194. *Sesquiterpenoids. Part X.* The Constitution of Lactucin.*

By D. H. R. Barton and C. R. Narayanan.

Lactucin, the active principle of "lactucarium," is a sesquiterpenoid lactone giving chamazulene on dehydrogenation. On selective hydrogenation lactucin affords dihydrolactucin, then two isomeric tetrahydrolactucins, and finally the known hexahydrolactucin. On the basis of these and other changes the constitution (I; R = H) has been deduced for lactucin.

THE sesquiterpenoid lactone lactucin, $C_{15}H_{16}O_5$, is the main bitter principle of the latex of *Lactuca virosa* L. (wild lettuce). The dried latex, known in pharmacy as "lactucarium" or lettuce opium, has for long enjoyed a reputation as a hypnotic, the activity being attributed to the presence of lactucin. Chemical investigations on lactucin were initiated over a century ago,[1] but the only contributions of structural significance are those by Späth, Lorenz, and Kuhn [2] and by Wessely, Lorenz, and Kuhn.[3] The last two references cite the extensive pharmaceutical literature in detail.

Prior knowledge about the constitution of lactucin can be summarised as follows. Lactucin contains a lactone grouping, two easily esterified hydroxyl groups, and a conjugated ketonic group ($\lambda_{max.}$ 257 mμ). The molecule is sensitive to both acid and base, giving intense colour reactions. Lactucin contains one *C*-Me group and gives formaldehyde on ozonolysis. Catalytic hydrogenation affords a saturated hexahydrolactucin which gives diesters and ketone derivatives. The hexahydro-compound is stable to lead tetra-acetate, is hydrolysed by alkali to a stable hexahydrolactucinic acid, and is oxidised by potassium permanganate to methylsuccinic acid. In spite of the presence of three ethylenic linkages lactucin consumes no per-acid at 0°. Both lactucin and hexahydrolactucin gave blue oils, which were not further characterised, on dehydrogenation with selenium.

Our investigations have shown that lactucin has the constitution (I; R = H). This structure is in accord with the earlier evidence cited above and is fully justified by the following experimental facts.

Lactucin showed bands in the infrared (Nujol) at 3320 and 3240 (OH), 1755 (γ-lactone), 1662 (C=C·CO·C=C; 5-membered ring) and 1623 and 1610 (C=C conjugated with carbonyl groups) cm.$^{-1}$. The diacetate (I; R = Ac) gave maxima (in $CHCl_3$) at 1770 (γ-lactone), 1735 and 1252 (acetate), 1690 (as for 1662 above) and 1623 and 1618 (C=C, as above) cm.$^{-1}$. Hydrogenation furnished hexahydrolactucin (II; R = H), which showed infrared bands at 3340 (OH), 1775 (γ-lactone), and 1728 (*cyclo*pentanone). The hexahydro-compound readily afforded a ditoluene-*p*-sulphonate (II; R = toluene-*p*-sulphonyl), thus confirming both hydroxyl groups as easily esterified.

On complete hydrogenation over platinum in acetic acid–perchloric acid, followed by dehydrogenation with palladised charcoal, lactucin (I; R = H) gave chamazulene (III).[4] This established the carbon skeleton of lactucin as already written.

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* Part IX, *J.*, 1957, 5041.

