courtesy of Mr. C. C. Calder, B.Sc., Director of the Botanical Survey of India. The alkaloid content of atis root appears to depreciate fairly rapidly on keeping, since unsatisfactory yields were obtained with material which had been bought in the open market in India. The method of extraction was a simplified procedure based on that used by Jowett (*loc. cit.*).

Our analytical results for atisine hydrochloride are not in agreement with the formula $C_{22}H_{31}O_2N$ of Wright and Jowett, but suggest rather $C_{22}H_{33}O_2N$, this being supported by the analysis of the *hydrochloride* of a dihydro-derivative, $C_{22}H_{35}O_2N$, formed by catalytic hydrogenation. Wright's data were obtained by a single analysis of the amorphous aurichloride, and Jowett's, by the analysis of the hydriodide and the nitrate; the hydrogen result for Jowett's first-named compound shows better agreement with the formula suggested here. Chandrasena (J., 1933, 740) claimed to have isolated atisine in crystalline form, and proposed the formula $C_{22}H_{35}O_4N$ in accordance with his analytical results: these, however, are almost identical with those reported here for atisine hydrochloride and it would therefore appear that his so-called crystalline atisine is actually the hydrochloride. Such a view is supported by the result of the determination of chlorine in atisine perchlorate reported by him.

Negative results in Zeisel and Zerewitinoff determinations, and the fact that atisine gives a precipitate with Gaebel's phloroglucinol–sulphuric acid reagent (*Arch. Pharm.*, 1910, **248**, 225), indicate that the two oxygen atoms in the molecule are present in a methylenedioxy-group. No coloration was observed, however, in the corresponding reaction with gallic acid, a fact which may be accounted for on the supposition that the group is not attached to an aromatic ring. An alkylimido-group also is present in atisine. This is probably a methylimide, since the action of potassium ethoxide produced a *base*, $C_{21}H_{31}O_2N$, not containing an alkylimido-group.

The extended formula for atisine is therefore $C_{20}H_{28}(CH_2O_2)(NMe)$ and the parent nucleus is $C_{20}H_{31}N$. Allowance being made for the presence of one double bond in the molecule, as shown by the formation of the dihydro-derivative, and CH_2 being substituted for NH in this formula, the alkaloid may be regarded as derived from the fully hydrogenated hydrocarbon $C_{21}H_{34}$. This, by comparison with the open-chain paraffin $C_{21}H_{44}$, indicates the presence of a pentacyclic system in the molecule.

On this basis, however, the relationship with aconitine is not obvious, because, allowing for the known substituent groups in this molecule, of which $C_{34}H_{47}O_{11}N$ is the accepted formula, the parent nucleus becomes $C_{19}H_{29}N$, as pointed out by Freudenberg (*Ber.*, 1936, **69**, 1962). This differs from atisine in being derived from a hexacyclic system.

Majima and Morio (*Ber.*, 1932, **65**, 599) suggested that there is a close relationship between atisine and lucidisculine (from *A. lucidisculum*). This alkaloid, $C_{24}H_{37}O_4N$, contains an acetyl, a hydroxyl, and a methylimido-group. The nature of the fourth oxygen atom is not known, but it is not likely to be present as hydroxyl, since only a monoacetyl derivative can be obtained. If this oxygen atom be considered as indifferent and present as a bridge linkage or as a carbonyl group, the parent nucleus becomes $C_{21}H_{35}N$, a formula which points to the alkaloid being derived, as has been suggested for atisine, from a pentacyclic system.

The oxidation of atisine with potassium permanganate or chromic acid, even under the mildest conditions, led to extensive decomposition. By the action of zinc dust, after removal of the methylenedioxy-group, however, a base was obtained involving the loss of one carbon atom only and having the formula $C_{20}H_{31}ON$.

