prepared from 2,6-dimethoxyphenyl duryl ketone by replacement of the methoxyl groups by the action of methylmagnesium iodide.

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Helenalin. I. Isolation and Properties

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Helenalin, the bitter principle of the common sneezeweed *Helenium autumnale*, is reported to be a severe local irritant of nose, eye and stomach.[1] Due to the wide distribution of the plant, its toxicity is of concern to the livestock industry. There are also reports on its activity as a vermifuge,[1] fish poison[2] and insecticide.[3]

According to Clark,[4] helenalin is also found in *Helenium macrocephalum* and *Helenium quadridentatum*, while four other *Helenium* species, *badium, tenuifolium, elegans* and *montanum*, yield the bitter principle tenulin. Helenalin, m. p. 167°, has been shown by the same author[2] to possess the formula $C_{15}H_{18}O_4$ and contains a hydroxyl group and two double bonds.

Since a supply of yet another *Helenium* species, *Helenium microcephalum*, was made available to us and since extraction of this material was found to give helenalin, a further study of this interesting substance has been undertaken. The present series of papers describes the results obtained to date.[5]

Proof for the identity of our product with helenalin was furnished by comparison with a sample of m. p. 165.5–166° from the collection of the late Dr. E. P. Clark.[6] This sample did not depress the melting point of a product, m. p. 167–168°, whose isolation is described in the experimental part, and the infrared spectra of the two were identical.

The melting point of the material obtained by extraction of *Helenium microcephalum* depends on the manner of crystallization, analytical samples melting fairly sharply at points within the temperature range 167–178°. Combustion of all fractions confirmed the formula $C_{15}H_{18}O_4$ and each sample gave the same derivatives. All fractions had $[\alpha]^{25}\mathrm{D}$ in the range -102.0 to $-102.8°$ a value which, within experimental error, coincided with that, $[\alpha]^{20}\mathrm{D} - 101.9°$, given by Clark. Infrared spectra determined in chloroform solution, where differences in crystal structure would be expected to disappear, were identical. This suggests that the material is structurally homogeneous and that variations in melting point may be attributed to differences in crystal structure. Nevertheless, the presence of small amounts of impurities capable of altering the melting point cannot be excluded.

Acetylation of helenalin gave a monoacetyl derivative which melted at 179.5–180.5°; the melting point of acetylhelenalin as given by Clark is 184°. The melting points of tetrahydrohelenalin and acetyltetrahydrohelenalin coincided with those reported by Clark.

Helenalin shows a weak yellow color on treatment with sulfuric acid which changes to deep brown on heating. It gives a positive Legal and Zimmermann test. Attempts to demonstrate the presence of an active methylene group by reaction with aromatic aldehydes have not led to the isolation of pure products. Acetylhelenalin reacts with piperonal in ethanolic hydrogen chloride, but since the product contains a molecule of hydrogen chloride, addition of which may have preceded condensation, the reaction does not provide sufficient evidence for the presence of such a group.

In view of a negative reaction with ferric chloride the hydroxyl group whose presence was demonstrated by Clark[2] is probably not phenolic or enolic. This group was further characterized by the formation of an *o*-bromobenzoate, a *p*-nitrobenzoate and a 3,5-dinitrobenzoate. It did not react with phthalic anhydride or phenyl isocyanate under stringent conditions, but the ease with which it is acetylated and the failure in all attempts at dehydration are arguments against the assumption that it is tertiary. In another paper[7] experimental data demonstrating that it is a secondary hydroxyl will be presented.

Helenalin gives no color with Schiff reagent and thus contains no aldehyde group but rapidly reduces Tollens reagent. This is in harmony with the ultraviolet spectrum[8] (Fig. 1) which is typical of an α,β-unsaturated ketone.[9] The position of the first maximum (λ = 223 mμ; ϵ = 11900) suggests that helenalin is a mono-

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[1] Lamson, *J. Pharmacol. Exptl. Therap.*, **4**, 471 (1913).

[2] Clark, THIS JOURNAL, **58**, 1982 (1936).

[3] McGovran, Mayer and Clark, U. S. Dept. Agr. Bur. Entomol. Plant Quarantine, *Entomol. Technic.*, E-572 (1942).

[4] Clark, THIS JOURNAL, **61**, 1836 (1939); **62**, 597 (1940).

[5] We wish to thank Mr. H. R. Reed, Bureau of Animal Industry, U. S. Department of Agriculture, Sonora, Texas, for a supply of this plant. It is noteworthy that tenulin, not helenalin, was obtained by extraction of *Helenium autumnale*, var. *canaliculata*, from the same source, indicating that this variety may actually be a different species. This experiment was carried out by B. F. Aycock and A. E. Senear.