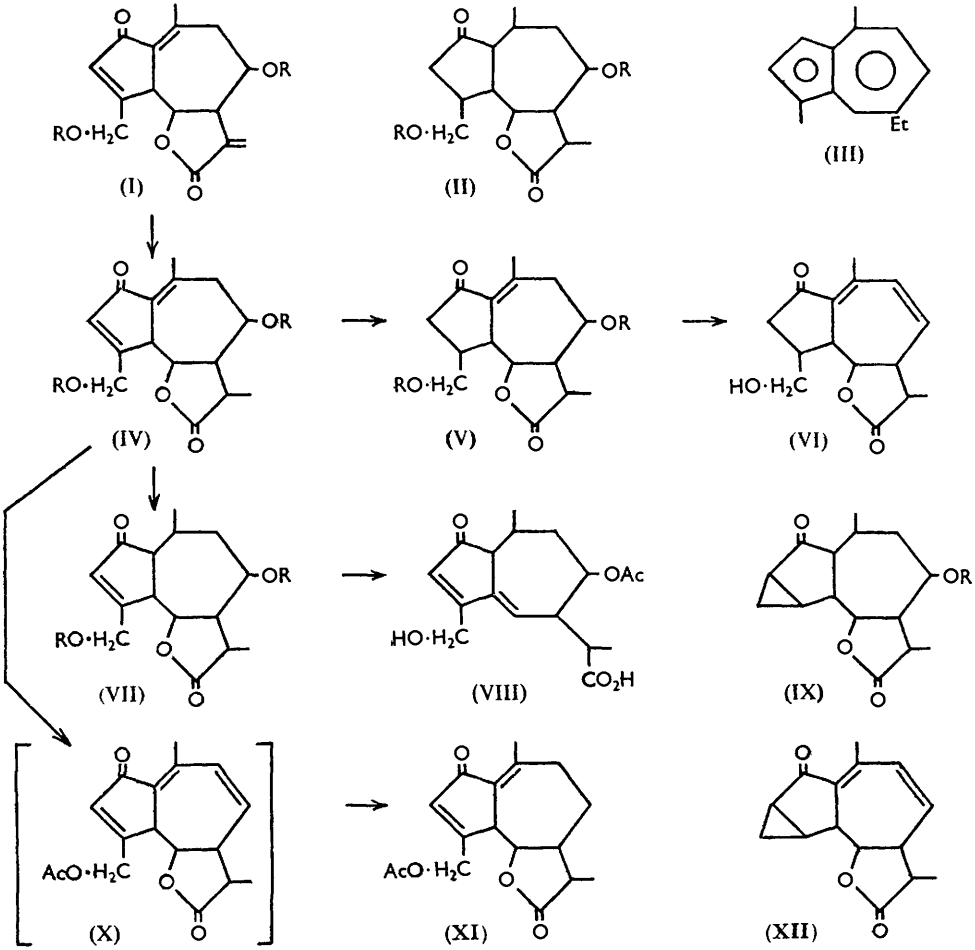
[1] Ludwig and Kromayer, *Arch. Pharm.*, 1847, **100**, 1; 1862, **161**, 1; cited by Zinke and Holzer, *Monatsh.*, 1953, **84**, 212.

[2] Späth, Lorenz, and Kuhn, *ibid.*, 1951, **82**, 114.

[3] Wessely, Lorenz, and Kuhn, *ibid.*, p. 323.

[4] Meisels and Weizmann, *J. Amer. Chem. Soc.*, 1953, **75**, 3865; Šorm, Herout, and Takeda, *Chem. Listy*, 1954, **48**, 281; Novak, Šorm, and Sicher, *ibid.*, p. 1648.

Carefully controlled catalytic hydrogenation of lactucin gave useful information on the positions of the ethylenic linkages. Absorption of one mol. of hydrogen afforded dihydrolactucin (IV; R = H), characterised as its diacetate (IV; R = Ac). Whereas lactucin gave formaldehyde on ozonolysis and contained one *C*-Me group (see above), its dihydro-derivative furnished no formaldehyde and contained two *C*-Me groups. The partial hydrogenation involves, therefore, the saturation of a grouping $>C=CH_2$. The main chromophore of lactucin ($\lambda_{max.}$ 257 mμ) is not altered by the hydrogenation (identical absorption from 235 to 350 mμ). A subtraction curve of the spectra of lactucin and dihydrolactucin showed a maximum at 208 mμ (ε 8600). This indicates that the $>C=CH_2$ system must be conjugated with the lactone-carbonyl group, a conclusion which is inescapable when the siting of the ketonic group and attendant ethylenic linkages is also taken into account (see below). In the infrared spectrum dihydrolactucin showed bands (in Nujol) at 3455 and 3210 (OH), 1765 (γ-lactone), 1680 (C=C·CO·C=C; 5-membered



ring), and 1630 and 1614 (C=C, conjugated with carbonyl group) cm.$^{-1}$. The diacetate (IV; R = Ac) gave maxima (in $CHCl_3$) at 1777 (γ-lactone), 1738 and 1219 (acetate), 1690 (as above), and 1640 and 1618 (C=C, as above) cm.$^{-1}$. The spectra are thus in accord with the proposed constitutions.

