[CONTRIBUTION FROM THE DABNEY CHEMICAL LABORATORY OF THE UNIVERSITY OF TENNESSEE]

The Bitter Principle of Helenium Tenuifolium. I

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Helenium tenuifolium, commonly known as sneeze weed, bitter weed, or yellow dog fennel, is widely found in the Southern States. When eaten by cattle, it imparts an undesirable, bitter taste to the milk. As far as we have been able to learn, MacDonald and Weathers[1] were the first to investigate the nature of this bitter principle. From the dried leaves and flower heads of the mature plant, these investigators succeeded in extracting a white, bitter, crystalline material. This task proved to be unusually laborious because of the low temperature necessary to minimize gum formation. In addition, the crystals, melting originally at 152–170°, even after repeated fractional crystallization, melted over a range of several degrees. On subjection to various tests, the original crystals were shown by MacDonald and Weathers to contain no elements other than carbon, hydrogen, and oxygen, to be unsaturated toward bromine in chloroform, to reduce Fehling's solution, and to be optically inactive.

Because of the indefinite nature of the 152–170° melting crystals and the extreme ease with which they form a gum on treatment with chemical reagents, our efforts have been concentrated on the compound, melting at 158°, which is obtained from the impure crystals by the use of sodium carbonate followed by acidification with hydrochloric acid. This compound appears to be identical with that obtained by MacDonald and Weathers from the same source on treatment with sodium hydroxide. In our later experiments, time has been saved and gum formation has been eliminated by preparing it directly from the bitter weed.

Although the relation between the 158° melting compound and the 152–170° melting crystals is not known, the former appears to be produced by transformation rather than by separation since the crystalline form undergoes a change. Besides, although the compound is also bitter, it appears to be less unsaturated than the wide melting crystals in that it does not respond to bromine in chloroform, to Fehling's solution, nor does it exhibit as great a tendency toward gum formation. A white, needle-like product, this compound has been assigned tentatively the formula, $C_{17}H_{22}O_5$.[2] Although it does not react with bromine in chloroform, alcohol, benzene, or water solutions, it does in ethyl acetate to form, by substitution, the compound, $C_{17}H_{21}O_5Br$. Similarly, attempts to reduce the 158° melting compound in alcohol were unsuccessful, but in ethyl acetate, in the presence of a platinum catalyst, it absorbs two atoms of hydrogen to form $C_{17}H_{24}O_5$. With phenylhydrazine the latter appears to form a phenylhydrazone, a test which, strangely enough, has thus far not been satisfactorily applied to the original compound and its bromination product.

Although no definite evidence has been obtained for other functional groups, the investigation is being continued.

Experimental

I. Extraction and Purification[3] of the Bitter Principle.—(a) About 250 g. of the dried leaves and flower heads of *Helenium tenuifolium* was placed in a 3-liter round-bottomed flask (several flasks could be extracted at one time), after which the weed was covered with boiling, distilled water and placed in a deep water-bath maintained at a temperature of from 70 to 73° for from two to three hours. The flask and its contents were shaken occasionally and after the dark brown, aqueous extract obtained had been filtered off through several thicknesses of gauze, the weed was again treated with distilled water at 70°. This procedure was repeated three times, the last portion of water being left on the weed overnight.

(b) The bitter principle was then removed from its aqueous solution by extraction with chloroform of an amount equal to one-half of that of the original solution. Three separate extractions were used for the first aqueous extract, two for the second, and one for the third. Occasionally an emulsion formed in the first chloroform extract, but this usually disappeared on standing.

(c) The combined chloroform extracts were distilled until about two-thirds of the solvent was removed. The solution remaining was heated carefully on a water-bath at 70° and a current of air was passed over it until the last traces of chloroform had disappeared. A greenish-yellow, sticky residue was obtained in which was the bitter principle.

(d) For purification the above residue was dissolved by stirring in water at 75° for twenty to thirty minutes and

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(1) MacDonald and Weathers, unpublished work of the Agricultural Experiment Station, University of Tennessee.

(2) Because of the high molecular weight of this compound and its derivatives, it has been difficult to determine with certainty the exact number of hydrogen atoms present. The formulas assigned check all the analyses best, although $C_{17}H_{23}O_5$ and the corresponding derivatives are not far removed.

(3) The method employed is essentially that of MacDonald and Weathers.

after filtration while hot, the filtrate was evaporated to a smaller volume on large watch glasses at room temperature with the aid of an electric fan. From time to time the gum, which formed on the surface of the solution, was removed and eventually yellow crystals were deposited. Seven hundred and fifty grams of air-dried plant material yielded about 22 g. of these yellow crystals and 15 g. of gum. By recrystallization from dilute acetic acid (1:10) almost white crystals melting at 152–170° were obtained.

