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OF
AETHUSA CYNAPIUM

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CHEMICAL EXAMINATION OF AETHUSA CYNAPIUM.[1]

BY FREDERICK B. POWER AND FRANK TUTIN.

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Aethusa Cynapium, Linn, or "Fool's Parsley," known also as the "Lesser Hemlock," in French as "La petite Ciguë," in Italian as "Cicuta minore," and in German as the "Kleiner Schierling," is a well-known annual garden weed, which is indigenous to Europe and Northern Asia, and is the only representative of the genus. The generic name is stated to be derived from the Greek αίθὐσσω, to make warm, on account of the acrid taste of the plant.

In all the botanical works that have been consulted which give a description of the *Aethusa*, as also in works on toxicology and many other publications, it is regarded as possessing poisonous properties. Numerous cases of poisoning have in fact been attributed to it, and in most of these it appears to have been mistaken for the common garden parsley. On the other hand, the investigations of the plant which have hitherto been recorded, both chemical and physiological, have led to widely differing conclusions respecting its constituents and properties, and thus its reputed poisonous action has alternately been affirmed and denied. It is evidently on account of the recognition or suspicion of its harmful character that the *Aethusa* has received such ex-

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[1] Presented, in abstract, at the Congress of Chemistry and Pharmacy, held at Liége, Belgium, July, 1905.

tended consideration in botanical and medical literature, and as some of the earlier observations concerning it are of interest and importance in connection with the present investigation, they may, so far as practicable, be briefly reviewed.

In the "Gardener's and Botanist's Dictionary," by Philip Miller, F.R.S., with additions by Thomas Martyn, F.R.S., Vol. I, Part I, London, 1807, the following reference occurs: "*Aethusa Cynapium*, Fool's Parsley, called also Lesser Hemlock, is a very common weed in kitchen gardens, and is in a slight degree poisonous." It is also remarked that this plant can only be confounded with true parsley and with chervil (*Anthriscus*) when in a very young state, and that "even then the leaves may be observed to have a different form, a darker hue, and, on being bruised, to emit in a slight degree a disagreeable venomous smell. Most cattle eat it, but it is said to be noxious to geese."

Stephenson and Churchhill in their "Medical Botany," Vol. I, London, 1831, give a detailed account of the *Aethusa*, and record several cases of poisoning attributed to it. They refer to its noxious qualities, and state that the leaves, when bruised, have a disagreeable odor. An instance is also cited by them where it had inadvertently been used as a medicine in place of hemlock (*Conium maculatum*) and with alarming results, thus indicating that at that early date the *Aethusa* was regarded as the more highly poisonous of these plants.

In Lindley and Moore's "Treasury of Botany," Vol. I, p. 26, the following is noted under *Aethusa*. "Its flavor and odor are unpleasant, and the seeds are very nauseous. The whole plant is said to be poisonous, and there are instances on record of persons having been made ill by eating it, even in the small quantities in which it is likely to have been present when mixed with parsley"

In Bentley and Trimen's "Medicinal Plants," Vol. II, No. 125, the *Aethusa* is noticed at considerable length. The following is there stated: "This plant is not official in any Pharmacopoeia, neither has it ever been used in regular medical practice; but it is introduced into the present work like *Oenanthe crocata* and *Cicuta virosa* on account of its poisonous properties; and hence, being a common indigenous plant, it ought to be well-known to medical practitioners and pharmacists. Its chief resemblance to parsley is in its leaves, but those of Fool's Parsley are more acute, of a darker green color, and when bruised they emit a peculiar, disagreeable odor, which is altogether different from the smell of parsley. The whole plant possesses poisonous properties, but it does not appear to be of so virulent a nature as *Oenanthe crocata* and *Cicuta virosa*, for although there are several cases of poisoning by it, only two appear to have terminated fatally. In referring to the statement by Miller[1] that "most cattle eat it," the authors remark that "in all recorded experiments with it on animals, it has had poisonous effects."

In Gray's "Manual of Botany of the Northern United States," sixth edition, p. 205, the author describes *Aethusa Cynapium* as "a fetid, poisonous European herb."