Selective hydrogenation of dihydrolactucin until a further mol. of hydrogen had been absorbed, or hydrogenation of lactucin itself to uptake of two mols., gave, after crystallisation, a sparingly soluble tetrahydrolactucin (V; R = H), characterised as its diacetate (V; R = Ac). There was no increase in *C*-Me content, but the maximum in the ultraviolet spectrum shifted to 252 mμ (ε 11,000). Further hydrogenation afforded the known hexahydrolactucin. In the infrared region tetrahydrolactucin showed maxima (in Nujol) at 3375 and 3240 (OH), 1760 (γ-lactone), 1685 (·CO·C=C; 5-membered ring), and 1600 (C=C, conjugated with carbonyl group) cm.$^{-1}$. Its diacetate gave bands (in $CHCl_3$) at 1773 (γ-lactone), 1735 and 1238 (acetate), 1710 (as for 1685 above), and 1619 (C=C, as above) cm.$^{-1}$. The intensity of the C=C band in these compounds was close to that of a ketone band. As is well known [5] this indicates a *cisoid* conformation for the enone system such as is presented in (V; R = H). Indeed lactucin and dihydrolactucin, and their respective diacetates, showed the same exaltation of the intensity of the C=C band at the *lower* wave-number.[6] The intensity of the other C=C band in these compounds was normal for a conjugated ketone.

Acetylation of the mother-liquors from the crystallisation of tetrahydrolactucin (V; R = H), followed by chromatography, gave an *iso*tetrahydrolactucin diacetate. This is formulated as (VII; R = Ac) for the following reasons. The infrared spectrum showed bands (in $CHCl_3$) at 1770 (γ-lactone), 1735 and 1238 (acetate), 1700 (·CO·C=C; 5-membered ring), and 1618 (C=C, intensity not exalted) cm.$^{-1}$. The ultraviolet absorption spectrum disclosed the band of an αβ-unsaturated ketone at 227 mμ. If one accepts (see spectral evidence above) a *cyclo*pentenone ring, then this can only have one substituent on the ethylenic linkage.[7] If the ketone group of lactucin is placed in the five-membered ring of the azulenoid skeleton, then only the chromophoric system of (I) will explain the formation of two tetrahydrolactucins with spectroscopic properties as listed above. It is of interest that the ultraviolet absorption of lactucin is not in accord with multiple maxima absorption found for comparable dienone systems contained in two six-membered rings.[8] The spectroscopic properties of such systems are clearly related to their conformations in a subtle way.[8]

Treatment of tetrahydrolactucin with alkali at room temperature gave, without acidification and, therefore, without opening of the lactone ring, a nicely crystalline dienone (VI) having an ultraviolet absorption maximum at 301 mμ. Its infrared spectrum (in $CHCl_3$) showed bands at 3455 to 3330 (OH), 1760 (γ-lactone), 1697 (*cyclo*pentanone with linear diene conjugation) and 1620 and 1573 cm.$^{-1}$ (C=C, the absorption of lower wave number showing the exaltation for the *cisoid* conformation). The formation of this compound places one (the secondary) hydroxyl vinylogously β with respect to the ketone group of lactucin.

Similar mild alkaline treatment of *iso*tetrahydrolactucin diacetate (VII; R = Ac) gave a dienone-acid (VIII). This showed an ultraviolet band at 281 mμ in keeping with the chromophore postulated. The infrared spectrum disclosed bands at 3375 (OH), 3110 (carboxylic acid), 1735 and 1248 (acetate), 1713 (carboxylic acid), 1680 (*cyclo*pentanone with linear diene conjugation), and 1630 and 1590 (C=C, both bands of normal intensity). The formation of this compound confirms the placing of the γ-lactone grouping with its " alcoholic " oxygen atom in a vinylogously β-position with respect to the ketone group.

In the formation of the acid (VIII) one of the acetate residues is removed by hydrolysis. We presume that this will be the residue attached to the primary hydroxyl group as indicated. The presence of such a primary hydroxyl group has been tacitly assumed so far. Such a group must be present (*a*) because of the *C*-Me content (2 groups) of

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[5] *Inter al.*, Hirschmann, Snoddy, Hiskey, and Wendler, *J. Amer. Chem. Soc.*, 1954, **76**, 4013: Wintersteiner and Moore, *ibid.*, 1956, **78**, 6193.