By the dehydrogenation of atisine with selenium, products probably corresponding to different stages in the reaction were isolated. Under mild conditions (at 200°), a base, $C_{20}H_{29}ON$, and a crystalline neutral *substance*, $C_{19}H_{27}O_2N$, were obtained. The base appears to be derived from the alkaloid by loss of the methylimido- and the methylenedioxy-group. Under more vigorous conditions (at 300—320°), these products were partly converted into an oily hydrocarbon, $C_{17}H_{16}$, which was isolated as the picrate and recovered crystalline. The physical characteristics of the derivatives suggest its being a substituted phenanthrene, but comparison of the picrate with those of known alkylphenanthrenes of this formula, and also with those of 4-*n*-propyl- and 4-*iso*propylphenanthrene, which were synthesised by Haworth's method (J., 1932, 1125), failed to disclose its identity. It is being further examined.

By the action of alcoholic potash on atisine, Jowett obtained a compound, isolated as the aurichloride, to which he ascribed the formula $C_{22}H_{31}O_2N,H_2O$. No product has been isolated in this laboratory by this reaction, but by the action of potassium ethoxide a crystalline base, $C_{21}H_{31}O_2N$, was obtained corresponding to the loss of the methyl group attached to the nitrogen atom. This compound could be extensively dehydrogenated without losing its basic character, yielding a derivative, $C_{17}H_{17}N$, which was obtained as the *picrate*. In addition to this base, the hydrocarbon previously obtained by the dehydrogenation of atisine was also formed. The neutral compound was however missing.

EXPERIMENTAL.

Extraction of Atisine.—The finely ground rhizomes were percolated with warm rectified spirit, the alcohol removed under reduced pressure, and the residue taken up with 2% sulphuric acid. Tarry matter and oil were extracted with chloroform, and the base shaken out of the alkaline liquor with ether. Purification was carried out by crystallisation of the hydrochloride from aqueous alcohol. The colourless needles obtained had m.p. 296° (decomp.), and the yield was *ca.* 0·25%. Atisine appears to be the only base in *A. heterophyllum* [Found: C, 69·1, 69·3, 69·2; H, 9·0, 8·9, 9·4; N, 3·3, 3·5, 3·8; Cl, 9·6; OMe, 0; active H, 0; CH_2O_2 (by the method of Clowes and Tollens, *Ber.*, 1899, **32**, 2841), 7·55; NMe, 6·0, 5·4; *M* (by titration with silver nitrate), 381. Calc. for $C_{22}H_{33}O_2N,HCl$: C, 69·6; H, 9·0; N, 3·7; Cl, 9·4; 1 CH_2O_2, 7·9; NMe, 7·65%; *M*, 379·5. $C_{22}H_{31}O_2N,HCl$ would require H, 8·5%].

Hydrogenation of Atisine.—Atisine hydrochloride (1 g.) was dissolved in acetic acid (20 c.c.) and hydrogenated in the presence of palladium-black (0·2 g.); 67 c.c. of hydrogen at 19°/758 mm. were taken up (2H requires 63 c.c.). The solution was freed from palladium, made alkaline, and extracted with ether. The colourless varnish remaining on removal of the ether was converted into the *hydrochloride*, which crystallised from alcohol in colourless needles, m.p. 319° (decomp.) (Found: C, 69·1; H, 9·4; N, 3·6. $C_{22}H_{35}O_2N,HCl$ requires C, 69·1; H, 9·4; N, 3·7%).

Action of Zinc Dust on Atisine.—Atisine, distilled over zinc dust, gave a varnish from which no crystalline product has yet been isolated. Removal of the methylenedioxy-group with hydrochloric acid, previous to the zinc dust treatment, led to the formation of a small amount of an amorphous base, from which a crystalline *picrate* was isolated as needles, m.p. 173° (Found: C, 58·6; H, 6·4; N, 10·4. $C_{20}H_{31}ON,C_6H_3O_7N_3$ requires C, 58·9; H, 6·4; N, 10·6%).