In "Luerssen's Medicinisch-Pharmaceutische Botanik," 1882, Bd. II, p. 769, the author states, regarding *Aethusa*, that "this poisonous plant may be distinguished from parsley, which it resembles in a young state, not only by the described botanical characters, but by lacking the peculiar odor of the latter plant."

In Orfila's "Treatise on Mineral, Vegetable, and Animal Poisons," second edition, Vol. II, pp. 249–250, London, 1818, reference is made to the poisonous action of *Aethusa*, and this is also the case in the work "On Poisons," by Taylor, p. 758, London, 1848, although in the third edition of the latter work the conclusions of Harley, as noted below, are accepted as final.

Dr. John Harley[2] made a number of physiological tests, by administering to a child and to adult persons the expressed juice of both immature and mature plants, collected in different counties in England, and, as no effects were observed, he came to the conclusion that the *Aethusa* is absolutely free from the noxious properties attributed to it. He states that "It is pleasant to the sight, smell and taste, and, in the absence of the more fragrant and succulent plants, might well be used as a pot-herb or a salad." It was stated, furthermore, that "these conclusions are independent both of locality and season, and that the only influence which these conditions have on Fool's Parsley, as on hemlock, is to increase or diminish its succulency."

In connection with the views expressed by Dr. Harley, it is of interest to note that so recently as 1904 a case of severe poisoning by Fool's Parsley was reported.[3] The plant, recognized as

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[1] *Loc. cit.*

[2] "Year Book of Pharmacy," 1876, p. 200, and *Pharm. Journ.*, 1880, 11, p. 437.

[3] *British Medical Journal*, July 16, 1904, p. 124.

Aethusa Cynapium, was stated to have been gathered in the kitchen garden and eaten in considerable quantity, but the symptoms of poisoning were not manifested until some twenty-four hours after ingestion. By the use of morphine (for the pain) and stimulants, a speedy recovery was effected. (Compare also Dr. Scott Sugdein, in the *Lancet*, July 7, 1888.)

Although the *Aethusa* appears never to have been subjected to a complete chemical examination, the statements that have been recorded respecting its constituents are quite as divergent as those pertaining to its physiological action. The earliest observation known to us in this connection is contained in the *Archiv des Apotheker Vereins im nördlichen Teutchland*, **24,** 251, Lemgo, 1828, from Kastner's *Archiv.*, **11,** 144, and is as follows: "The *Aethusa Cynapium*, which is often confused with parsley, contains, according to Professor Ficinus, an alkaloid, *cynapine*, which crystallizes in rhombic prisms, and is soluble in water and alcohol, but not in ether; the sulphate crystallizes in prisms."

Walz,[1] by the direct distillation of the ripe fruit of the *Aethusa*, and also by distillation of an alcoholic extract of the fruit with lime, obtained an alkaline distillate, which, when neutralized with sulphuric acid and extracted with ether-alcohol, left a residue of ammonium sulphate, while a substance dissolved which formed a brown, salt-like mass. The latter, when heated with a solution of caustic potash, gave a strongly alkaline distillate, having an odor resembling that of both coniine and nicotine, which afforded precipitates with various metallic salts and with the usual alkaloid reagents. He therefore concluded that the fruit of *Aethusa* contains "a volatile base, very similar in odor and chemical behavior to coniine, and probably identical with it." As minor constituents, he also observed the presence of an essential oil, a fatty oil, and two resins, one of which was soluble and the other insoluble in ether.

Bernhardt,[2] by the distillation of the fruit of *Aethusa* with milk of lime, obtained a reddish yellow liquid, floating like oil in the aqueous distillate. Both the oily liquid, in alcoholic solution, and the aqueous distillate possessed a strongly alkaline reaction, and an exceedingly penetrating, offensive odor, resembling that of rancid fish oil. The oily substance was found to contain nitrogen, and was therefore regarded as a volatile alkaloid. It

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[1] *Neues Jahrbuch für Pharmacie*, **12,** 351–356 (1859).

[2] *Archiv. Pharm.* [3], **16,** 117, Halle, 1880, also *Year Book of Pharmacy*, 1880, p. 186.

was also stated that the odor of the substance, when in a concentrated state, caused persistent headache, and if developed in food by the action of an alkali on the plant, as in the use of soda for softening leguminous fruits, no one would dispute its tendency to produce nausea and vomiting.