[6] Braude and Timmons, *J.*, 1955, 3766.

[7] Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 76; Gillam and West, *J.*, 1942, 486.

[8] Beaton, Johnston, McKean, and Spring, *J.*, 1953, 3660; Beaton, Shaw, Spring, Stevenson, Strachan, and Stewart, *J.*, 1955, 2606.

dihydrolactucin and all of the more hydrogenated compounds including hexahydrolactucin and (*b*) because it is not possible to place an easily esterifiable (and therefore primary or secondary) hydroxyl group at the remaining secondary position in lactucin without its being detected in the chromophore of the " anhydro "-compound (VI). Indeed in this eventuality the latter would, in fact, be an ene-1 : 4-dione and not a dienone.

Reduction of dihydrolactucin diacetate (IV; R = Ac) with zinc dust and acetic anhydride[9] afforded a deacetoxy-compound. This had the same chromophore (ultraviolet absorption spectrum) as dihydrolactucin and, after allowance for the acetate residue, the same *C*-Me content. The infrared spectrum (in $CHCl_3$) disclosed bands at 1780 (γ-lactone), 1740 and 1238 (acetate), 1693 (C=C•CO•C=C; 5-membered ring), and 1642 and 1618 cm.$^{-1}$ (conjugated C=C, the band of lower wave-number showing the *cisoid* exaltation). The compound must, therefore, be formulated as (XI). We consider that it arises by vinylogous β-elimination of the secondary acetate residue to give an intermediate (X) which is then reduced. In agreement with this suggestion the dienone chromophore of compound (VI) was completely removed under the same reaction conditions.

The position of the primary hydroxyl group of lactucin was established by the following experiments. First, ozonolysis of tetrahydrolactucin (V; R = H) afforded a product which gave 0·38 mol. of iodoform when subjected to the iodoform test. *iso*Tetrahydrolactucin (VII; R = H), under the same conditions, gave no iodoform. Secondly, treatment of hexahydrolactucin ditoluene-*p*-sulphonate (II; R = *p*-Me·C_6H_4•SO_2) with triethylamine furnished a monotoluene-*p*-sulphonate (XI; R = *p*-Me•C_6H_4•SO_2). This showed infrared bands (in $CHCl_3$) at 1768 (γ-lactone), 1718 (*cyclo*pentanone conjugated with a *cyclo*propane ring),[10] and 1600 (C=C of toluene-*p*-sulphonate) cm.$^{-1}$ in agreement with the assigned constitution. When tetrahydrolactucin was converted into its ditoluene-*p*-sulphonate (V; R = *p*-Me•C_6H_4•SO_2) and this treated with triethylamine in the same way, *both* toluene-*p*-sulphonate residues were eliminated to furnish the dienone (XII). This compound, isolated *without* acidification, showed ultraviolet absorption at 238 and 291 mμ (more intense). The spectrum is different from that of the analogous dienone (VI), but not by a degree unexpected in view of the strain introduced by the formation of the *cyclo*propane ring. The infrared spectrum (in $CHCl_3$) exhibited bands at 1773 (γ-lactone), 1693 (•CO•C=C; 5-membered ring; with " extra " conjugation from the *cyclo*propane ring), 1632 (C=C of normal intensity), and 1590 cm.$^{-1}$ (C=C of exalted intensity due to the *cisoid* conformation), all of which are in agreement with the assigned constitution. A dienone of the type (XII) with the additional *cyclo*propane ring could not, of course, have been formed if the primary hydroxyl group of lactucin had been in the alternative position.