[6] Supplied by Dr. R. C. Roark, Bureau of Entomology and Plant Quarantine, U. S. Department of Agriculture, Washington, D. C.

[7] Adams and Herz, THIS JOURNAL, **71**, 2554 (1949).

[8] Ultraviolet spectra were determined by Mrs. Dorothy C. Brantley on 0.001 *N* solutions in 95% ethanol.

[9] Woodward, THIS JOURNAL, **63**, 1123 (1941); **64**, 76 (1942).

substituted α,β-unsaturated ketone if the absorbing group is a member of a straight chain or a six-membered ring or that it is a disubstituted α,β-unsaturated ketone if the chromophore is part of a five-membered ring.[10] The ultraviolet spectrum of acetylhelenalin (λ_1 = 221 mμ, ϵ_1 = 12600; λ_2 = 316 mμ, ϵ_2 = 61) is very similar to that of helenalin. On the other hand, the spectrum of tetrahydrohelenalin (Fig. 1) has only one peak at 288 mμ (ϵ = 31), a position corresponding to the absorption due to a normal ketone group.[11] Evidently at least two of the hydrogen atoms taken up during the reduction of helenalin to tetrahydrohelenalin have added to a conjugated ketone system.

These conclusions are corroborated by an examination of the infrared spectra[12] of helenalin and its derivatives. Figure 2 shows the infrared spectra of helenalin and tetrahydrohelenalin[13]; the spectra of all other compounds reported in this paper were also determined but will not be described in detail.

All samples except acyl derivatives contained a strong —OH stretching frequency. In helenalin, this occurs in the region of bonded hydroxyl around 3300 cm.$^{-1}$, while in tetrahydrohelenalin it is 150–200 cm.$^{-1}$ higher, in the region of free —OH. This may be due to differences in hydrogen bonding in the crystal lattice of the samples. On the other hand, saturation of the double bonds of helenalin might possibly reduce the degree of chelation between the hydroxyl and a carbonyl group, the latter accounting for the absorption at 1702–1713 cm.$^{-1}$ in helenalin and its esters and at 1737 cm.$^{-1}$ in tetrahydrohelenalin. Chelation (between the ketone and hydroxyl), however, is ruled out by the circumstance that the carbonyl frequency in the esters, where no hydroxyl is present, is only slightly higher than in helenalin itself. Therefore, the shift in the position of the carbonyl band from 1702 to 1737 cm.$^{-1}$ is due to the change from a conjugated to an unconjugated carbonyl group, especially since it is accompanied by the disappearance of a relatively weak absorption at about 1580 cm.$^{-1}$ which has been ascribed to highly conjugated C=C.

The position of the carbonyl frequency in tetrahydrohelenalin (1737 cm.$^{-1}$) is higher than in most unconjugated acids, aldehydes and ketones except for cyclopentanones. Similarly, the frequency of the conjugated carbonyl group in helenalin and its derivatives (1702–1713 cm.$^{-1}$) is exceedingly high and the band ascribed to conjugated C=C (1580 cm.$^{-1}$) is unusually low compared with the bands reported for normal α,β-unsaturated ketones.[14] According to a recent report[15] the carbonyl maxima of several conjugated 17-keto steroids occur at 1716 cm.$^{-1}$, while the carbonyl maxima of saturated 17-ketosteroids lie in the range 1735–1745 cm.$^{-1}$. This suggests the possible presence of a cyclopentenone ring in helenalin.

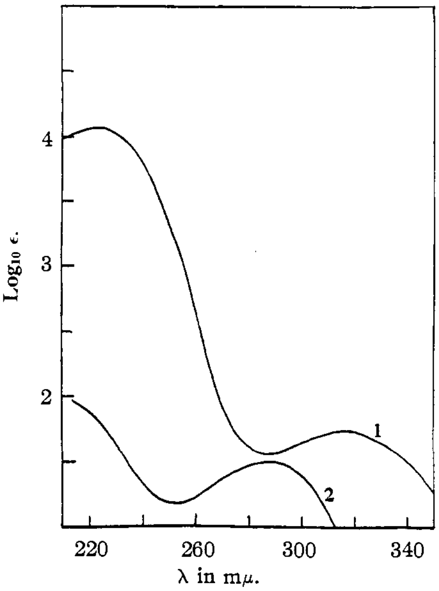

Fig. 1.—Ultraviolet absorption spectra of: 1, helenalin: 2, tetrahydrohelenalin: in 95% ethanol.

All spectra contain another band in the carbonyl region which occurs in the range 1750–1777 cm.$^{-1}$. This band usually has the highest frequency (1770 cm.$^{-1}$ or higher) when the hydroxyl group is protected. Reduction does not affect it to any great extent and it can only be attributed to the presence of an ester or lactone group. Since helenalin contains no methoxyl groups,[2] the two oxygen atoms furnished by an ester or lactone, together with the oxygen contained in the hydroxyl and carbonyl groups, satisfactorily account for all oxygens of the formula $C_{15}H_{18}O_4$.

