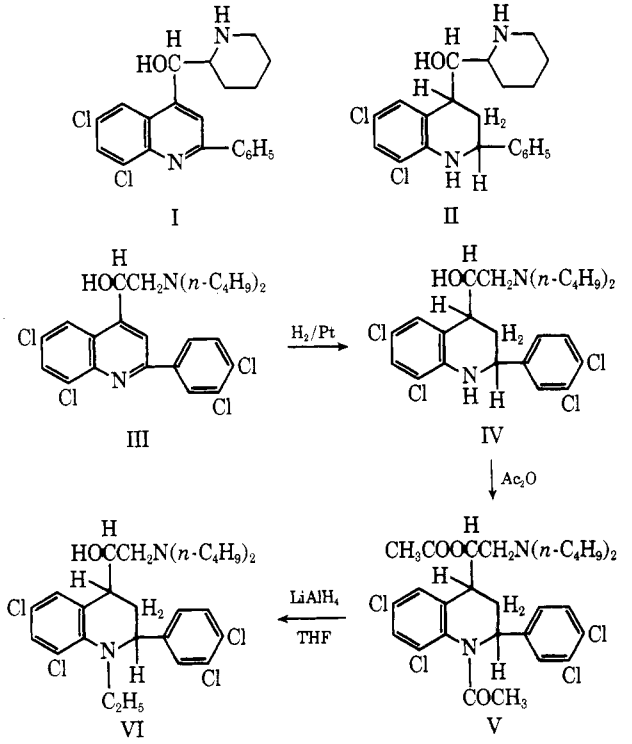

nine sulfate. Subsequent clinical studies have shown III to have an acceptably low phototoxicity in man.[7]

In the standard antimalarial test used previously[1] IV was "active" at 40 mg/kg, gave one cure at 80 mg/kg, three cures at 160 mg/kg, and five cures at 320 mg/kg. Compound VI was "active" at 80 mg/kg and gave three cures at 320 mg/kg and five cures at 640 mg/kg. Compound V was inactive even at 640 mg/kg.

The minimum effective phototoxic dose[8] of IV was found to be 400 mg/kg, while that of III was just 50 mg/kg. The phototoxic index (PI) is defined as the ratio of the minimum effective phototoxic dose (ip) to the dose required to produce an increase of 6–8 days in the mean survival time of mice inoculated with *Plasmodium berghei* (5.0 mg/kg for III, 40 mg/kg for IV). For both III and IV the PI = 10. Thus, we record another unsuccessful attempt to prepare potent quinolinemethanol drugs with acceptably low phototoxicity. The search was abandoned when nonphototoxic antimalarials became available in the Army program.

No attempt was made to separate the diastereoisomeric mixtures in which IV–VI occurred. The significant decrease in phototoxicity in these compounds was accompanied by negligible absorption above 310 nm. Unreduced phototoxic 2-phenylquinolinemethanols(such as III) all have strong absorption in the 320–360-nm region.

Experimental Section

Melting points were obtained in capillaries and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., and by the late Dr. S. M. Nagy (Belmont, Mass.). Satisfactory uv and ir spectra were recorded for IV–VI.

α-(Di-*n*-butylaminomethyl)-2-phenyl-3′,4′,6,8-tetrachloro-1,2,3,4-tetrahydro-4-quinolinemethanol Hydrochloride (IV·HCl). Compound III·HCl (kindly provided by the Division of Medicinal Chemistry, Walter Reed Army Institute of Research) was converted to its free base,‡ mp 130–132°. The latter was reduced by the procedure described[1] for the reduction of I to II and IV·HCl was isolated (80–90%) as a cream-colored flocculent solid, mp 100–160° dec. *Anal.* ($C_{25}H_{32}Cl_4N_2O$·HCl) H, N; C: calcd, 54.12; found, 54.06; Cl: calcd, 31.95; found, 30.41.

Tlc (SiO_2, MeOH–2% NH_3) showed that no unreduced material was present. The chlorine content of the products of other runs varied from 29 to 31% showing that some loss of chlorine occurred during the catalytic reduction.