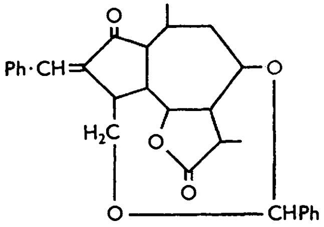
Hexahydrolactucin (II) gave a strongly positive Zimmermann test in agreement with the presence of the grouping $-CH_2$•CO–. Furthermore, treatment with benzaldehyde under basic conditions sufficiently mild to leave the γ-lactone ring intact afforded an amorphous benzylidene ketone with the correct ultraviolet absorption spectrum. Further condensation with benzaldehyde in the presence of acid then furnished a nicely crystalline dibenzylidene derivative (XIII). This had the expected ultraviolet absorption and showed bands in the infrared (in $CHCl_3$) at 1775 (γ-lactone), 1707 (•CO•C=C; 5-membered ring), 1614 (C=C of exalted intensity due to the *cisoid* conformation), 1577 (aromatic C=C), and 1116 (C–O–C) cm.$^{-1}$. There was no hydroxyl absorption in the infrared spectrum, and the compound was recovered unchanged on attempted acetylation.

When hexahydrolactucin itself was treated with benzaldehyde in the presence of acid under the same conditions it was recovered unchanged. However, if the hexahydrolactucin were first treated with a mild base it was isomerised to an oily *iso*hexahydrolactucin. This, when warmed with benzaldehyde under the same acid conditions, readily afforded a crystalline benzylidene derivative (XIV). The latter showed infrared maxima

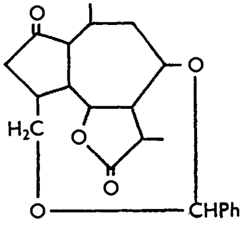
[9] Cf. Woodward, Sondheimer, Taub, Heusler, and McLamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4223.

[10] Eastman, *ibid.*, 1954, **76**, 4115.

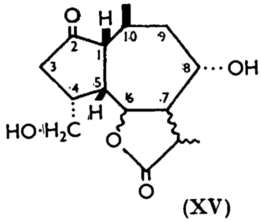
(in $CHCl_3$) at 1777 (γ-lactone), 1740 (*cyclo*pentanone), 1603 (aromatic C=C), and 1118 (C–O–C) cm.$^{-1}$. There was no hydroxyl absorption.



(XIII)



(XIV)



(XV)

The formation of these benzylidene derivatives throws considerable light on the stereochemistry of hexahydrolactucin. Models show that the benzylidene bridge can be formed only if the stereochemistry at positions 1, 5, and 4, 8 is as shown in formula (XV) (or its mirror image).* If we assume that hydrogenation of the 1 : 10-double bond gives *cis*-hydrogen addition at positions 1 and 10, and further that the isomerisation of hexahydro- to *iso*hexahydro-lactucin involves inversion at position 1, then the 1 : 10-hydrogen atoms in the latter are *trans*-related, giving the orientation at position 10 as in formula (XV) (or its mirror image).

On digestion with methanolic sodium hydroxide lactucin and dihydrolactucin afford formic acid. Tetrahydrolactucin, *iso*tetrahydrolactucin (as judged by acetyl determinations under comparable conditions), the dienone (VI), and hexahydrolactucin gave no formic acid in this way. The formic acid must arise from the primary hydroxyl group. By $\beta\gamma$-shift of a 3 : 4-ethylenic linkage this would be converted into a formyl group. Whenever an ethylenic linkage could be tautomerised to the 1 : 5-position then a vinylogous β-aldehydo-ketone would result. Such compounds are, of course, subject to ready deformylation by alkali. It is, therefore, not difficult to account for the observed selectivity in the generation of formic acid.

Lactucin is of interest biogenically as the first sesquiterpenoid lactone of the azulene series with a proven carbonyl group at $C_{(2)}$.†

EXPERIMENTAL

M. p.s were taken on the Kofler block. Unless specified to the contrary, $[\alpha]_D$ are in $CHCl_3$; ultraviolet absorption spectra were determined in EtOH on the Unicam S.P. 500 Spectrophotometer. Infrared spectra were kindly determined by Dr. G. Eglinton and his colleagues. The alumina for chromatography was acid-washed, neutralised, and standardised according to Brockmann's method.[13] Unless stated to the contrary the light petroleum used was of b. p. 60—80°. Microanalyses were carried out by Mr. J. M. L. Cameron and his associates.

