

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 $C_7H_8N_4O_4$: C, 40.00; H, 2.88. Found: C, 40.15; H, 2.95.

(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).

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.

URBANA, ILLINOIS

RECEIVED FEBRUARY 11, 1949

[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 conditions² 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 ($\lambda_{\text{max.}} = 309\text{ m}\mu$, $\epsilon_{\text{max.}} = 43$) and acetylhelenalin oxide ($\lambda_{\text{max.}} = 268\text{ m}\mu$, $\epsilon_{\text{max.}} = 600$). Compared with the spectrum of tetrahydrohelenalin ($\lambda_{\text{max.}} = 288\text{ m}\mu$),¹ substitution of the epoxide ring in the α -position has shifted the peak of helenalin oxide $20\text{ m}\mu$ toward the red and the peak of acetylhelenalin oxide $20\text{ m}\mu$ 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

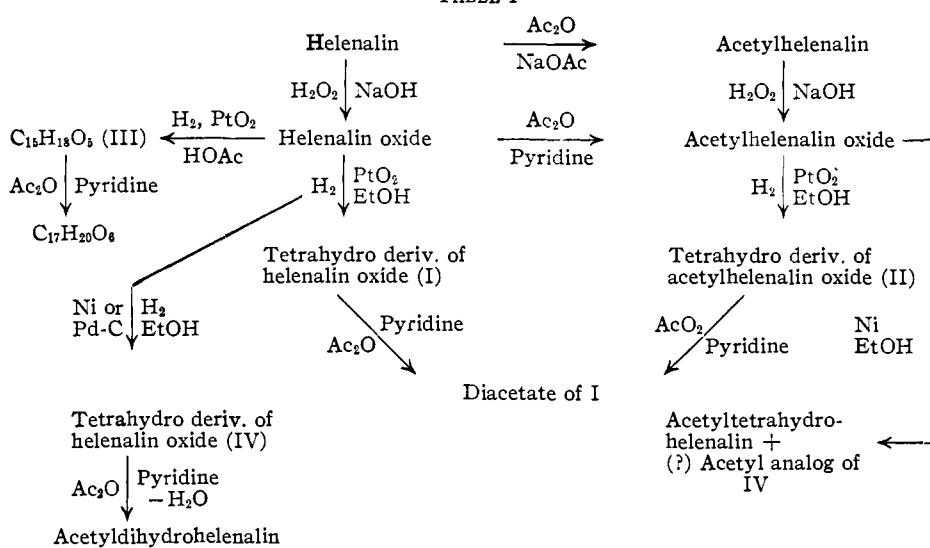
(3) Karrer, *Helv. Chim. Acta*, **30**, 1780 (1947).

(4) An epoxide ring α 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 ($\lambda_{\text{max.}} = 288\text{ m}\mu$, $\epsilon_{\text{max.}} = 54$) 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 -phenylpropiofenone [Ramart-Lucas and Salmon-Legagneur, *Bull. soc. chim.*, **51**, 1069 (1932)] are similarly displaced by $8-12\text{ m}\mu$.

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

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

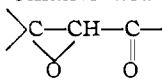
TABLE I



evidence we hesitate to ascribe this difference to a rearrangement which might accompany the acetylation of helenalin and helenalin oxide.

Efforts were made to convert helenalin oxide to a diketone, α -hydroxyketone or glycol by a number of methods previously employed in studies of keto-epoxides.⁵ The only crystalline products isolated so far were formed by the action of sulfuric acid. Very dilute aqueous sulfuric acid gave a hydrated helenalin oxide whose reactions with lead tetraacetate and periodic acid suggest that it is the expected α,β -dihydroxy ketone, while methanolic sulfuric acid gave the corresponding β -methoxy derivative. Due to the low yields the degradation of these substances has not yet been studied in detail.