1-Acetyl-α-(di-*n*-butylaminomethyl)-2-phenyl-3′,4′,6,8-tetrachloro-1,2,3,4-tetrahydro-4-quinolinemethanol Acetate Hydrochloride Monohydrate (V·HCl·H_2O). A solution of 4.6 g (0.0083 mol) of IV·HCl in 25 ml of Ac_2O was heated at reflux for 2 hr. After dilution with water and hydrolysis of excess Ac_2O the solution was acidified with excess 6 *N* HCl to precipitate V·HCl, which was washed on the filter with 2 *N* HCl and dried at 25° (1 mm) to give 4.1 g (75%), mp 90–200° slow dec. Unlike IV·HCl and VI·HCl, V·HCl was significantly soluble in H_2O; it was much less soluble in dilute HCl. *Anal.* ($C_{29}H_{36}Cl_4N_2O_3$·HCl·H_2O) C, H, Cl, N.

α-(Di-*n*-butylaminomethyl)-1-ethyl-2-phenyl-3′,4′,6,8-tetrachloro-1,2,3,4-tetrahydro-4-quinolinemethanol Hydrochloride (VI·HCl). A solution of 2 g (0.00313 mol) of V·HCl in 20 ml of dry THF was added dropwise to a stirred suspension of 2.5 g (0.0066 mol) of $LiAlH_4$ in 70 ml of THF. The free base VI was isolated in the usual way and converted to its HCl salt in dry ether solution. After drying at 35° (1 mm) VI·HCl was obtained as a tan powder (77%), mp 75–110° slow dec. The uv spectrum was qualitatively identical with that of IV and the ir spectrum showed no carbonyl absorption. *Anal.* ($C_{27}H_{36}Cl_4N_2O$·HCl) N; C: calcd, 55.64; found, 56.40; h; calcd, 6.30; found, 6.94; Cl: calcd, 30.41; found, 28.12.

It was apparent that some loss of Cl occurred during the reduction reaction. When the reaction was prolonged, Cl values fell as low as 25%; after shorter reaction times Cl values were higher, but the product contained residual carbonyl, detected by ir. Direct alkylation of IV to VI by a variety of standard procedures failed.

‡ Lutz, *et al.*,[9] record mp 128–129°.

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Antineoplastic Agents. 34. *Helenium autumnale* L.[1,2]

George R. Pettit,* John C. Budzinski, Gordon M. Cragg, Peter Brown, and LaRea D. Johnston

Cancer Research Laboratory and Department of Chemistry, Arizona State University, Tempe, Arizona 85281.
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One of the common sneezeweeds, *Helenium autumnale* L. var. *montanum* (Nutt.) Fern. (Compositae family), displays several to many heads of bright yellow flowers and is found widely distributed throughout the western United States. The animal toxicity associated with this plant and other *Helenium* species is well known.[2,3a] In addition, severe nasal and eye irritation is generally encountered with *H. autumnale.*

During the process of evaluating Oregon plants for antineoplastic agents, we found that extracts of *Helenium autumnale* L. var. *montanum* (Nutt.) Fern. showed significant inhibitory activity in both *in vitro* (9 KB cell culture) and *in vivo* (P-388 lymphocytic leukemia) studies[4] performed under auspices of the National Cancer Institute. Encouraged by these initial biological results, sepa-

Table I. Antineoplastic Activity of Helenalin,[a] T/C (mg/kg)

PS[b]	KB (ED_{50})[c]	WA[d]	LE[e]	LL[f]	B-16[g]
Tox (24)	0.19	Tox (20)	Tox (28)	100 (6)	126 (6)
125 (12)		42 (10)	Tox (16)	95 (3)	126 (3)
145 (11)		53 (5)	104 (14)	100 (1.5)	126 (1.5)
145 (10)			112 (12)		
137 (9)			117 (8)		
168 (8)			106 (7)		
145 (7)			106 (3.5)		
163 (6)			95 (2)		
145 (5)			101 (1)		
145 (4)					
220 (3)					
135 (1.5)					

[a]Except for the KB values the T/C (mg/kg) results recorded in Table I were maximum for the dosage reported and screening protocols with evaluation methods have been summarized in ref 4. [b]P-388 lymphocytic leukemia. [c]9 KB cell culture; human epidermoid carcinoma of the nasopharynx. [d]Walker carcinosarcoma 256 (subcutaneous). [e]Lymphoid leukemia L1210. [f]Lewis lung carcinoma. [g]Melanocarcinoma B-16.