Lactucin.—The bitter principle was extracted from crude lactucarium, essentially by the method of Späth, Schenck, and Schreber.[14] Recrystallised from acetone, methanol or ethyl acetate, it had m. p. 213—217°, $[\alpha]_D$ +49° (*c* 0·90 in MeOH), +69° (*c* 0·98 in pyridine), $\lambda_{max.}$ 257 mμ (ε 14,000) (Found: C, 65·35; H, 6·05; *C*-Me, 8·6, 5·3, 8·9. Calc. for $C_{15}H_{16}O_5$: C, 65·2; H, 5·85; *C*-Me, 5·45%). Lactucin gives no colour with ferric chloride solution. It developed

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* For the numbering used for these lactones see Barton, de Mayo, and Shafiq, *J.*, 1957, 929.

† Braun, Herz, and Rabindran [11] have suggested that tenulin also possesses this feature, although, of course, the earlier work of Barton and de Mayo [12] excludes such a possibility. In a personal communication Professor Herz (Florida State University) has very kindly informed us that he now accepts the 3-position for the ketonic group in tenulin.

[11] Braun, Herz, and Rabindran, *J. Amer. Chem. Soc.*, 1956, **78**, 4423.

[12] Barton and de Mayo, *J.*, 1956, 142.

[13] Brockmann and Schodder, *Ber.*, 1941, **74**, 73.

[14] Späth, Schenck, and Schreber, *Arch. Pharm.*, 1939, **277**, 203.

a strong colour in 2·5% ethanolic potassium hydroxide, the spectrum showing $\lambda_{max.}$ 430 mμ (ε 13,200; maximum intensity) after 30 minutes at room temperature. During the development of this chromophore the original band at 257 mμ disappeared.

Treatment with pyridine–acetic anhydride for 6 hr. at room temperature gave lactucin diacetate, m. p. 159—163° (from acetone–light petroleum), $[\alpha]_D$ +87° (*c* 0·74).

Dihydrolactucin.—Palladised calcium carbonate (1%; 117 mg.), suspended in 95% ethanol (10 ml.), was saturated with hydrogen. Lactucin (1·38 g.) in the same solvent (70 ml.) was added and hydrogenated until one mol. had been consumed. Crystallisation from methanol gave *dihydrolactucin* (1·14 g.), m. p. 176—180°, $[\alpha]_D$ +6° (*c* 0·74 in MeOH), $\lambda_{max.}$ 257 mμ (ε 15,000) (Found: C, 64·95; H, 6·25; *C*-Me, 10·1. $C_{15}H_{18}O_5$ requires C, 64·75; H, 6·5; 2*C*-Me, 10·8%). Dihydrolactucin gave the same colour reaction as lactucin in 2·5% ethanolic alkali, showing $\lambda_{max.}$ 430 mμ (ε 10,800; maximum intensity). Treatment with pyridine–acetic anhydride at room temperature for 6 hr. gave *dihydrolactucin diacetate*, m. p. (from methanol) 204—208°, $[\alpha]_D$ +20° (*c* 0·89) (Found: C, 63·0; H, 6·1; *C*-Me, 15·8. $C_{19}H_{22}O_7$ requires C, 62·95; H, 6·1; 4*C*-Me, 16·6%).

Tetrahydrolactucin.—(a) *Hydrogenation of dihydrolactucin.* Palladised calcium carbonate (1%; 136 mg.), suspended in 95% ethanol (10 ml.), was saturated with hydrogen. Dihydrolactucin (600 mg.) in the same solvent (70 ml.) was added and hydrogenated until 1 mol. had been consumed. Crystallisation from ethyl acetate furnished *tetrahydrolactucin* (69 mg.), m. p. 293—295°, $[\alpha]_D$ +6° (*c* 0·68 in pyridine), $\lambda_{max.}$ 252 (ε 11,000) (Found: C, 64·05; H, 7·05; *C*-Me, 10·0. $C_{15}H_{20}O_5$ requires C, 64·25; H, 7·2; 2*C*-Me, 10·75%).