It was hoped that reduction of helenalin oxide might give better yields of α -hydroxy ketones or glycols suitable for degradation studies.⁶ Unexpected results were obtained. The course of the reaction was affected markedly by the catalyst and conditions of reduction. The ketone could be reduced to an alcohol with retention of the epoxide group intact, or the epoxide could be reduced to an alcohol with the ketone group unchanged. By some procedures the isolated double bond was unreduced, in others it was saturated. The reactions are summarized in Table I.

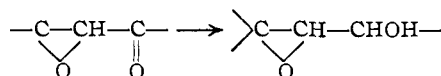
Reduction of helenalin oxide in ethanol with platinum oxide destroyed the  grouping since the resulting tetrahydro derivative of helenalin oxide (I) no longer oxidized potassium iodide. Formation of a diacetate established the

(5) Jörländer, *Ber.*, **49**, 2783 (1916); Weitz and Scheffer, *ibid.*, **54**, 2344 (1921); Baker and Robinson, *J. Chem. Soc.*, 1798 (1932); Allen and Gates, *THIS JOURNAL*, **65**, 1230 (1943).

(6) Temnikova and Martynov, *Zhur. Obshhei Khim.*, **15**, 499 (1945); Temnikova and Kropachev, *ibid.*, **18**, 692 (1948).

presence of a new hydroxyl group. The failure of lead tetraacetate to oxidize I ruled out the structure >CH-CHOH-C(=O)- . The disappearance

of the ketone frequency from the infrared and ultraviolet spectrum showed that the new hydroxyl group had been formed by reduction of the ketone. The absence of a C=C band indicated saturation of the double bond, which had been unaffected by the oxidation, by the second molecule of hydrogen. The reduction therefore proceeded according to the scheme

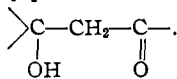


When the reduction was carried out in acetic acid, the separation of a high-melting substance (III) isomeric with helenalin oxide was noted. This substance retained the keto-epoxy grouping, one hydroxyl group and the isolated double bond, although the hydrogen uptake was considerable. Since helenalin oxide may be recrystallized unchanged from acetic acid, the isomerization cannot be ascribed solely to that solvent.

The solvent appears to exert no influence on the reduction of acetylhelenalin oxide with platinum oxide catalyst. Chemical and physical properties of the product (II) showed it to be analogous to I. Acetylation of I and II gave the same diacetate.

Reduction of helenalin oxide in ethanol using palladium charcoal or Raney nickel yielded a second tetrahydro derivative of helenalin oxide of different structure (IV). In contrast to I, IV appears to have retained the ketone group as shown by the presence of the low carbonyl frequency in the infrared and a strong band at 268 μ in the ultraviolet. Reduction of the isolated double bond and formation of a new hydroxyl

group by reduction of the oxide ring is also indicated by the spectrum. Since IV is not oxidized by lead tetraacetate, the only partial structure satisfying all requirements is



Acetylation of IV leads to the loss of water, regeneration of the α,β -unsaturated ketone and the formation of acetyldihydrohelenalin, also obtained by acetylation of dihydrohelenalin.⁷ The facile loss of water indicates that the newly introduced hydroxyl group is tertiary and that the β -carbon atom of helenalin contains no hydrogen.

Reduction of acetylhelenalin oxide with Raney nickel gives rise to a mixture. One of the components has been identified as acetyltetrahydrohelenalin. This compound may have been formed on dehydration and subsequent reduction of the primary reduction product, the acetyl analog of IV, which has not been obtained in the pure state.

Experimental⁸

Helenalin Oxide.—A solution of 500 mg. of helenalin in 15 ml. of methanol was thoroughly chilled in a freezing mixture and slowly treated with a cold mixture of 0.5 ml. of 30% hydrogen peroxide, 0.5 ml. of water and 0.5 ml. of 4 *N* sodium hydroxide solution, care being taken to keep the temperature at about -10° . A precipitate appeared toward the end of the addition. The mixture was kept in the freezing mixture for five minutes and was then filtered and washed with water. The solid weighing 321 mg. was recrystallized repeatedly from methanol and melted at $215\text{--}216^\circ$ when immersed at 214° . The carbon content was consistently low, even after thorough drying.