Helenalin and its derivatives are insoluble in cold sodium carbonate, but dissolve gradually in cold strong base and immediately on warming with the formation of a deep red color. Acidification reprecipitates crude helenalin, but prolonged boiling causes extensive decomposition. Fully-reduced derivatives, like tetrahydrohelenalin, show no red color on treatment with base and may be recovered on acidification. This behavior suggests the presence of a lactone rather than of a true ester; however, attempts to isolate

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(10) Gillam and West, *J. Chem. Soc.*, 486 (1942).

(11) Gillam and West, *ibid.*, 95 (1945).

(12) We are indebted to Mrs. Agatha Roberts Johnson for the determination and interpretation of these spectra.

(13) The spectrum of helenalin shown in Fig. 2 is the nujol mull spectrum of a fraction, m. p. 167–168°, whose isolation is described in the experimental part, and is identical with the infrared spectrum of a sample prepared by Clark.[2] The curve for tetrahydrohelenalin is the nujol mull spectrum of an early sample which differed slightly from the spectrum of later preparations. These differences were ascribed to the presence of two different crystalline modifications since the spectra in chloroform solution, where isomerization would not be expected to occur, were found to be identical.

(14) Barnes, Gore, Liddel and Williams, "Infrared Spectroscopy," Reinhold Publishing Corp., New York, N. Y., 1944.

(15) Jones, Williams, Whalen and Dobriner, THIS JOURNAL, **70**, 2024 (1948).

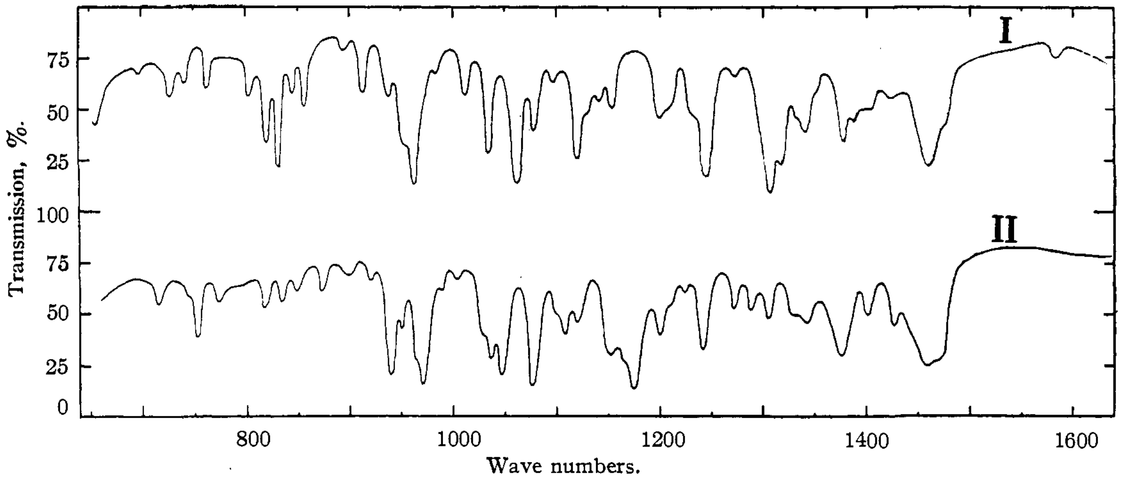

Fig. 2.—Infrared absorption spectra of: I, helenalin; II, tetrahydrohelenalin. (These samples were prepared by grinding the crystalline compounds with paraffin oil to reduce light scattering. Absorptions due to the C–H frequencies of the paraffin oil occur at 2920, 2855, 1459 and 1378 cm.$^{-1}$ and partially mask the C–H frequencies of the compounds.)

an acid by careful neutralization of the basic solution with dilute acid have not been successful nor has it been possible to prepare an amide or ester.

A weak band at 1671 cm.$^{-1}$ in the helenalin spectrum is shifted to about 1660 cm.$^{-1}$ and is somewhat stronger in the acyl derivatives. Its position and strength indicate that it is due to conjugated C=C, thus accounting for the second double bond observed by Clark. The absence of phenyl frequencies in the infrared and ultraviolet spectra shows that helenalin contains no benzene rings.

The results of C-methyl determinations suggest that at least one of the double bonds of helenalin is part of a terminal vinyl group. Helenalin gives 0.87 mole of acetic acid, tetrahydrohelenalin 2.05 moles. This conclusion is supported by the ozonolysis of helenalin and acetylhelenalin which gives a 50–60% yield of formaldehyde. No other volatile aldehydes or ketones were detected. The neutral fraction was negligible; the acid fraction from which no well-defined products have as yet been isolated gave no test with Schiff reagent and liberated no iodoform. The failure of these tests shows that the terminal double bond cannot be part of the structures —$CH{=}CH_2$ or $RC(CH_3){=}CH_2$.