In opposition to the preceding observations it is recorded that Tanret, in a communication made to the Society of Pharmacists of Paris, affirms to have found in the *Aethusa* neither an alkaloid nor a glucoside, nor any other substance to which a toxic action can be attributed. (Compare Planchon et Collin, "Les Drogues Simples," 1896, Tome II, p. 221, and Dorvault, "L'Officine," 1898, p. 376).

EXPERIMENTAL.

Our attention having been directed to the *Aethusa* as a plant which merited a more complete chemical examination than had hitherto been made of it, this was undertaken, and with a twofold object. In the first place it was evidently desirable that the constituents of the plant should be more precisely determined, and in the second place it was hoped that thereby it might be possible to arrive at a correct conclusion respecting its physiological action, which, as we have indicated, has long been a subject of dispute.

The importance of employing absolutely authentic material for this investigation was fully recognized, not only for the accurate determination of its constituents, but also in view of the possibility that the existing discrepancies of statement respecting the properties of the *Aethusa* are attributable to a confusion of plants of the same family which superficially resemble each other. That a confusion of this nature is possible, especially with umbelliferous plants, was shown by one of us several years ago,[1] when an investigation of a number of cases of poisoning, stated to have been caused by the so-called Wild Parsnip, revealed the fact that in every instance the virulent *Cicuta maculata* had been mistaken for the *Pastinaca sativa*, the latter, even in the uncultivated state, being perfectly innocuous.

The *Aethusa Cynapium* used in this investigation was collected during the months of July and August, at a time when the fruits were fully developed, but still green, as it was then presumed to be in a condition most favorable for the determination of its

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[1] *Pharm. Rundschau*, New York, **9**, 162 (1891).

constituents and properties. It was gathered in districts both north and south of London, comprising a somewhat large area, for it was not very abundant in any particular locality. After its collection, each individual plant was carefully examined by a competent botanist, Mr. P. E. F. Perrédès, of London, and we had thus the assurance, not only of a proper identification, but also of the absolute freedom of the material from any contamination. The leaves of these plants, when bruised, had a faintly aromatic, herbaceous odor, and were entirely devoid of the disagreeable characters attributed to them in most botanical works. The green fruit, when bruised, differed only in having a somewhat stronger parsley-like odor.

A quantity of the entire fresh plants, amounting to 135½ pounds (about 61½ kg.), was dried in a warm atmosphere, and then weighed 26½ pounds (12 kg.), having lost about four-fifths of the original weight.

As a preliminary experiment, 25 grams of the ground dry herb were digested with Prollius' fluid, and evidence of the presence of a very small amount of alkaloid was thus obtained. Both the leaves and the fruit of the curled garden parsley, when tested in the same manner, afforded no reaction for an alkaloid.

In order to determine the constituents of the plant, 11 kg. of the air-dried material were completely extracted with hot alcohol. After the removal of the greater portion of the alcohol, the residual dark colored extract was brought into a flask, water added, and steam passed through the liquid until oily drops were no longer visible in the condenser. There then remained in the distillation flask a quantity of resinous substance (*A*) and a very dark colored aqueous liquid (*B*), both of which will be subsequently described.

Examination of the Steam Distillate.—The aqueous distillate was a milky liquid, containing some greenish oil on the surface. It was shaken out several times with ether, the ethereal liquid washed with water, dried with anhydrous sodium sulphate, and the ether removed. The residual oil was distilled under 20 mm. pressure, when it passed over between 80 and 175° C., leaving only a small quantity of dark, non-volatile substance The distillate, amounting to 8.4 grams, was at first colorless, but soon became dark brown, and had a peculiar, rather unpleasant odor. On redistillation it was resolved chiefly into two fractions, one boiling between 80 and 100° C., and the other larger fraction between 160 and 170° C., under 20 mm. pressure, but these were too small for further examination.