*Anal.*⁹ Calcd. for $\text{C}_{15}\text{H}_{18}\text{O}_5$: C, 64.73; H, 6.52. Found: C, 64.21, 64.28; H, 6.67, 6.77.

When the product was warmed with a solution of potassium iodide in acetic acid, iodine was liberated. It was also subjected to the action of sodium acetate and acetic acid, ethanolic and aqueous sodium hydroxide and hydrogen chloride, but no well-defined products were isolated.

The action of peracetic and performic acid on helenalin was also investigated; helenalin was recovered in all instances. Perphthalic acid appears to attack helenalin only very slowly; a crystalline product was not isolated.

Acetylhelenalin Oxide.—Because of the small solubility of acetylhelenalin in cold methanol, acetone was used for the oxidation of 500 mg. of the helenalin derivative. The product separating on dilution of the reaction mixture with water (335 mg.) was purified by solution in 10 ml. of hot methanol, concentration to 5 ml., dilution with an equal volume of water and allowing to stand. The large plates melted at 187° after several recrystallizations. Iodine was liberated from this compound when heated with a solution of potassium iodide in acetic acid.

Anal. Calcd. for $\text{C}_{17}\text{H}_{20}\text{O}_6$: C, 63.74; H, 6.29. Found: C, 63.45; H, 6.45.

This compound was also prepared by the acetylation of 200 mg. of helenalin oxide in 1.5 ml. of pyridine with 0.3 ml. of acetic anhydride. The white crystals melted at $187.5\text{--}188^\circ$.

Anal. Found: C, 63.69; H, 6.56.

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

(8) Infrared spectra were determined and interpreted by Mrs. Agatha Johnson; ultraviolet spectra were determined by Mrs. Dorothy C. Brantley on 0.001 *N* solutions in 95% ethanol.

(9) Analyses by Mrs. Jane Wood, Miss Emily Davis and Miss Theta Spoor.

Acetylhelenalin Dioxide.—In the course of an earlier experiment 1 g. of acetylhelenalin was suspended in 20 ml. of methanol at 0° and treated with alkaline hydrogen peroxide in the usual manner.² After several hours the clear solution was diluted with water, acidified and the methanol removed in an air stream. Separation of 0.65 g. of low-melting material occurred. This was taken up in 15 ml. of hot methanol, filtered and chilled. After three days a crop of 185 mg. of hard white crystals was collected, m. p. 206° .

Anal. Calcd. for $\text{C}_{17}\text{H}_{20}\text{O}_7$: C, 60.70; H, 5.99. Found: C, 60.49, 60.65; H, 6.07, 6.15.

The ultraviolet spectrum had a shoulder at $264\text{ m}\mu$ ($\epsilon = 42$) and a band at $315\text{ m}\mu$ ($\epsilon = 46$). It is likely that the second oxygen atom has added to the unconjugated double bond since the 1660 cm.^{-1} frequency is missing from the infrared spectrum.

Hydration of Helenalin Oxide.—A mixture of 920 mg. of helenalin oxide, 20 ml. of water and 0.2 ml. of concentrated sulfuric acid was refluxed gently for three hours. The oxide slowly dissolved. The solution was filtered and concentrated in an air stream to 4 ml. The light yellow crystals weighed 360 mg. and were recrystallized from a small volume of water with much loss. The mother liquors yielded additional material. The product melted at 205° (dec.).

Anal. Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_8$: C, 60.80; H, 6.80. Found: C, 60.82; H, 6.96.

Tests with periodic acid and lead tetraacetate were positive but attempts to isolate crystalline oxidation products were not successful. Refluxing of 200 mg. of helenalin oxide with 5 ml. of methanol containing a few drops of concentrated sulfuric acid gave 47 mg. of white crystals, m. p. 219° , isolated and purified as described in the preceding paragraph. The product was oxidized by periodic acid.