Additional evidence for the terminal double bond is furnished by the spectrum of melted helenalin (not shown) which contains only one methyl deformational frequency at 1384 cm.$^{-1}$ whereas tetrahydrohelenalin contains three separate bands at 1370, 1380 and 1394 cm.$^{-1}$. However, the complexity of the helenalin spectrum in the 850–1000 cm.$^{-1}$ region is such that conclusions regarding the degree of substitution around the double bond[16] cannot be based on it.

The carbonyl group of helenalin has not yet been characterized satisfactorily. We have been unable to isolate a semicarbazone and while evidence for the formation of a 3,5-dinitrophenylhydrazone has been secured the derivative has not been obtained in pure form. Reaction with hydroxylamine under a variety of conditions finally yielded a high-melting compound whose analysis indicated that two molecules of hydroxylamine had reacted with one molecule of ketone, presumably forming a hydroxylimino oxime. Evolution of acetone on boiling helenalin with aluminum isopropoxide in isopropyl alcohol, however, established the presence of a reducible keto group. The spectrum of the glassy product showed the disappearance of the ketone and conjugated C=C absorption.

The parallel results reported by Clark[2] differ significantly from our observations only in bromination studies. Bromination of helenalin always led to a dibromohelenalin which decomposed at 130°. Analysis and spectrum indicated saturation of the conjugated double bond. On standing, or on recrystallization from various solvents, this product lost hydrogen bromide and yielded a monobromohelenalin melting at 164.5°, while Clark reported the isolation of a dibromohelenalin, m. p. 161°, which could be recrystallized without change. The ultraviolet spectrum of our bromohelenalin ($\lambda_{1\,\max} = 248$ mμ, $\epsilon_{1\,\max} = 6300$; $\lambda_{2\,\max} = 314$ mμ, $\epsilon_{2\,\max} = 97$) was typical of an α-bromo-α,β-unsaturated ketone[17]; its infrared spectrum

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[16] Thompson and Torkington, *Trans. Faraday Soc.*, **51**, 246 (1945): Thompson and Whiffen, *J. Chem. Soc.*, 1412 (1948).

[17] Few data are available on such compounds. Recently Djerassi and Scholz[18] reported an average maximum of 256 mμ for several α-bromo-β-alkylsubstituted α,β-unsaturated ketones of the steroid series. The predicted value[7] was 235 mμ. If the difference of 21 mμ is considered the normal shift due to the replacement of hydrogen by bromine, a theoretical maximum for bromohelenalin of 244 mμ is obtained by adding 21 mμ to the maximum of 223 mμ observed in helenalin. This is in good agreement with the actual maximum of 248 mμ.

[18] Djerassi and Scholz, THIS JOURNAL, **69**, 2404 (1947); *ibid.*, **70**, 1911 (1948).

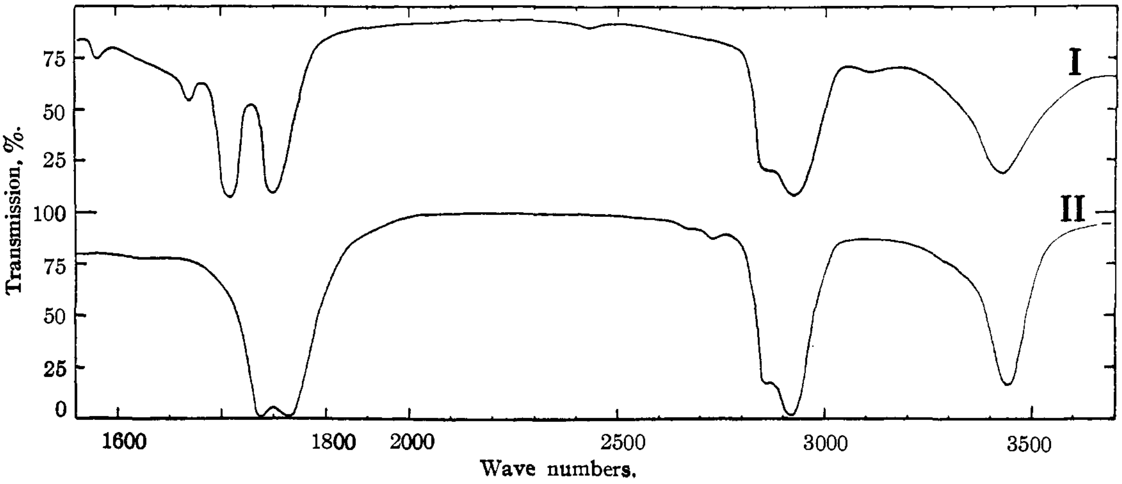

Fig. 2.

also showed that the elimination of hydrogen bromide had resulted in the regeneration of α,β-unsaturation. The hydrogen necessary for elimination must have been furnished by the carbon atom *alpha* to the ketone group. This suggests that the α-carbon originally contains no substituent other than hydrogen, *i. e.*, that the group R—CO—CH=CR$_2$ is present in helenalin.