The aqueous liquid from which the volatile oil had been extracted contained a small amount of an acid, which was converted into a barium salt and found to consist chiefly of *formic acid.*

(*A*) *Examination of the Resins.*—The resinous substance contained in the steam distillation flask was removed from the aqueous liquid, washed with hot distilled water, and dried on a water-bath. It had a tarry consistency, a dark green color, and weighed 450 grams. In order to ascertain the character of this resin, 50 grams of it were mixed with prepared sawdust, the mixture dried and extracted successively in a Soxhlet apparatus, with the following solvents: Petroleum (b.p. 40°–50° C.) extracted 28.4 grams or 56.8 per cent.; ether, 7.1 grams or 14.2 per cent.; chloroform, 2.2 grams or 4.4 per cent.; ethyl acetate, 0.1 gram or 0.2 per cent.; alcohol, 3.3 grams or 6.6 per cent. Total, 82.2 per cent.

After extracting with these solvents the sawdust still retained a very dark color, and, as a considerable portion of the original substance had not been recovered, it was evident that this had undergone some change which had rendered it insoluble in alcohol.

The petroleum extract was a dark green, thick liquid, the other extracts were all resinous in character, and of a greenish or dark brown color.

The total remaining portion of resinous substance (400 grams) was then extracted successively in the above manner with light petroleum, ether, chloroform and alcohol.

(I) *Petroleum Extract of the Resins.*—About 250 grams of this extract were boiled for two hours with an alcoholic solution of 75 grams of potassium hydroxide. The alcohol was then removed, the dark greenish brown mass dissolved in water, in which it was only sparingly soluble, and the liquid shaken out with five successive portions of ether. The ethereal liquid was washed with water, dried with calcium chloride, and the ether removed. A quantity of dark orange-brown matter was thus obtained, which, when dissolved in alcohol and allowed to stand, deposited a crystalline substance. This substance, although repeatedly crystallized from alcohol and from ethyl acetate, persistently retained a yellow color. It melted at 72–74° C.

and was not acted on by metallic sodium. In order to further purify it, it was distilled under 10 mm. pressure, when a colorless distillate was obtained, which was dissolved in ethyl acetate and allowed to crystallize It was then obtained in white glistening leaflets, melting sharply at 74° C., and was optically inactive.

0.0840 gram gave 0.2612 gram CO_2 and 0.1105 gram H_2O. $C = 84.8$; $H = 14.6$. $C_{35}H_{72}$ requires $C = 85.4$; $H = 14.6$ per cent.

This substance, therefore, appeared to be the hydrocarbon *pentatriacontane*, $C_{35}H_{72}$, the melting-point of which is given as 74° and 74.7° C.[1] So far as known to us, it is the first instance in which this hydrocarbon has been isolated from a plant.

The original alcoholic mother-liquors from the pentatriacontane were of a very dark brown color, and appeared to contain a large amount of resinous matter. After standing for some days, they deposited a small quantity of a substance in the form of crystalline plates, which was separated by filtration, and recrystallized four times from ethyl acetate containing some dilute alcohol. It was thus obtained in handsome pearly leaflets, which melted at 140–141° C. On analysis it gave the following results:

0.4000 gram, on drying at 110° C., lost 0.0213 gram $H_2O = 5.3$ per cent. $C_{26}H_{44}O,H_2O$ requires $H_2O = 4.6$ per cent.; $C_{24}H_{40}O,H_2O$ requires $H_2O = 5.0$ per cent.

0.1041 gram of anhydrous substance gave 0.3179 gram CO_2 and 0.1087 gram H_2O. $C = 83.3$; $H = 11.6$ per cent.; $C_{26}H_{44}O$ requires $C = 83.9$; $H = 11.8$ per cent.; $C_{24}H_{40}O$ requires $C = 83.7$; $H = 11.6$ per cent.

0.3787 gram of anhydrous substance, dissolved in 25 cc. of chloroform, gave $\alpha_D - 1°.5'$ in a 2 dcm. tube, whence $[\alpha]_D - 35.7°$.

When a small quantity of this substance was dissolved in chloroform, a little acetic anhydride added, and then a drop of concentrated sulphuric acid, a deep rose color was at once produced which rapidly changed to violet, then to an intense blue, and, after standing a short time, became green.

