[CONTRIBUTION FROM DIVISION OF INSECTICIDE INVESTIGATIONS, BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, UNITED STATES DEPARTMENT OF AGRICULTURE]

Helenalin. I. Helenalin, the Bitter Sternutative Substance Occurring in *Helenium Autumnale*

BY E. P. CLARK

From the plant *Helenium autumnale* Reeb[1] obtained a crystalline compound which he designated as "helenic acid (d'acide helenique)." He assigned the formula $C_8H_{10}O_2$ to the material, but the combustion data presented indicate that his results were miscalculated. In reality his figures are in good agreement with the formula $C_{15}H_{18}O_4$, which will be shown in the experimental part to be the correct composition of the substance.

Later Lamson,[2] working with some of Reeb's preparations, studied their physiological action and made some chemical observations. He designated the material "helenin," and on the basis of one combustion analysis arrived at the molecular formula $C_{20}H_{25}O_5$, a formula which inspection shows to be impossible. His analytical figures are in moderate agreement with Reeb's results, but they constitute insufficient evidence upon which to base a correct formula.

Since Reeb states that the crystalline material is a vermifuge and our experiments indicate that it is a fairly effective fish poison, its possibilities as an insecticide are being investigated. In the course of this work a method of preparing the material in a pure condition has been elaborated, and sufficient chemical data have been obtained to indicate that the compound has the molecular formula $C_{15}H_{18}O_4$, as suggested by Reeb's analysis.

The compound is a colorless, crystalline, optically active material, which melts at 167°. It has a bitter taste, and its dust causes violent sneezing. A 1–5000 aqueous solution kills *ca.* 3 g. goldfish in three hours.

From a chemical standpoint the compound is highly unsaturated. In the presence of catalysts it absorbs 4 atoms of hydrogen per molecule, indicating that it has two double bonds. It adds bromine to give a dibromide, and it forms monoacyl derivatives, indicating the presence of one hydroxyl group. The acetyl compound was prepared with ease, but as acetyl determinations on this preparation were not entirely satisfactory, a methoxyacetyl derivative was prepared, and the methoxyl value was taken as an indication of the number of acyl groups present. In this way it was proved definitely that only a monoacyl derivative was formed. The compound has no methoxyl groups and is neutral.

Tests for other functional groups have not yet been successful, but further work is in progress.

It is proposed to designate the compound "helenalin," a euphonious combination of syllables of the generic and specific names of the plant. This nomenclature is adopted because Reeb's name, "helenic acid," does not apply inasmuch as the material is not an acid, and Lamson's name, "helenin," has been applied for a long time to alantolactone.[3]

Experimental

Preparation and Properties of Helenalin.—Twenty-five hundred grams of the ground whole plant of *Helenium autumnale*[4] was moistened with 2 liters of chloroform and allowed to stand in a tight container overnight. The drug was then packed in a percolator and extracted with 10 liters of chloroform. The percolate was concentrated under reduced pressure to a thick sirup and then dissolved in 1.5 liters of hot ethanol. The alcoholic liquid was diluted with 6 liters of boiling water and acidified (litmus) with acetic acid, and a solution of 20 g. of normal lead acetate was added. After standing overnight the solution cleared and was filtered through a folded filter paper. The filtrate was evaporated under reduced pressure to 1 liter and then extracted with chloroform.

The chloroform extract was dried with sodium sulfate and evaporated *in vacuo* to a thick sirup, which was then dissolved in 50 cc. of hot benzene. The solution was allowed to crystallize at low temperature, after which the crystals were separated from the mother liquor by filtration and washed with cold benzene. The crude material melted at 167°. The yield varied considerably with different lots, but from 27.5 kg. 97.7 g. of helenalin, or a yield of 0.36%, was obtained.

The material was recrystallized from boiling benzene. Thus obtained it consisted of colorless rods and irregular fragments which melted at 167°. In parallel polarized light (crossed nicols) the extinction was straight and the elongation was positive. The refractive indices as determined by the immersion method were η_α, 1.550 (crosswise

---

[1] E. Reeb, *J. Pharm. Elsass Lothringen*, **37**, 149 (1910).

[2] P. D. Lamson, *J. Pharmacol.*, **4**, 471 (1913).

[3] L. Gerhardt, *Ann.*, **34**, 192 (1840); J. Kallen, *Ber.*, **6**, 1506 (1873); **9**, 154 (1876).

[4] This material was obtained through the coöperation of H. R. Reed, Bureau of Animal Industry, U. S. Department of Agriculture, McNeill, Miss.

on rods); η_β, 1.568 (common, crosswise on rods), η_γ, 1.603 (lengthwise).[5]

Helenalin is optically active; 0.5017 g. dissolved in 10 cc. of 95% alcohol at 20° rotated the plane of polarized light in a 1-dm. tube 5.11° to the left; therefore $[\alpha]^{20}_D$ is $-101.9°$.