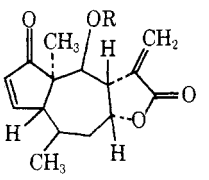
ration of the extracts was undertaken in order to isolate the active constituent(s).

Separation of the *H. autumnale* extracts was carried out making extensive use of Sephadex column chromatography. Fractionation was followed and directed by bioassay (KB and PS). From the active fraction the pseudoguaianolide type sesquiterpene lactones helenalin (I, R = H),[3b,5] autumnolide (II),[6,7] and mexicanin I (III)[8,9] were isolated and identified by comparison with authentic specimens. Further evidence supporting the ring system and substituent locations for autumnolide (II) nicely proposed by Herz and colleagues[6] was obtained by a mass spectral study.[7] The mass spectrum of autumnolide displayed a molecular ion at m/e 280 ($C_{15}H_{20}O_5$) and the diagnostic pseudoguaianolide peaks[7] at 95 (75% C_7H_{11}–25% C_6H_7O), 96 (30% C_7H_{12}–70% C_6H_8O), 122 ($C_8H_{10}O$), 123 ($C_8H_{11}O$), and 124 ($C_8H_{12}O$). Interestingly, the ions of mass 123 and 124 are singlets, and the isobaric fragments $C_7H_7O_2$ and $C_7H_8O_2$ found[7] in helenalin and other pseudoguaianolides bearing an exocyclic methylene functionality were not detected with autumnolide under high-resolution conditions (res ~10,000).

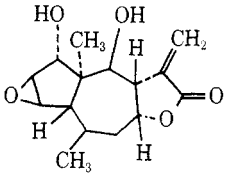
Observation of prominent ions at m/e 262 (M − 18) and 244 (M − 36) betrayed the presence of two hydroxyl groups. The diagnostic peak[7] at m/e 138 (50% $C_8H_{10}O_2$) shows that a hydroxyl group does *not* reside at either C-9 or C-10 and that the lactone is closed to C-8 rather than C-6. A further diagnostic ion[7] of mass 151 ($C_9H_{11}O_2$) demonstrates the presence of one hydroxyl group at C-6. While the present report was in press, we succeeded in obtaining the crystal structure of autumnolide by X-ray techniques.† Thus, the structure and sterochemistry depicted by II accurately represents autumnolide.

Interestingly, helenalin was isolated in significant quantities (1–2% of the dried flowers). The ubiquitous plant constituents mannitol and β-sitosterol were also readily isolated. Other constituents of *H. autumnale* were readily available employing Sephadex separation procedures but were not further identified due to their low level of antineoplastic activity.

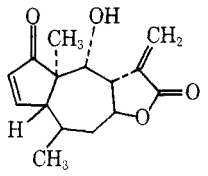
Helenalin[2] was considered primarily responsible for the *in vivo* (P-388 system) antineoplastic activity (*cf.* Table I) shown by the crude plant extract. Autumnolide, *e.g.*, did not inhibit the course of the P-388 murine leukemia over the dose range studied (6.25–25 mg/kg). Cytotoxicity (KB) was attributed to helenalin (ED_{50} 0.19), autumnolide (ED_{50} 3.1), and other sesquiterpene lactones present in the plant. Although helenalin has for some time been known to exhibit considerable cytotoxicity,[9,10] *in vivo* activity has been noted only very recently.[2,11] While handling the pure compound, both nasal and eye irritations similar to that associated with the whole plant were noted. The results of evaluating helenalin against a number of different tumor systems are presented in Table I.[4] Helenalin was found able to provide significant life extension in the P-388 lymphocytic leukemia system and, in addition, inhibited growth of two experimental solid tumors (Walker 256 and B-16 melanoma).[4]