Anal. Calcd. for $\text{C}_{16}\text{H}_{22}\text{O}_8$: C, 61.92; H, 7.15. Found: C, 61.84; H, 7.35.

Tetrahydro Derivative of Helenalin Oxide (I).—The reduction of 308 mg. of helenalin oxide in 50 ml. of absolute ethanol with 50 mg. of platinum oxide proceeded very rapidly at first. After one and one-half hours the theoretical volume of hydrogen had been absorbed and hydrogen uptake stopped completely. The residue obtained on evaporation at reduced pressure was taken up in 20 ml. of hot ethyl acetate and concentrated to 10 ml. after treatment with charcoal. The product weighed 102 mg. and after one recrystallization melted at 207° . The mother liquors yielded viscous material.

Anal. Calcd. for $\text{C}_{15}\text{H}_{22}\text{O}_5$: C, 63.81; H, 7.86. Found: C, 63.75; H, 8.12.

This product did not liberate iodine when heated with a solution of potassium iodide in acetic acid and was not oxidized by lead tetraacetate. It exhibited no specific absorption in the ultraviolet.

Tetrahydro Derivative of Acetylhelenalin Oxide (II).—The reduction of 380 mg. of acetylhelenalin oxide in 50 ml. of absolute ethanol was carried out as above, using 60 mg. of platinum oxide. Two moles of hydrogen were absorbed. The residue weighed 197 mg. after recrystallization from pure ethyl acetate. Further recrystallizations raised the melting point to $228\text{--}229^\circ$ (dec.) if the capillary was immersed at a bath temperature of 220° . The substance did not liberate iodine. The same compound was obtained by reduction of acetylhelenalin oxide in acetic acid.

Anal. Calcd. for $\text{C}_{17}\text{H}_{24}\text{O}_6$: C, 62.94; H, 7.46. Found: C, 63.07; H, 7.66.

The reduction of 1.2 g. of acetylhelenalin in 100 ml. of absolute ethanol with Raney nickel required the equivalent of 2.4 moles of hydrogen. Most of the solvent was removed on the steam-bath. The viscous residue obtained on dilution with water solidified on keeping in a desiccator. A number of recrystallizations failed to give material having a sharp m. p., the various fractions melting in the range $210\text{--}225^\circ$.

The mother liquors from the first two recrystallizations (solvent ethyl acetate-hexane) were combined and evaporated. The residue melted at 144° after several recrystallizations from aqueous methanol. A mixed m. p. with acetyltetrahydrohelenalin showed no depression.

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 65.98; H, 8.09.

Diacetate of I.—Acetylation of 88 mg. of tetrahydrohelenalin oxide (I) in pyridine yielded 54 mg. of white crystals after dilution of the reaction mixture with water and partial removal of the solvents in an air stream. After recrystallization from water the product melted at 165.5°. The same compound was obtained by acetylation of acetyltetrahydrohelenalin oxide.

Anal. Calcd. for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15. Found: C, 62.06; H, 7.20.

Tetrahydro Derivative of Helenalin Oxide (IV).—The reduction of 405 mg. of helenalin oxide in 50 ml. of absolute ethanol was carried out as usual, but with 230 mg. of palladium-charcoal as catalyst. Slightly more than two moles of hydrogen was taken up. The residue was recrystallized from ethyl acetate and weighed 193 mg. Two further recrystallizations raised the m. p. to 224° when the capillary was immersed at a bath temperature of 210°. Lower-melting products were isolated from the mother liquors. The compound gave an impure 2,4-dinitrophenylhydrazone and was not oxidized by lead tetracetate.

Anal. Calcd. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.86. Found: C, 64.09; H, 8.00.

The same product was obtained by reduction of helenalin oxide in ethanol using Raney nickel.

Anal. Found: C, 63.96; H, 7.75.