When 6.46 mg. of helenalin was dissolved in 49.26 mg. of camphor, the melting point of the latter was depressed 17.5°. This corresponds to a molecular weight of 300.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92; mol. wt., 262. Found: C, 68.60; H, 6.91; mol. wt., 300.

Acetylhelenalin.—A mixture of 1 g. of helenalin, 0.25 g. of dry sodium acetate and 4 cc. of acetic anhydride was boiled for ten minutes. Approximately one-half the acetic anhydride was then removed by distillation, and the residue was treated with 5 cc. of methanol. After the reaction had subsided, water was added to the solution, and the acetyl compound was allowed to crystallize. The yield was 1 g. It was recrystallized from its solution in methanol by adding an equal volume of water. Thus obtained, it consisted of colorless crystals which melted at 184°.

Anal. Calcd. for monoacetate $C_{17}H_{20}O_5$: C, 67.09; H, 6.63; mol. wt., 304. Found: C, 67.15; H, 6.67; mol. wt. (Rast), 333.

Methoxyacetylhelenalin.—A solution of 0.5 g. of helenalin in 2 cc. of pyridine was treated with 1 cc. of methoxyacetic anhydride. The liquid was heated to its boiling point and then allowed to cool and stand for two hours. Water was then added, and the oil which separated crystallized at once. The yield of the crude product was 0.55 g., and its melting point was 131–132°. It was recrystallized by adding 5 volumes of water to its methanolic solution, which had been filtered through norit. The purified product consisted of colorless six-sided rods that melted at 135°. In parallel polarized light (crossed nicols) its extinction is straight and its elongation is positive. In convergent polarized light (crossed nicols) fragments showing sections perpendicular to the acute bisectrix are common. The optic sign is negative and the axial angle (2E) is small. The refractive indices determined by the immersion method are: η_α, 1.525 (usually shown crosswise); η_β, 1.580; η_γ, 1.590 (usually shown lengthwise), all ±0.003.

Anal. Calcd. for $C_{18}H_{22}O_6$: C, 64.66; H, 6.44; OCH_3 (1), 9.28. Found: C, 64.27; H, 6.80; OCH_3, 9.39.

Tetrahydrohelenalin.—Five grams of helenalin dissolved in 150 cc. of ethyl acetate was reduced at atmospheric pressure with hydrogen and the platinum catalyst of Voorhees and Adams.[6] Two mols of hydrogen was absorbed. After the catalyst had been removed, 50 cc. of *n*-butyl ether was added to the solution, and the ethyl acetate was removed by distillation. Practically a quantitative yield of tetrahydro compound was obtained. It melted at 174–175°, and in a high vacuum it could be sublimed or distilled.

Recrystallized from boiling *n*-butyl ether, it consisted of long, colorless needles which melted at 176°. In parallel polarized light (crossed nicols) the extinction is straight and the elongation is negative. Many of the fragments do not extinguish sharply. In convergent polarized light (crossed nicols) many fragments show sections perpendicular to the acute bisectrix and extinguish in a hazy, indefinite manner. The optic sign is positive and the axial angle (2E) is small. Its refractive indices as determined by the immersion method are η_α, 1.545 (lengthwise on rods); η_β, 1.550; η_γ 1.570 (crosswise on rods) all ±0.003.

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.78; H, 8.40.

Acetyltetrahydrohelenalin.—This compound was made and purified in the same manner as acetylhelenalin. Its melting point was 145°.

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.22; H, 7.85; mol. wt., 308. Found: C, 66.39; H, 8.0; mol. wt., 321.

Dibromohelenalin.—A solution of 1 g. of helenalin in 10 cc. of chloroform was treated with a chloroform solution of 0.63 g. of bromine. The liquid was soon decolorized without the evolution of hydrobromic acid. The solvent was removed in a current of air, and the residue dissolved in hot ethanol. Two volumes of hot water were then added to the alcoholic liquid, and the dibromide was allowed to crystallize. It was recrystallized to a constant melting point of 161° from 50% acetic acid.

Anal. Calcd. for $C_{15}H_{18}O_4Br_2$: Br, 37.88. Found: Br, 37.87 and 37.97.

Summary

A method for the preparation of the physiologically active material that occurs in *Helenium autumnale* has been developed. The name "helenalin" has been proposed for this compound. It has been shown by analysis of the material itself, as well as of several of its derivatives, that it has the formula $C_{15}H_{18}O_4$ and that the molecule contains a hydroxyl group and two double bonds.

WASHINGTON, D. C.

RECEIVED AUGUST 1, 1936

---

[5] The optical crystallographic data were determined by George L. Keenan, of the Food and Drug Administration, U. S. Department of Agriculture.

[6] V. Voorhees, and R. Adams, THIS JOURNAL, **44**, 1397 (1922).