I, R = H (helenalin)



II, autumnolide



III, mexicanin I

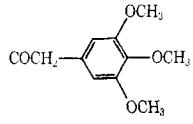
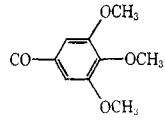
The structure–activity relationships among sesquiterpene lactones in respect to demonstrated cytotoxicity have become of increasing interest.[9-11] Recent studies have shown that structural changes such as saturation and adduct formation involving the α-methylene-γ-lactone or the α,β-unsaturated units result in a significant decrease in cytotoxicity. On the premise that such structure–activity relationships would hold in part for *in vivo* antineoplastic activity, we chose to modify helenalin by ester formation with the C-6 hydroxyl and possibly improve the already significant *in vivo* activity.

In order to obtain sufficient quantities of pure helenalin for esterification studies, it was necessary to simplify isolation of helenalin from *Helenium autumnale*. A modification of the Clark[3a,c] procedure was developed which entailed extraction of the plant with chloroform at room temperature, followed by a series of solvent separations. This method proved very convenient for obtaining larger quantities of helenalin.

Helenalin acetate and propionate were readily prepared using the corresponding acid anhydrides. Additional ester derivatives were obtained by the method of Parish and Stock,[12] which utilizes the mixed anhydride prepared from trifluoroacetic anhydride and the required carboxylic

†G. R. Pettit, R. von Dreele, and G. M. Cragg, unpublished results.

Table II. Antineoplastic Activity of Helenalin (I, R = H) Esters

	R	Formula	Mp, °C	KB (ED_{50})	PS	T/C (mg/kg)[a]
1	$COCH_3$[b]	$C_{17}H_{20}O_5$	179–180	2.2	Tox (20), 160 (10), 150 (8), 160 (5), 150 (4), 125 (2)	
2	$COCH_2CH_3$	$C_{18}H_{22}O_5$	155–156	0.19	Tox (40), 155 (20), 135 (10), 115 (5)	
3	$COCH(CH_3)_2$	$C_{19}H_{24}O_5$	104.5–105.7	0.74	Tox (30), 125 (15), 140 (10), 131 (5), 118 (2.5)	
4	$CO(CH_2)_{14}CH_3$	$C_{31}H_{48}O_5$	Oil		Tox (20), Tox (10), 77 (5)	
5		$C_{26}H_{30}O_8$	183–186	0.10	118 (10), 118 (5), 118 (2.5)	
6		$C_{25}H_{28}O_8$	163.8–165	0.71	118 (10), 127 (5), 127 (2.5)	

[a]See ref 4. [b]See ref 3a.

acid as an intermediate. Biological results for the helenalin esters are presented in Table II.‡ Among the several types of helenalin esters studied, none proved more effective than the parent alcohol (helenalin) in both the PS (at the dose levels viewed) and KB screening systems. Further studies involving modification of helenalin are in progress.

Experimental Section

All solvents were redistilled. Ligroine refers to the fraction boiling at 68–72° unless otherwise noted. Melting points were recorded employing a Kofler melting point apparatus and are uncorrected. Purity of compounds was confirmed by tlc on Merck silica gel HF_{254} plates. Chromatograms were performed with chloroform–methanol (9:1) as solvent and visualized with uv light or developed with an overspray of 3% $CeSO_4$ in 10% aqueous H_2SO_4, followed by heating. Microanalytical data were provided by the laboratory of Dr. A. Bernhardt, Mikroanalytishes Laboratorium, 5251 Elbach über Engelskirchen, West Germany. The ir spectra were recorded in KBr using a Beckmann Model 14 instrument by Miss K. Reimer. Nmr spectra were also provided by Miss K. Reimer. Here, unless otherwise noted, $CDCl_3$ (TMS internal standard) was used as solvent with a Varian A-60 or XL-100 instrument. The mass spectral data were determined by Messers R. Scott and E. Kelley using Atlas CH-4B and SM-1B (equipped for field ionization or electron impact) instruments.