Acetylhelenalin was subjected to a similar series of reactions. When acetylhelenalin was brominated in glacial acetic acid solution, the first product was dibromoacetylhelenalin. However, prolonged boiling was required to dehydrohalogenate this dibromide completely, whereas the unacetylated dibromide was transformed slowly even in the cold.

Experimental

Helenalin.—The procedure of Clark was satisfactory for the extraction of ground whole plants of *Helenium microcephalum*. After two recrystallizations from benzene and absolute ethanol the product melted in the range 164-169°; this was deemed sufficiently pure for further work. The average yield from an extraction of 25 lb. of the dried plant was 38.5 g. (0.38%); individual yields of five extractions varied from 27-43 g. A sixth extraction, carried out without modification of the above procedure, gave 95 g. (0.81%). Each extraction gave considerable quantities (4-19 g.) of slightly-colored lower-melting crystals which were combined and recrystallized to give an additional 18 g. of helenalin. The mother liquors contained appreciable amounts of non-crystalline material and were reserved for later investigation.

When the product was recrystallized several times from benzene, the melting point rose to 169-172°.

Rotation.—0.0925 g. made up to 2 ml. with 95% ethanol gave α_D −4.74°; *l*, 1; $[\alpha]^{25}_D$ −102.4°.

Anal.[19] Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.90; H, 7.10; C-methyl (Kuhn-L'Orsa), 0.87 mole.

The infrared nujol mull spectrum of this sample indicated that it was a mixture of two forms isolated in the following manner. Helenalin, m. p. 164-169°, was recrystallized three times from absolute ethanol. The last fraction melted at 176-178°.

Rotation.—0.0302 g. made up to 1 ml. with 95% ethanol gave α_D −3.08°; *l*, 1; $[\alpha]^{25}_D$ −102.0°.

Anal. Found: C, 68.85; H, 7.15.

The mother liquors were combined, evaporated to dryness at reduced pressure and the residue recrystallized three times from pure benzene. The last fraction melted at 167-168°; the melting point of a mixture with Clark's sample of m. p. 165.5-166° was 166-168°.

Rotation.—0.0728 g. made up to 2 ml. with 95% ethanol gave α_D −3.78°; *l*, 1; $[\alpha]^{25}_D$ −102.8°. The nujol mull spectrum of this sample is given in Fig. 1 and is identical with the spectrum of Clark's sample.

Anal. Found: C, 68.59; H, 6.92.

While the nujol mull spectra of these fractions differed slightly probably due to differences in crystal structure, the spectra were completely identical when determined in chloroform solution or as a melt. The possibility of a chemical reaction with ethanol was ruled out by refluxing a sample of helenalin for forty-eight hours with absolute ethanol. The same fractions were isolated from the reaction mixture.

Only starting material was isolated when helenalin and phenyl isocyanate were refluxed together, either without or with solvent. No reaction was observed when helenalin was refluxed with phthalic anhydride in benzene solution or when the reactants were fused at 180°. Helenalin may be purified by sublimation and does not decompose appreciably on being heated above its melting point.

The Zimmermann test[20] gave an immediate red color changing to purple. Three modifications of the Legal test were applied. Method A[21] gave a deep purple color which changed to greenish-yellow on acidification. Method B[22] gave a purple color which faded slowly. The third method[23] gave a deep purple color fading to a faint yellow green after sufficient base had been added to make the solution alkaline; further addition of nitroprusside did not cause reappearance of the purple color.

Acetylhelenalin.—This compound was prepared by the method of Clark and melted at 179.5-180.5° after several recrystallizations from aqueous methanol. Its infrared spectrum showed the absence of unacetylated hydroxyl groups.

Anal. Calcd. for $C_{17}H_{20}O_5$: C, 67.09; H, 6.63. Found: C, 67.09; H, 6.86.

Piperonylidene Derivative of Acetylhelenalin.—A solution of 115 mg. of acetyltetrahydrohelenalin and 64 mg. of

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[19] Analyses by Miss Theta Spoor, Mrs. Jane Wood and Miss Emily Davis. C-Methyl determinations by Mr. Howard C. Clark.

(20) Zimmermann, *Z. physiol. Chem.*, **233**, 257 (1935).