A portion of the substance was acetylated by boiling with acetic anhydride and anhydrous sodium acetate for about ten minutes. After the addition of water a product was obtained which, when crystallized from alcohol, formed colorless plates of a silky lustre, melting at 123–124° C

It is evident from these characters that the above-mentioned

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[1] Compare Krafft: *Ber.*, **15**, 1715 (1882).

substance is either an isomeride of *phytosterol*, $C_{26}H_{44}O$, or a lower homologue.

The alkaline liquid, from which the pentatriacontane and phytosterol had been removed by means of ether, was concentrated, acidified with sulphuric acid, and distilled in steam. The distillate contained a small quantity of a greenish oil, which was removed by filtration and discarded. The acids contained in the filtrate were made into a barium salt, the concentrated solution of which gave the reactions of *formic acid*, and, when acidified with sulphuric acid, developed the odor of *butyric acid*.

The distillation flask contained a large quantity of a soft, dark green resin, which gave no indication of containing any fatty acids, and a brown aqueous liquid. The latter was decanted from the resin, and repeatedly extracted with ether, but it yielded nothing.

(II) *Ether Extract of the Resins.*—This extract was a dark green, nearly hard mass, which appeared to contain nothing crystalline. About 35 grams of it were fused with 200 grams of potassium hydroxide in the usual manner, the temperature of the melt being allowed to rise gradually to 260° C. After being allowed to cool, the mass was dissolved in water, acidified with sulphuric acid, and distilled in steam. The acids contained in the distillate were converted into a barium salt, and were thus identified as *formic* and *butyric acids*.

The liquid remaining in the distillation flask was decanted from a quantity of a friable, black resin, and repeatedly shaken out with ether. The ethereal liquid afforded a very small amount of a substance which gave the characteristic color reaction of *protocatechuic acid*.

(III) *Chloroform Extract of the Resins.*—This extract was relatively small in amount, and consisted of a friable, black resin, from which nothing crystalline could be obtained.

(IV) *Alcohol Extract of the Resins.*—This final extract, representing the portion of original resin which had remained undissolved by treatment with the preceding solvents, was dark brown in color, and appeared to contain nothing crystalline. On fusing 26 grams of it with 120 grams of potassium hydroxide, and treating the resulting product in the manner described in connection with the ether extract, it yielded the same substances as the latter, namely *formic* and *butyric acids*, together with a substance which, after recrystallization, melted at 192° C. and gave the color reaction of *protocatechuic acid.*

(*B*) *Examination of the Aqueous Liquid.*—The aqueous liquid which was separated from the resinous matter after the distillation of the original alcoholic extract with steam, as previously described, was of a very dark brown color. It was concentrated to a thick syrup on the water-bath, then mixed with prepared sawdust, the mixture completely dried in a vacuum desiccator, and extracted in a Soxhlet apparatus with alcohol. This extract was concentrated and allowed to stand for some time, when a considerable quantity of a crystalline substance slowly separated, which was collected by filtration at the pump, washed with alcohol, and recrystallized from dilute alcohol. It was thus obtained in colorless needles, and was found to consist of an organic substance associated with potassium nitrate and chloride, from which it was impossible to free it by recrystallization. In order to isolate the organic compound, the possibility of its being an alcohol was considered, and the following method was therefore adopted. It was boiled for about five minutes with an excess of acetic anhydride and a little anhydrous sodium acetate, and the liquid, after being allowed to cool, shaken with a considerable quantity of water. A crystalline substance was thus precipitated, which was collected by filtration at the pump, washed with water, dissolved in hot alcohol, and allowed to crystallize. It then formed octahedral crystals, which melted at 122–123° C., and this melting-point was not changed by further crystallization; it was also recovered unchanged when again boiled with acetic anhydride for half an hour. When heated at 115° C. it did not lose in weight.

0.1025 gram gave 0.1875 gram CO_2 and 0.0568 gram H_2O. $C = 49.9$; $H = 6.1$. $C_{18}H_{26}O_{12}$ requires $C = 49.8$; $H = 6.0$ per cent.

0.4949 gram dissolved in 25 cc. of chloroform, gave $\alpha_D + 0°.52'$ in a 2 dcm. tube, whence $[\alpha]_D + 21.9°$.