We are indebted to Professors W. Herz and J. Romo for the authentic specimens of autumnolide, helenalin, and mexicanin I. The mutual identity of isolated and authentic samples was established by infrared spectral comparison, tlc, and mixture melting point determination.

Plant Collection. The entire plant corresponding to *Helenium autumnale* L. var. *montanum* (Nutt.) Fern. in the flowering stage was collected by one of us (G. R. P. assisted by W. E., M. S., and M. J. Pettit) in August 1967 in the Winema National Forest at an elevation of 1000–2000 ft along the Sprague River (*ca.* 10 miles northwest of the town of Sprague River, Ore.). Additional collections were made as noted in August 1971 and by two of us (G. R. P. and G. C.) in August and September of 1972. The plant was divided into flowers, stems and leaves, and roots. Each of these three parts was extracted separately.

Isolation Procedure.§ The dried flowers (357 g) were separated from the rest of the plant and extracted with ligroine (5.5 l.) in a Soxhlet apparatus for 48 hr. The solution was filtered and concentrated at room temperature to give A (10.6 g). The residual plant material was extracted with 95% ethanol (5.5 l.) in a Soxhlet apparatus for 43 hr. The ethanol solution was filtered and concentrated at room temperature to yield B (28.2 g) which was extracted with chloroform at room temperature for 24 hr. Concentration of the filtered chloroform extract gave fraction C (21 g). The chloroform-insoluble residue was extracted with methanol (200 ml) for 24 hr at room temperature. Concentration of this extract gave fraction D (6.6 g).

Isolation of Autumnolide. A 5.28-g sample of chloroform-soluble fraction C was dissolved in 5.0 ml of methanol and carefully layered onto the top of a Sephadex LH-20 column (430 g, 5 × 85 cm) in methanol. Elution was carried out with methanol (void volume 550 ml) and 7.0-ml fractions were collected and combined according to tlc analysis. Between volumes 1148–1218 ml fraction E (0.75 g, R_f 0.60, 0.30, 0.10) was obtained. Further elution between volumes 1250–1415 ml gave fraction F (2.1 g, R_f 0.53, 0.41), while elution between volumes 1420–1505 ml gave a clear oil (R_f 0.41) which crystallized from acetone–ligroine as colorless needles (0.170 g) to afford compound G: mp 199–201°; nmr ($CDCl_3$ + 1 drop of D_2O) δ 1.25 (3 H, s), 1.39 (3 H, d, J = 6 Hz), 1.8–2.5 (~5 H, m), 3.60 (3 H, m), 4.22 (1 H, br s), 5.10 (1 H, dt, J = 8.3 Hz), 6.10 (1 H, d, J = 2.5 Hz), 2.73 (1 H, d, J = 2.5 Hz). This compound was shown to be identical with authentic autumnolide.[6] The diacetate of autumnolide, prepared by acetic anhydride–pyridine treatment of autumnolide exhibited an nmr spectrum identical with that reported.[6]

Isolation of Miscellaneous Constituents. Treatment of fraction E (0.75 g) with methanol (5 ml) gave a white solid which was recrystallized from acetone–ligroine to give β-sitosterol (7 mg), mp 134–136°, identified by its mass spectrum. The residue remaining after removal of the methanol was chromatographed on silica gel (50 g, 0.05–0.2 mm, E. Merck). Elution of the column with 10% methanol–chloroform gave a colorless gum (0.13 g, R_f 0.10) which was crystallized from acetone–ligroine to give colorless needles of compound H: mp 217–218°; pmr (DMSO-d_6) δ 1.13 and 1.22 (~10 H, br s), 1.73 (1 H, br s, $W_{1/2}$ = 5 Hz), 2.10 (3 H, s), 3.10 (~8 H, br m), 3.32 (3 H, s), 3.66 (1 H, br s, $W_{1/2}$ = 4 Hz), 3.87 (2 H, m), 4.29 (1 H, br t, J = 7 Hz), 4.98 (1 H, br t, J = 4 Hz), 5.20 (1 H, d, J = 4 Hz), 6.18 (1 H, d, J = 3 Hz). Compound H appeared to be a sesquiterpene lactone but was not further identified.