Action of Potassium Ethoxide on Atisine.—Atisine (1 g.) was added to 20% alcoholic potassium ethoxide (30 c.c.), and the mixture boiled for 6 hours. Water was added, and the alcohol evaporated under reduced pressure. After some time crystals separated. These were removed, washed with a little ether, and recrystallised from ethyl acetate, forming colourless plates, m.p. 147° (Found: C, 75·7, 75·8; H, 10·1, 10·5; N, 4·3. $C_{21}H_{31}O_2N$ requires C, 76·5; H, 9·4; N, 4·3%). The *hydrochloride* of this *base* crystallised from aqueous alcohol in needles, m.p. 278° (decomp.) (Found: C, 68·6, 67·0; H, 9·0, 9·1; N, 4·6, 5·0; *M*, 369, 371;

NMe, 0; test for methylenedioxy-group, positive. $C_{21}H_{31}O_2N,HCl$ requires C, 69·0; H, 8·9; N, 3·8%; *M*, 365·5).

Dehydrogenation of Atisine with Selenium.—Atisine (2 g.) was heated with powdered selenium (10 g.) at 300—320° for 10 hours. The tarry material was then extracted (Soxhlet) with ether, from which the basic material was shaken out with dilute hydrochloric acid. The aqueous solution was made alkaline with caustic soda, and the base extracted with ether. On evaporation of the ether, and fractional distillation of the remaining oil, a colourless varnish was obtained, b.p. 190—200°/1 mm. This was converted into the *picrate*, which crystallised from acetone–alcohol in yellow needles, m.p. 242—243° (decomp.) (Found: C, 58·7; H, 6·1; N, 10·1. $C_{20}H_{29}ON,C_6H_3O_7N_3$ requires C, 59·1; H, 6·1; N, 10·6%). The amorphous base regenerated from the purified picrate was converted into the *hydrochloride*, which crystallised from alcohol–ether in clusters of prisms, m.p. 265° (Found: C, 71·5; H, 8·9; N, 4·3; NMe, 0; OMe, 0; methylenedioxy-test, negative. $C_{20}H_{29}ON,HCl$ requires C, 71·5; H, 8·9; N, 4·2%).

The ether containing the neutral substances from the dehydrogenation was removed, and the residue fractionally distilled, giving three fractions: (1) b.p. 130—160°/1 mm., a colourless oil yielding a *picrate*. This was recrystallised from alcohol and formed fine orange needles, m.p. 129° (Found: C, 61·8; H, 4·5; N, 9·0. $C_{17}H_{16},C_6H_3O_7N_3$ requires C, 61·5; H, 4·2; N, 9·35%). The *trinitrobenzene* derivative of the hydrocarbon was also prepared, and formed yellow felted needles, m.p. 140° (Found: C, 63·3; H, 4·55; N, 9·6. $C_{17}H_{16}, C_6H_3O_6N_3$ requires C, 63·7; H, 4·4; N, 9·7%). The hydrocarbon recovered from the picrate crystallised from alcohol in colourless plates, m.p. 41°. (2) b.p. 170—200°/1 mm., a viscous brown oil showing a green fluorescence; a crystalline derivative could not be isolated. (3) b.p. above 220°/1 mm., colourless felted needles, m.p. 240°, very soluble in alcohol, sparingly in ether. This *substance* was recrystallised from alcohol–ether (Found: C, 76·05; H, 9·25; N, 4·7. $C_{19}H_{27}O_2N$ requires C, 75·75; H, 9·0; N, 4·65%).

When atisine was dehydrogenated at 200°, the only products which could be isolated were the base $C_{20}H_{29}ON$ and (3). Both of these gave (1) at the higher temperature.

Dehydrogenation with Selenium of the Base obtained from Atisine by the Action of Potassium Ethoxide.—The method was that previously described for the dehydrogenation of atisine. From the ethereal extract of the products two substances were isolated: (1) a base, b.p. 150—160°/1 mm.; this was obtained as a green fluorescent oil, the *picrate* of which crystallised from acetone–alcohol in felted yellow needles, m.p. 206° (Found: C, 59·1; H, 4·3; N, 12·2. $C_{17}H_{17}N,C_6H_3O_7N_3$ requires C, 59·45; H, 4·3; N, 12·1%); (2) the hydrocarbon $C_{17}H_{16}$ previously obtained by the dehydrogenation of atisine.

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