(21) Jacobs and Hoffman, *J. Biol. Chem.*, **67**, 333 (1926).

(22) Meyer, "Analyse und Konstitutionsermittlung organischer Verbindungen," 6th ed., p. 550 (1938).

(23) Paist, Blout, Uhle and Elderfield, *J. Org. Chem.*, **6**, 273 (1941).

piperonal in 2 ml. of absolute ethanol was treated with 5 ml. of absolute ethanol saturated with hydrogen chloride in the cold. After eighteen hours, the purple solution was concentrated to small volume at reduced pressure; the pale yellow crystals weighing 97 mg. were filtered and, after two recrystallizations from benzene-pentane, melted at 214°. The Legal and Zimmerman tests were negative.

Anal. Calcd. for $C_{25}H_{25}O_7Cl$: C, 63.49; H, 5.33; Cl, 7.50. Found: C, 63.57; H, 5.62; Cl, 7.50.

Dilution of the mother liquor with water yielded yellow material of unsharp melting point which also contained chlorine. A similar product was obtained when attempts were made to prepare a piperonylidene derivative of helenalin. The action of ethanolic hydrogen chloride alone on helenalin and acetylhelenalin was also investigated; the solutions acquired a deep purple color but no crystalline material was isolated.

_o_-Bromobenzoylhelenalin.—The crude product obtained by condensation of 540 mg. of helenalin and 0.3 ml. of *o*-bromobenzoyl chloride in pyridine weighed 137 mg. and after recrystallization from benzene–ligroin, melted at 162–163°.

Anal. Calcd. for $C_{22}H_{21}O_5Br$: C, 59.34; H, 4.75. Found: C, 59.45; H, 4.97.

_p_-Nitrobenzoylhelenalin.—The analysis of the material obtained by recrystallization from benzene–ligroin, m. p. 111° with foaming, indicated the presence of one-half molecule of benzene of crystallization.

Anal. Calcd. for $C_{22}H_{21}NO_7 \cdot 0.5C_6H_6$: C, 66.65; H, 5.37; N, 3.11. Found: C, 66.65; H, 5.77; N, 3.29.

The solvent was removed by drying the sample at 100°. The m. p. was unchanged but no foaming was observed.

Anal. Calcd. for $C_{22}H_{21}NO_7$: C, 64.22; H, 5.15. Found: C, 64.61; H, 5.32.

3,5-Dinitrobenzoylhelenalin.—The fine needles obtained on recrystallization from benzene–ligroin could not be freed of solvent. On immersion at 180° the product melted sharply at 183° with gas evolution, but when the melt was cooled and reheated, it melted at 215°.

Anal. Calcd. for $C_{22}H_{20}N_2O_9 \cdot 0.5C_6H_6$: C, 60.61; H, 4.68; N, 5.66. Found: C, 60.62; H, 4.89; N, 5.95.

Recrystallization from acetone–water gave a product melting at 213° whose analysis still indicated the presence of a small amount of solvent after prolonged drying.

Anal. Calcd. for $C_{22}H_{20}N_2O_9$: C, 57.87; H, 4.44; N, 6.14. Found: C, 58.43; H, 4.94; N, 5.88.

Tetrahydrohelenalin.—This compound was prepared by the method of Clark and melted at 175–176°. It gave a positive Legal and Zimmerman test and consumed one mole of alkali on being refluxed with an excess of 0.1024 *N* sodium hydroxide solution.

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.62; H, 8.22; C-methyl (Kuhn-L'Orsa), 2.05 moles.

Acetyltetrahydrohelenalin.—This substance, obtained by acetylation of tetrahydrohelenalin, after several recrystallizations from methanol–water, melted at 145°.

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.22; H, 7.85. Found: C, 66.28; H, 7.92.

It was also prepared by reduction of acetylhelenalin in ethyl acetate solution with platinum oxide. Its spectrum (λ_{max} = 287 mμ; ϵ_{max} = 36) was similar to that of tetrahydrohelenalin.

Dibromohelenalin.—A solution of 50 mg. of helenalin in 1 ml. of glacial acetic acid was treated with a solution of 1.03 g. of bromine in 15 ml. of acetic acid at room temperature. The color was permanent after 0.49 ml., corresponding to 33 mg. of bromine, had been added. The calculated uptake was 31 mg. The product obtained on dilution with water weighed 71 mg. and was purified by reprecipitation with water from its solution in ethanol. It became brown above 120° and decomposed at 130° with gas evolution. When the preparation was carried out in chloroform, the product decomposed at 130–133°.

Anal. Calcd. for $C_{15}H_{18}O_4Br_2$: C, 42.68; H, 4.30. Found: C, 42.74; H, 4.60.