II. Conversion of the Bitter Principle into the 158° Melting Compound.—Two-tenths gram of 152–170° melting crystals was treated with 50 cc. of 5% sodium carbonate solution at room temperature. Upon standing several minutes, the crystals became light and fluffy, after which the mixture was acidified slightly. The crystals were removed and after several crystallizations from dilute acetic acid (1:10), were white and melted sharply at 158°.

III. Extraction and Recovery of the Bitter Principle as the 158° Melting Compound.—To accomplish this end the sticky residue from Ic was dissolved in 1 liter of distilled water at 75°. After being stirred at this temperature for about twenty minutes, the mixture was filtered to remove any undissolved solid. This filtrate was treated with 50 g. of animal charcoal,[4] after which the mixture was shaken vigorously, heated to 100°, and maintained there for fifteen minutes. The charcoal was then filtered off from the hot solution through a heated funnel and the filtrate, upon cooling, deposited slightly yellow, needle-shaped crystals. The weight of these crystals from 500 g. of the original weed varied from 10 to 15 g. Upon recrystallization from freshly boiled, distilled water, usually twice, about 6 or 7 g. of white crystals, melting at 158°, was obtained.

Anal. Calcd. for $C_{17}H_{22}O_5$: C,[5] 66.63; H, 7.21; mol. wt., 306. Found: C, 66.91; H, 7.48; mol. wt. (Rast), 317.

IV. Derivatives of the 158° Melting Compound. (a) The Bromination Product.—Five grams of the 158° melting compound was dissolved in dry ethyl acetate, after which a solution of bromine in ethyl acetate was dropped into the bitter solution, drop by drop with shaking, until the bromine color just persisted. Since hydrogen bromide is soluble in ethyl acetate, there was no evolution of this gas. After removing the solvent in a current of air, slightly colored, transparent crystals remained. These were crystallized first from a mixture of 200 cc. of absolute ethanol and 400 cc. of distilled water and then from 50% acetic acid. The crystals were white and melted at 200°.

Anal. Calcd. for $C_{17}H_{21}O_5Br$: C, 52.98; H, 5.50; Br, 20.75; mol. wt., 385. Found: C, 53.05; H, 5.68; Br, 20.75; mol. wt. (Rast), 388.

(b) The Reduction Product.—Five grams of the 158° melting compound was dissolved in 150 cc. of dry ethyl acetate and to this was added 0.3 g. of platinum oxide catalyst. The mixture was then subjected to hydrogen at 20 lb. (1.3 atm.) pressure in a Burgess–Parr catalytic reduction apparatus. In thirty minutes the pressure dropped 2.5 lb. and then the mixture was filtered and the filtrate was evaporated to dryness in a current of air. The transparent crystals remaining were taken up in 30 cc. of hot ethanol to which solution there was added 60 cc. of hot distilled water. Upon cooling, diamond-shaped crystals appeared. Another recrystallization from *n*-butyl ether gave white crystals melting at 150.8°.

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.19; H, 7.85; mol. wt., 308. Found: C, 66.60; H, 8.09; mol. wt. (Rast), 319.

(c) The Supposed Phenylhydrazone of the Reduction Product.—To 1 g. of the reduced compound dissolved in 10 cc. of absolute ethanol, distilled water was added dropwise until the cloudiness, which first formed, just disappeared. Then there was added 1 cc. of pure phenylhydrazine, after which the solution was warmed and 5 drops of glacial acetic acid was added. After about an hour, clear, almost white crystals began to form. When filtered off, washed with distilled water, and dried, they melted at 205–210°. By dissolving these in hot absolute ethanol and adding water again until the cloudiness just disappeared, white crystals melting at 209–210° soon formed.

Anal. Calcd. for $C_{23}H_{30}O_4N_2$: N, 7.04; mol. wt., 398. Found: N, 6.96; mol. wt. (Rast), 400.

Summary

A method for the isolation of the bitter principle of *Helenium tenuifolium* has been described. Because of the difficulty of purifying this solid and its sensitivity toward gum formation, a compound of greater stability, derived from it by alkali treatment, has been investigated. This compound, tentatively given the formula $C_{17}H_{22}O_5$, reacts with bromine by substitution and absorbs two hydrogen atoms. Only the reduction product reacts with phenylhydrazine to form what appears to be a phenylhydrazone.

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[4] The best results were obtained with a product from The Will Corporation. Apparently the calcium phosphate present as an impurity produced the effect desired.

[5] All the analyses for C and H were microdeterminations made by the Arlington Laboratories, Arlington, Va.