The acetylated product thus agreed in composition with an hexaacetyl derivative of an hexahydric alcohol, which was evidently mannitol. For the purpose of comparison some hexaacetyl-*d*-mannitol was prepared from pure *d*-mannitol. Aftes recrystallization from alcohol, it melted at 122–123° C., not ar 119° C., as has been stated,[1] and a mixture of equal parts of thit

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[1] Beilstein's "Handbuch der organischen Chemie," Bd. I, p. 417.

preparation and the acetyl derivative of the crystalline substance obtained from the plant also melted at 122–123° C.

Further confirmation of the identity of our acetylated product was obtained by hydrolyzing it with 30 per cent. sulphuric acid, when it afforded a handsomely crystalline substance melting at 165–166° C. On analysis it gave the following result:

0.1114 gram gave 0.1616 gram CO_2 and 0.0768 gram H_2O. $C = 39.5$; $H = 7.7$. $C_6H_{14}O_6$ requires $C = 39.6$; $H = 7.7$ per cent.

The crystalline organic substance isolated from the *Aethusa* was thus definitely proved to be *d-mannitol.*

The sawdust with which the aqueous syrupy liquid had been mixed for the purpose of extraction with alcohol, as above described, was subsequently extracted with hot water, and to this aqueous extract was added the liquids from which the crystalline substance, consisting of mannitol and inorganic salts, had been obtained. The whole was then somewhat concentrated, and a solution of basic lead acetate added until no further precipitate was produced. A large quantity of a brownish yellow precipitate was thus obtained, which was separated from the aqueous liquid by filtration at the pump, and washed with a little water. A portion of this precipitate was suspended in water, decomposed by hydrogen sulphide, and the filtered liquid concentrated under diminished pressure. It afforded, however, only a dark brown syrup, containing uncrystallizable coloring-matter.

The filtrate from the basic lead acetate precipitate was freed from lead by means of hydrogen sulphide, again filtered, and the liquid concentrated under diminished pressure. A brown syrup was thus obtained from which nothing crystalline separated on standing. On warming a portion of this syrupy liquid with phenylhydrazine acetate, it readily afforded a crystalline glucosazone melting at 218° C., and evidently contained a large amount of *i-glucose.* The syrup, when warmed with potassium hydroxide, evolved ammonia, and it afforded precipitates with all the usual alkaloid reagents. Although these reactions might be attributed to substances of a proteid nature, the possibility of an alkaloid also being present was considered. The syrup was accordingly diluted with water, made alkaline with ammonia, and repeatedly shaken out with chloroform until nothing further was removed. The aqueous liquid, when acidified, was still precipitated by alkaloid reagents, but this behavior was doubtless due to proteid matter. The chloroform solution was shaken out several times with dilute hydrochloric acid, the acid liquid then made alkaline with potassium hydroxide, and again shaken out with chloroform. This chloroformic liquid was washed with a little water, dried by means of potassium carbonate, and the chloroform removed. A small quantity of a thick, brown liquid was thus obtained, which possessed the characteristic, unpleasant odor of coniine. It was dissolved in dilute alcohol, and the solution, which had an alkaline reaction, exactly neutralized with hydrochloric acid. This liquid was then decolorized with animal charcoal, and evaporated in a vacuum desiccator, when a small brownish residue, containing needle-shaped crystals, was obtained. The solution of this substance gave precipitates with the usual alkaloid reagents, and with chlorauric and chloroplatinic acids.

As the characters of the substance above described suggested the presence of coniine or a closely related alkaloid, an attempt was made to obtain some further evidence of its identity. On account of the very small quantity of substance available, and the lack of specific reactions for the detection of small amounts of coniine, consideration was taken of the fact that this alkaloid on oxidation readily affords butyric acid.[1] The crystalline residue was therefore dissolved in water, and oxidized by heating with chromic acid on a water-bath. Steam was then passed through the liquid, and the acid contained in the distillate converted into the calcium salt. The solution of the latter, on evaporation, afforded a small amount of a salt which, when acidified with sulphuric acid, gave the odor of butyric acid, and, when warmed with absolute alcohol and sulphuric acid, developed the characteristic odor of ethyl butyrate.