Bromohelenalin.—When an attempt was made to recrystallize dibromohelenalin from 50% ethanol, the shiny white platelets which separated on cooling were found to melt at 164.5°. The same compound was isolated when dibromohelenalin was recrystallized from 50% acetic acid as suggested by Clark, although it required three recrystallizations to bring the melting point up to 164.5°.

Anal. Calcd. for $C_{15}H_{17}O_4Br$: C, 52.81; H, 5.02. Found: C, 53.49; H, 5.50.

Reduction of 405 mg. of bromohelenalin dissolved in 40 ml. of ethanol, using platinum oxide catalyst, gave 270 mg. of crude tetrahydrohelenalin which, after purification, melted at 174–176°.

Dibromoacetylhelenalin.—A solution of 100 mg. of acetylhelenalin in 1.5 ml. of glacial acetic acid absorbed 56 mg. of bromine (calcd. 52 mg.) when exposed to light from an ordinary light bulb. The product was precipitated with water and, after reprecipitation from acetic acid, decomposed at 153–154°.

Anal. Calcd. for $C_{17}H_{20}O_5Br_2$: C, 43.98; H, 4.34. Found: C, 44.69; H, 4.49.

Bromoacetylhelenalin.—A solution of 296 mg. of crude dibromoacetylhelenalin in 5 ml. each of ethanol and water was boiled for one-half hour. The precipitate which separated on dilution with water weighed 220 mg. and was recrystallized from dilute ethanol. The long needles melted at 153.5°.

Anal. Calcd. for $C_{17}H_{19}O_5Br$: C, 53.28; H, 5.00. Found: C, 53.31; H, 5.24.

Reaction of Helenalin with Hydroxylamine Hydrochloride.—A mixture of 262 mg. of helenalin, 130 mg. of hydroxylamine hydrochloride, 150 mg. of anhydrous sodium acetate and 2 ml. of absolute ethanol was refluxed for sixteen hours. On cooling and diluting with water a white solid separated. It was extracted with hot ethanol; the ethanol extract was concentrated and diluted with water. Another recrystallization from dilute ethanol gave a small amount of amorphous solid which melted at 200–203° with foaming.

Anal. Calcd. for $C_{15}H_{22}N_2O_5$: C, 58.06; H, 7.15. Found: C, 58.37; H, 7.50.

Reduction of Helenalin with Aluminum Isopropoxide.—A solution of 1 g. of helenalin and 4 g. of aluminum isopropoxide in 20 ml. of dry isopropyl alcohol was refluxed for five hours. At the end of this period, the solvent was removed by slow distillation. After one hour, 20 ml. of isopropyl alcohol was added and the distillation continued until the distillate no longer gave a test for acetone. The mixture was evaporated to dryness at reduced pressure and, after decomposition with 25 ml. of 10% sulfuric acid, was exhaustively extracted with ether. After drying, the ether was removed *in vacuo;* the residue could not be induced to crystallize. Approximately 100 mg. of the crude product was purified by evaporative distillation at 200–230° (bath temperature) and 0.1 mm. The distillate was analyzed immediately.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.29; H, 8.15.

The product reacted with a variety of alcohol reagents, but yielded no solid esters. Phenyl isocyanate gave a mixture of phenylurethans which could not be separated into its components.

In the course of one reduction 29 mg. of white crystalline material with m. p. 196–201° separated during the decomposition with dilute acid. The spectrum of this material was quite different from that of the normal product, since it showed a strong band at 1693 cm.$^{-1}$ (a normal carbonyl frequency) and very strong C=C absorption at 1627 cm.$^{-1}$. No frequency corresponding to the former conjugated C=C was observed. While the analysis does not permit a clear-cut distinction between the two formulas $C_{15}H_{18}O_4$ and $C_{15}H_{20}O_4$, the spectrum strongly suggests that this compound is the product of an intramolecular oxidation-reduction reaction in which the carbonyl and hydroxyl functions of helenalin have been interchanged.[24]

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.40; H, 7.31.

Ozonolysis of Helenalin.—A solution of 1 g. of helenalin in 30 ml. of glacial acetic acid was ozonized for two hours with a current of oxygen containing 2.5–3% ozone corresponding to a flow of 0.24–0.26 millimole per minute. The acetic acid solution of the ozonide was diluted with 30 ml. of water and steam distilled for one and one-half hours. The volume of distillate was 400 ml. After treatment of 100 ml. of the distillate with 150 ml. of a saturated aqueous solution of methone, the mixture deposited during twelve hours 159 mg. of the methone derivative of formaldehyde, m. p. 187–188° (57%). Recrystallization from ethanol raised the melting point to 189°.

Another 100 ml. of distillate was treated with 100 ml. of a saturated ethanolic solution of 2,4-dinitrophenylhydrazine. No precipitate was observed. Concentration of the mixture to 125 ml. and cooling yielded yellow needles which, after three recrystallizations from ethanol, melted at 162–163°. The product proved to be formaldehyde 2,4-dinitrophenylhydrazone.