Acetyldihydrohelenalin.—Acetylation of 200 mg. of the above yielded 193 mg. of crude product after dilution with water and partial removal of the solvents. Recrystallization from water afforded white needles, m. p. 166°, which proved to be identical with an authentic sample of acetyldihydrohelenalin, m. p. 166–167°.

Anal. Calcd. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.51; H, 7.49.

Isomerization of Helenalin Oxide.—A solution of 374 mg. of helenalin oxide in 40 ml. of acetic acid was reduced with 80 mg. of platinum oxide. The reduction was stopped after three and one-half hours when approximately 2.5 moles of hydrogen had been taken up. The residue obtained on evaporation to dryness *in vacuo* was taken up in 50 ml. of hot ethyl acetate, decolorized and allowed to cool after concentration to 5 ml. The white needles, which weighed 123 mg., were recrystallized several times from ethanol-water. The m. p. was difficult to determine due to decomposition; the highest value was 285–287° (dec.) when the sample was immersed at 282° and the bath was heated up rapidly. The test with potassium iodide-acetic acid was positive. The mother liquors yielded more material of slightly lower melting point.

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.59; H, 6.62.

The ultraviolet spectrum of this material had bands at 216 $m\mu$ ($\epsilon = 14500$) and at 304 $m\mu$ ($\epsilon = 62$). Acetylation of 68 mg. in the usual manner yielded 27 mg. of pink solid, purified twice by solution in acetone-water and treatment with charcoal. On removal of the acetone crystals melting at 188–191° were obtained.

Anal. Calcd. for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.81; H, 6.35.

Summary

Additional proof that helenalin is an α,β -unsaturated ketone has been furnished by the preparation of keto-epoxides from helenalin and acetylhelenalin.

Helenalin oxide was converted to a glycol by the action of dilute sulfuric acid. The reduction of helenalin and acetylhelenalin oxide yielded a variety of products depending on the reaction conditions. In some instances, the ketone was reduced to an alcohol with retention of the epoxide group, in others the epoxide was reduced to an alcohol with retention of the ketone group.

URBANA, ILLINOIS

RECEIVED FEBRUARY 11, 1949

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

Helenalin. III. Reduction and Dehydrogenation

BY ROGER ADAMS AND WERNER HERZ

Catalytic reduction of helenalin is reported to saturate two double bonds, thus leading to the formation of tetrahydrohelenalin.^{1,2} Reduction of helenalin under a variety of conditions has now led to the isolation of other reduction products whose reactions, together with those of tetrahydrohelenalin, have been investigated in order to elucidate the structure of the bitter principle.

The low pressure reduction of helenalin was studied using a variety of solvents and catalysts. In each instance tetrahydrohelenalin was obtained, the best yields reaching 60–70%. By stopping the reduction of helenalin after the absorption of one mole of hydrogen, it was possible to isolate in small amounts a dihydrohelenalin, m. p. 224–225°.

(1) Clark, *THIS JOURNAL*, **58**, 1982 (1936).

(2) Adams and Herz, *ibid.*, **71**, 2546 (1949).

The ultraviolet absorption spectrum³ of dihydrohelenalin ($\lambda_{1 \max} = 227 m\mu$, $\epsilon_{1 \max} = 7200$; $\lambda_{2 \max} = 314 m\mu$, $\epsilon_{2 \max} = 59$) is very similar to that of helenalin,² indicating that catalytic reduction preferentially saturates the unconjugated double bond. This is confirmed by the infrared spectrum⁴ from which the bands due to unconjugated C=C are missing, while the bands ascribed to conjugated C=O and C=C are comparable to those in the helenalin spectrum. Chemical evidence is furnished by the failure to obtain formaldehyde on the ozonolysis of dihydrohelenalin, and by the results of C-methyl determinations which yielded 2.20 moles of acetic acid as compared with 0.85 mole from helenalin.

(3) Ultraviolet spectra were determined by Mrs. Dorothy C. Brantley on 0.001 *N* solutions in 95% ethanol.

(4) Infrared spectra were determined and interpreted by Mrs. Agatha Roberts Johnson.