(b) *Hydrogenation of lactucin.* Palladised calcium carbonate (1%; 350 mg.), suspended in 95% ethanol (10 ml.), was saturated with hydrogen. Lactucin (1·38 g.) in 95% ethanol (70 ml.) was added and hydrogenated until 2 mol. had been consumed. Crystallisation as above gave the same tetrahydrolactucin (270 mg.), affording, as above, a *diacetate*, m. p. (from acetone–light petroleum) 138—140°, $[\alpha]_D$ −14° (*c* 1·10) (Found: C, 62·85; H, 6·7; Ac, 23·35. $C_{19}H_{24}O_7$ requires C, 62·6; H, 6·65; Ac, 23·6%).

iso*Tetrahydrolactucin.*—The oily residues remaining after crystallisation of tetrahydrolactucin (obtained from either lactucin or dihydrolactucin) contained an isomeric compound showing $\lambda_{max.}$ 227 mμ. This was separated as follows. The oily material (3·6 g.) in pyridine (18 ml.) and acetic anhydride (18 ml.) was kept at room temperature for 7 hr. The crude acetate was chromatographed over silica (160 g.) in benzene solution. The first 15 eluates (500 ml. portions) contained mixtures of dihydro- and tetrahydro-lactucin diacetate. Fractions 18 to 20, eluted with 5, 10, and 25% ether–benzene respectively consisted mainly of the desired material (ultraviolet spectrum). Crystallisation of these combined fractions from carbon tetrachloride and then from acetone gave iso*tetrahydrolactucin diacetate* (180 mg.), m. p. (needles from acetone) 176—180°, $[\alpha]_D$ +127° (*c* 1·00), $\lambda_{max.}$ 227 mμ (ε 8500) (Found: C, 62·5; H, 6·5; Ac, 23·1. $C_{19}H_{24}O_7$ requires C, 62·6; H, 6·65; Ac, 23·6%).

Hexahydrolactucin.—Complete hydrogenation of lactucin using palladised charcoal (5%) in 95% ethanol gave the known [2,3] hexahydrolactucin, m. p. (from ethyl acetate) 180—182°, $[\alpha]_D$ +95° (*c* 0·66 in MeOH), +85° (*c* 0·72 in pyridine) (Found: C, 63·75; H, 7·85; *C*-Me, 10·25. Calc. for $C_{15}H_{22}O_5$: C, 63·8; H, 7·85; 2*C*-Me, 10·65%). The same compound (m. p., mixed m. p., rotation, and infrared spectrum) resulted from the hydrogenation of tetrahydrolactucin under the same conditions. A Zimmermann test on hexahydrolactucin was strongly positive.

Treatment of hexahydrolactucin (300 mg.) in dry pyridine (25 ml.) with purified toluene-*p*-sulphonyl chloride (2·46 g.) at room temperature for 16 hr. gave *hexahydrolactucin ditoluene*-p-*sulphonate* (143 mg.), m. p. (from acetone) 152—153°, $[\alpha]_D$ +33° (*c* 0·52), $\lambda_{max.}$ 226 mμ (ε 21,000) (Found: C, 59·1; H, 6·25; S, 10·1. $C_{29}H_{34}O_9S_2$ requires C, 58·95; H, 5·8; S, 10·85%). The infrared spectrum (Nujol) showed bands at 1773 (γ-lactone), 1733 (*cyclo*pentanone), 1596 (aromatic C=C) and 1172 ($C_6H_4Me{\cdot}SO_3$) cm.$^{-1}$.

Treatment of Hexahydrolactucin Ditoluene-p-*sulphonate with Triethylamine.*—The ditoluene-*p*-sulphonate (200 mg.) was refluxed with anhydrous triethylamine (dried over Na wire) (20 ml.) for 11 hr. The triethylamine was removed *in vacuo* and the residue dissolved in chloroform and washed with 0·5N-hydrochloric acid and then with saturated aqueous sodium hydrogen carbonate. Crystallisation from acetone–light petroleum afforded the *monotoluene*-p-*sulphonate* (XI; R = toluene-*p*-sulphonyl) (rectangular plates) (90 mg.), m. p. 201—203°, $[\alpha]_D$ +55° (*c* 0·60), $\lambda_{max.}$ 226 mμ (ε 7200) (Found: C, 62·95; H, 6·05; S, 7·5. $C_{22}H_{26}O_6S$ requires C, 63·15; H, 6·25; S, 7·65%). This compound gave a negative Zimmermann test.