In order to determine approximately the amount of volatile alkaloid contained in the fresh plant, about 40 kg. of the *Aethusa* were extracted with alcohol, and, after the removal of the greater portion of the solvent, caustic potash was added, and steam passed through the mixture. The distillate, which had an alkaline reaction, was acidified with hydrochloric acid, filtered to remove a small amount of essential oil, and the acid liquid concentrated under diminished pressure. It was then made alkaline with potassium hydroxide, shaken out repeatedly with chloroform,

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[1] Compare Blyth: *J. Chem. Soc.*, 1, 361 (1849).

the chloroformic liquid washed with water, dried with potassium carbonate, and the solvent removed. The residual oily liquid was dissolved in dilute alcohol, exactly neutralized with hydrochloric acid, the solution decolorized with animal charcoal, and evaporated to dryness in a vacuum desiccator. A residue containing needle-shaped crystals of the hydrochloride of the alkaloid was thus obtained, amounting to 0.12 gram, which is equivalent to 0.0003 per cent. of the weight of the entire fresh plant If the base be regarded as coniine, this would correspond to 0.093 gram or 0.00023 per cent. of the latter in the plant.

The small amount of alkaloidal salt obtained in the above-described operation was dissolved in a little water, and a solution of gold chloride added. An oily precipitate was thus produced, which did not become crystalline, even after standing for several days. It was finally dissolved in warm alcohol, and the solution filtered and concentrated, when a crystalline substance was obtained, but it was too small in amount to permit of further examination.

Physiological Tests.—In order to obtain further evidence respecting the character of the alkaloid found in the *Aethusa*, the following physiological tests were made:

(*a*) Five hundred grams of the ground, air-dry herb were extracted with acidulated water, the liquid made alkaline with caustic potash, and distilled in steam. The alkaline distillate was acidified with hydrochloric acid, concentrated under diminished pressure, again made alkaline with caustic potash, and shaken out with chloroform. The chloroformic solution was then extracted with very dilute acetic acid, and the whole of this liquid was administered *per os* to a small dog. Vomiting ensued within fifteen minutes, and was succeeded by profuse salivation which lasted for twenty-four hours. These effects were accompanied by an appearance of general weakness. After three days the animal had completely recovered.

(*b*) Five hundred grams of the ground, air-dry herb were completely extracted with hot alcohol, the solvent removed, and the resulting extract mixed with water. The aqueous liquid, separated from the soft resin by filtration, was concentrated under diminished pressure, and the whole of this preparation was administered to a small dog. Vomiting occurred within half an hour, and after this the animal seemed perfectly well.

(*c*) The whole of the resin separated from the preceding extract was administered to a dog but no effect of any kind could be observed.

It is evident from these results that the physiological action of the *Aethusa* is due to the volatile alkaloid, and the symptoms produced by the latter are those characteristic of coniine poisoning.

SUMMARY AND CONCLUSIONS.

In summarizing the results of this investigation the following essential facts may be noted.

The material employed consisted of the true *Aethusa Cynapium*, Linn., the identity of each plant having been carefully verified by a competent botanist, and it was perfectly free from any contamination. Both the fresh leaves and the green fruit of these plants, when bruised, were entirely devoid of the disagreeable odor attributed to them in most botanical works.

The more important constituents of the plant were found to be as follows:

(1) A small amount of an *essential oil*, of rather unpleasant odor. When first distilled it was colorless, but rapidly acquired a deep brown color. The amount of this oil obtained from an alcoholic extract corresponded to 0.015 per cent. of the weight of the entire fresh plant. The aqueous distillate from which the oil was separated contained a small amount of *formic acid*.

(2) An amount of *resinous substances* corresponding to 0.8 per cent. of the weight of the entire fresh plant. From the portion of this resin extracted by light petroleum there were isolated, after boiling with an alcoholic solution of potassium hydroxide, a small amount of a crystalline hydrocarbon, *pentatriacontane*, $C_{35}H_{72}$ (m. p. 74° C.), and a crystalline alcohol (m. p. 140–141° C.; $[\alpha]_D—35.7°$), which is either an isomeride of *phytosterol*, $C_{26}H_{44}O$, or a lower homologue. The alkaline liquid from which these crystalline substances had been extracted was acidified with sulphuric acid, which caused the separation of a quantity of soft resin, and the mixture, when subsequently distilled, yielded small amounts of *formic* and *butyric acids*. The portions of the original resin obtained by its subsequent extraction with ether and alcohol respectively, when fused with potassium hydroxide, yielded, in both cases, *formic*, *butyric*, and *protocatechuic acids*.