Continued elution of the column gave a light yellow solid. Recrystallization from methanol afforded 0.25 g: mp 295–297°; high-resolution mass spectrum m/e 300.06381 ($C_{16}H_{12}O_6$); pmr (DMSO-d_6) δ 3.80 (3 H, s), 5.73 (1 H, s), 5.87 (1 H, s), 6.06 (2 H, d, J = 8 Hz), and 7.05 (2 H, d, J = 8 Hz); ir (KBr) 3300, 1650, 1600, 1560, 1550, 1480, 1360, 1245, 993, and 825 cm^{-1}. The above data suggest a compound of the flavone of isoflavone type; however, the structure was not futher determined.

Isolation of Mexicanin I. Fraction E (1.6 g obtained by repeating the separation) was rechromatographed on Sephadex LH-20 (2.5 × 70 cm column) in chloroform using upward flow of solvent. Elution with chloroform gave, between volumes 250–280 ml, a yellow oil (0.40 g) which when rechromatographed on a Sephadex LH-20 column in chloroform using descending flow gave between volumes 400–467 ml a clear oil (0.170 g, R_f 0.55) which crystallized from acetone–ligroine to give fine colorless needles: mp 261–265°; pmr ($CDCl_3$) δ 7.81 (1 H, dd, J = 6, 1 Hz), 6.51 (1 H, d, J = 3 Hz), 6.26 (1 H, m, 5 peaks), 5.76 (1 H, d, J = 3 Hz), 4.90 (1 H, br m), 4.63 (1 H, br s, $W_{1/2}$ = 8 Hz), 3.16 (1 H, br m), 2.0–3.0 (envelope), and 1.26 (~6 H, br s); ir (KBr) 1767 and 1706 cm^{-1}. The compound was identified by comparison with authentic mexicanin I (III).[8]

‡Esters 1–4 have previously been prepared and screened against other systems (see ref 11).

§The assistance of Messrs. J. Day, G. Bryan, and L. Vanell at this stage of the study is gratefully acknowledged.

Isolation of Helenalin. Fraction F (2.07 g) was chromatographed on Sephadex LH-20 (90 g, 2.5 × 70 cm) in chloroform. Elution between volumes 250–385 ml gave colorless needles of helenalin (1.25 g, R_f 0.50, 1.4% dry weight of flowers): mp 170.5–174.5°; mass spectrum (70 eV) 262 (M^+), 244, 234, 151, 137, 124 (base peak), 109, and 96; ir (KBr) 1765, 1710, 1465, 1301, 1275, 1060, and 825 cm^{-1}; pmr ($CDCl_3$) δ 0.97 (3 H, s), 1.25 (3 H, d, J = 6 Hz), 1.62–2.53 (3 H, m), 3.04 (1 H, br s), 3.27 (1 H, br s), 3.58 (1 H, m), 446 (1 H, br s), 4.98 (1 H, d t, J = 7, 2 Hz), 5.81 (1 H, d, J = 3 Hz), 6.03 (1 H, ddd, J = 6, 5, 3 Hz), 6.37 (1 H, d, J = 3 Hz), and 7.69 (2 H, ddd, J = 6, 5, 2 Hz). Further elution of the column gave between volumes 385–560 ml, 0.40 g of a compound which after recrystallization from acetone–ligroine was shown (as above) to be autumnolide.[6]

The methanol-soluble fraction D (4.23 g) was chromatographed on Sephadex LH-20 (430 g, 5 × 85 cm) in methanol. Elution between volumes 1184–1304 ml gave a yellow gum (1.05 g) which, on trituration with methanol, gave a solid (0.070 g), mp 169–170°, identical (as above) with an authentic specimen of mannitol. Further elution gave a compound in volumes 1312–1512 ml which after crystallization from 95% ethanol melted at 240–243° (0.060 g) and was not further identified.