Anal. Calcd. for $C_7H_6N_4O_4$: C, 40.00; H, 2.88. Found: C, 40.15; H, 2.95.

The residue remaining after steam distillation was separated into neutral and acidic fractions in the usual manner. The neutral fraction was insignificant; the acidic fraction was a red gum whose spectrum and chemical behavior still indicated the presence of α,β-unsaturation. The Schiff and iodoform tests were negative. Attempts to obtain solid derivatives by reaction with alcohol and ketone reagents were unsuccessful.

Variation of time of ozonization, solvent and manner of working up the ozonide gave similar results. Ozonolysis of acetylhelenalin in the manner described produced a 45% yield of formaldehyde as the methone derivative. The behavior of the acidic fraction resembled that of the gum obtained by ozonolysis of helenalin.

Summary

Helenalin has been isolated from *Helenium microcephalum.* The empirical formula, $C_{15}H_{18}O_4$, as well as the presence of two double bonds and of a hydroxyl group has been confirmed by the preparation of a number of derivatives.

Chemical and physical evidence establishes the presence of the grouping R—CO—CH=CR$_2$, possibly part of a five-membered ring, and makes likely the presence of a lactone ring. These functional groups account satisfactorily for all four oxygen atoms and for one of the double bonds. The other double bond is unconjugated and part of a terminal methylene group.

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[24] The possibility of dismutation in high-molecular weight hydroxy-ketones is discussed briefly by Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937), who cites the conversion of dehydroandrosterone to testosterone. Another example is reported by Wintersteiner and Ruigh, THIS JOURNAL, **64**, 2453 (1942).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Helenalin. II. Helenalin Oxide

BY ROGER ADAMS AND WERNER HERZ

The present paper reports the reaction of helenalin with alkaline hydrogen peroxide which supports previously cited evidence that helenalin is an α,β-unsaturated ketone.[1] The properties of the resulting keto-epoxide have been investigated in an effort to find a way for the degradation of helenalin.

The reaction of helenalin with alkaline hydrogen peroxide under the usual conditions[2] generally led to complicated mixtures, apparently due to further oxidation of the primary product. However, helenalin and acetylhelenalin formed the expected keto-epoxides in fair yield when the reactants were chilled to $-10°$ and the solid separating in the course of addition was filtered immediately. The infrared spectra of these compounds are completely analogous and show that indeed the conjugated and not the isolated double bond has been attacked. The absorption near 1660 cm.$^{-1}$ corresponding to isolated C=C is still present, while the band at 1580 cm.$^{-1}$ has disappeared and the low frequency carbonyl absorption has moved from 1702 to 1735 cm.$^{-1}$. The presence of a keto-epoxy group is also indicated by the liberation of iodine from acetic acid–potassium iodide solution.[3]

The relation between helenalin oxide and acetylhelenalin oxide has been further demonstrated by acetylation of the former which gives rise to the same compound as is formed by the action of hydrogen peroxide and acetylhelenalin. This makes all the more surprising a difference in the ultraviolet absorption spectra of helenalin oxide ($\lambda_{\max.} = 309$ mμ, $\epsilon_{\max.} = 43$) and acetylhelenalin oxide ($\lambda_{\max.} = 268$ mμ, $\epsilon_{\max.} = 600$). Compared with the spectrum of tetrahydrohelenalin ($\lambda_{\max.} = 288$ mμ),[1] substitution of the epoxide ring in the α-position has shifted the peak of helenalin oxide 20 mμ toward the red and the peak of acetylhelenalin oxide 20 mμ toward the blue. The second shift is accompanied by a considerable increase in the intensity of absorption.[4] Because of the complete lack of other

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[1] Adams and Herz, THIS JOURNAL, **71**, 2546 (1949).

[2] Weitz and Scheffer, *Ber.*, **54**, 2327 (1921).

[3] Karrer, *Helv. Chim. Acta*, **30**, 1780 (1947).

[4] An epoxide ring *alpha* to a carbonyl group might possibly be expected to shift the carbonyl frequency toward a slightly longer wave length and produce greater intensity of absorption. This would appear to be borne out by our measurements on the oxide of mesityl oxide ($\lambda_{\max.} = 288$ mμ, $\epsilon_{\max.} = 54$) as compared with the spectrum of methyl isobutyl ketone [Wolf, *Z. physik. Chem.*, **B2**, 39 (1929)]. The peak absorptions of benzalacetophenone oxide, if compared with the spectrum of β-phenylpropiophenone [Ramart-Lucas and Salmon-Legagneur, *Bull. soc. chim.*, **51**, 1069 (1932)] are similarly displaced by 8-12 mμ.