(3) A small amount of *d-mannitol* (m. p. 165–166° C.) from which a hexaacetyl derivative (m. p. 122–123° C.; $[a]_D + 21.9°$) was prepared. The mannitol, when first obtained, was associated with some potassium nitrate and chloride, and could only be separated from these inorganic substances by its conversion into the acetyl derivative.

(4) A considerable amount of inactive *glucose* and amorphous *coloring-matter.*

(5) An exceedingly small amount of a *volatile alkaloid*, having the peculiar, characteristic odor of coniine, and which, like the latter, yielded butyric acid on oxidation.[1] It was accompanied by a considerable amount of ammonia, which was probably produced for the most part by the decomposition of proteid substances contained in the plant. The amount of hydrochloride of the alkaloid obtained was 0.12 gram from 40 kg. of the entire fresh plant, which is equivalent to 0.0003 per cent. If the base be regarded as coniine, this would correspond to 0.00023 per cent. of the latter in the plant.

The isolation of a volatile alkaloid from the *Aethusa* may be regarded as of considerable interest, inasmuch as it was stated many years ago by Walz[2] that the fruit of this plant "contains a volatile base, very similar in odor and chemical behavior to coniine, and probably identical with it." A similar observation was recorded some years later by Bernhardt[3] while, on the other hand, Tanret[4] has subsequently stated that he could find in the *Aethusa* "neither an alkaloid nor a glucoside, nor any other substance to which a toxic action can be attributed."

It is, however, not only from a chemical point of view, but also from that of the toxicologist, that the verification of the presence of a volatile alkaloid in this plant merits consideration, particularly on account of the conflicting opinions which have so long prevailed respecting its reputed poisonous properties.[5] Although the amount of alkaloidal substance obtained from the plant was so small that its identity could not be definitely established by analytical data, a consideration of its physical and chemical characters, such as volatility, tendency to resinify, peculiar odor, and particularly the formation of butyric acid by its

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[1] Compare *J. Chem. Soc.*, **1**, 361 (1849).

[2] *Neues Jahrbuch für Pharmacie*, **11**, 351–356 (1859).

[3] *Archiv. Pharm.* [3], **16**, 117 (1880).

[4] See Planchon et Collin, "Les Drogues Simples," 1896, Tome II, p. 221.

[5] Compare, especially, Dr. John Harley, *Pharm. Journ.*, **11**, 437 (1880).

oxidation, may reasonably lead to the assumption that it is either coniine or, possibly, a mixture of bases such as is obtained in a similar manner from *Conium maculatum*.

The fact that the proportion of alkaloid found by us in the *Aethusa* was so very small, and that the plant apparently contains no other substance to which a toxic action can be attributed, would seem to afford some justification for the conclusion of Dr. Harley[1] that it is free from the noxious properties which it has been stated to possess. It is quite possible, however, that this conclusion, based upon the results of physiological experiments with the expressed juice of the plant, may only be correct within certain limitations. It has been observed, for example, in the case of *Conium*, that the plant varies in narcotic power according to the stage of its development, and to the weather and climate, being most active when the fruit is still green, in hot and dry seasons, and in warm countries.[2]

Notwithstanding the contradictory nature of the statements that have been recorded respecting the properties of the *Aethusa*, and whatever may be the explanation of these discrepancies, there remains the important and positive fact that, in accordance with the observations of earlier investigators, the plant examined by us contained a small amount of a volatile alkaloid resembling coniine in its physical and chemical characters, and, as we have shown, also in its physiological action. In view of this fact, it can not be considered improbable that, under favorable conditions of growth, the proportion of alkaloid may be increased to such an extent as to impart to the plant the poisonous properties ascribed to it.

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[1] *Loc. cit.*

[2] Compare Farr and Wright: *Pharm. Journ.* [4], **18**, 185; "United States Dispensatory," Eighteenth Edition, p. 447, also Millspaugh: *Loc. cit.*