Large-Scale Isolation of Helenalin from *Helenium autumnale.* The flowers, leaves, and stems of air-dried *H. autumnale* L. var. *montanum* (Nutt.) Fern. (10.96 kg) were broken into 2-in. sections, placed in muslin bags, and submerged in chloroform (50 l.) for 24 hr at room temperature. The solution was filtered and concentrated (*in vacuo*) to 4 l. at room temperature. The chloroform extract was washed with H_2O (4 × 1 l.). After filtering the $CHCl_3$ solution through a cotton plug (premoistened with $CHCl_3$) the solvent was removed (*in vacuo*) at room temperature to give a greenish brown gum (470 g) which was extracted with methanol (5 × 500 ml). The methanol extract was filtered, diluted with 300 ml of water, and extracted with ligroine (4 × 900 ml). Evaporation of solvent from the ligroine extract gave 95 g of black oily residue. The aqueous methanol solution was reduced (*in vacuo*) to 0.5 l. and diluted with water to 3 l. The resulting aqueous solution was extracted with $CHCl_3$ (4 × 500 ml). The combined chloroform extract was filtered through a cotton plug (premoistened with $CHCl_3$) and concentrated at room temperature to dryness. The residue (338 g) was dissolved in a minimum amount of hot benzene (100 ml) and the solution was poured slowly into a rapidly stirred solution of diethyl ether (1200 ml). The ether solution was decanted, filtered, decolorized with charcoal, and allowed to evaporate slowly at room temperature. Crystalline helenalin separated and was recrystallized from acetone–ligroine to yield 17 g of pure material. Further slow evaporation of the ether solution afforded (after recrystallization) another 22 g of pure helenalin. The mother liquors were added to the remaining ether-soluble material to give (after evaporation of solvent) 74 g of a brown semisolid which contained (by tlc analysis) considerable quantities of both helenalin and autumnolide. In addition, substantial quantities of both compounds remained (by tlc analysis) in the ether-insoluble material (225 g).

Preparation of Helenalin Esters. The acetate and propionate esters of helenalin were prepared (typically) by mixing 1.0 g of helenalin with 15 ml (large excess) of the anhydride in 25 ml of anhydrous pyridine. After stirring the mixture for 48 hr solvent was removed (*in vacuo*). The residue was triturated with methanol and hexane and both were evaporated (*in vacuo*). A solution of the residue in acetone was decolorized with charcoal and recrystallized from acetone–hexane to give the solid derivatives.

A modification of the method of Parish and Stock[12] was used for preparation of the remaining helenalin esters as follows. In a typical example, helenalin (1.0 g) was added to a solution prepared from benzene (25 ml), trifluoracetic anhydride (10 ml), and the respective acid (5.0 g). After 24 hr at room temperature (reaction followed by tlc) 10% aqueous NaOH (50 ml) was added. The mixture was stirred for 1 hr and the benzene solution was decanted, washed with saturated $NaHCO_3$ solution and saturated sodium chloride solution, and dried over $MgSO_4$. Solvent was removed *in vacuo* and the residue was recrystallized from acetone–hexane. All of the esters gave satisfactory ir, nmr, and elemental analysis and a single spot on a thin-layer chromatogram.

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Synthesis and Biological Activities of Analogs of the Luteinizing Hormone-Releasing Hormone (LH-RH) Modified in Position 2

Richard W. A. Rees,* Theodore J. Foell, Sie-Yearl Chai, and Norman Grant

Research and Development Division, Wyeth Laboratories Inc., Radnor, Pennsylvania 19101. *Received March 25, 1974*

After the primary structure of luteinizing hormone-releasing hormone (LH-RH) from porcine[1] and ovine[2] hypothalami was shown to be <Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2 and had been synthesized, reports on various structural modifications rapidly began to appear. One of these investigations[3] indicated that changes at the 2 position of the LH-RH molecule diminished or eliminated the agonist activity and elicited LH-RH antagonism. In the interim further reports of modification of LH-RH in this position have appeared in the literature,[4-11] but with the exception of [D-Ala^2]-LH-RH (Monahan, *et al.*[9]) no other derivative of LH-RH wherein histidine was replaced by a D-amino acid has come to our attention.