*Tetrahydrolactucin Ditoluene-*p*-sulphonate and its Reaction with Triethylamine.*—Tetrahydrolactucin, treated with toluene-*p*-sulphonyl chloride as for the hexahydro-derivative (see above), gave *tetrahydrolactucin ditoluene-*p*-sulphonate.* Recrystallised from alcohol and then from acetone–light petroleum this (thin plates) had m. p. 156—157°, $[\alpha]_D$ $-33°$ (*c* 0·80), $\lambda_{max.}$ 226 and 250 mμ (ε 29,000 and 13,000 respectively), infrared maxima ($CHCl_3$) at 1775 (γ-lactone), 1708 (*cyclo*pentenone), 1613 (strong; *cisoid* C=C conjugated with ketone), 1598 (aromatic C=C), and 1175 cm.$^{-1}$ (toluene-*p*-sulphonate) (Found: C, 59·35; H, 5·8; S, 10·45. $C_{29}H_{32}O_9S_2$ requires C, 59·15; H, 5·5; S, 10·9%).

The ditoluene-*p*-sulphonate (520 mg.) was refluxed with anhydrous triethylamine (200 ml.) for 11 hr. (spectrophotometric control). The triethylamine was removed *in vacuo* and the residue extracted into ether and washed with saturated sodium hydrogen carbonate solution. The product was chromatographed in benzene over alumina (Grade III; 5 g.), elution being with benzene. Crystallisation from acetone–light petroleum afforded the desired *dienone* (XII) (200 mg.), m. p. (after sublimation) 157—162°, $[\alpha]_D$ $+142°$ (*c* 0·62), $\lambda_{max.}$ 238 and 291 mμ (ε 4500 and 9800 respectively) (Found: C, 73·75; H, 6·65. $C_{15}H_{16}O_3$ requires C, 73·75; H, 6·6%).

Ozonolyses.—(*a*) Lactucin (138 mg.) in anhydrous tetrahydrofuran (40 ml.) was ozonised at $-40°$ to $-60°$ for 75 min. (disappearance of ultraviolet band at 258 mμ). Addition of water and steam-distillation into aqueous dimedone solution gave the formaldehyde dimedone derivative (42 mg. crude; 34 mg. pure; 23%), identified by m. p. and mixed m. p.

(*b*) Dihydrolactucin, ozonised under the same conditions, gave no formaldehyde dimedone derivative.

(*c*) Tetrahydrolactucin (100 mg.) in methanol (60 ml.) was ozonised at $-50°$ to $-70°$ until the ultraviolet absorption at 251 mμ had disappeared (100 min.). Water (5 ml.) was added and the solution evaporated to dryness *in vacuo* on the steam-bath. The residue was subjected to the iodoform test as described by Fieser,[15] to furnish iodoform (52 mg., 38%), identified by m. p. and mixed m. p. The appropriate controls, run at the same time, gave no iodoform. Acetophenone (50 mg.) tested also under the same conditions gave iodoform (107 mg., 65%).

(*d*) *iso*Tetrahydrolactucin (100 mg.) in chloroform (40 ml.) was ozonised at $-50°$ to $-60°$ until the ultraviolet max. at 227 mμ had disappeared (60 min.). Water (5 ml.) was added and the mixture of solvents removed *in vacuo*. The residue gave no iodoform when tested as above.

Treatment of Lactucin and its Derivatives with Alkali.—Lactucin (305 mg.) was refluxed with methanolic sodium hydroxide (N; 116 ml.) for 3 hr. The methanol was purified first by refluxing it with solid potassium hydroxide then by rectification. The appropriate control was also run. Most of the methanol was removed by distillation. Sulphuric acid (45 ml.; 2 : 1 water : H_2SO_4) was added and the volatile acid steam-distilled and titrated with 0·1N-sodium hydroxide (0·4 equiv. of acid). The volatile acid was characterised as formic acid by the infrared spectrum of its sodium salt.

A similar determination on dihydrolactucin gave 0·95 mol. of formic acid. In contrast tetrahydrolactucin, the dienone (VI), and hexahydrolactucin did not furnish formic acid under these conditions.

The formation of excess of volatile acid under acetyl-determination conditions also indicated the presence of formic acid. Thus acetyl determinations on lactucin and dihydrolactucin, carried out with preliminary alkali treatment,[16] gave 30·75 and 28·55% of Ac instead of the theoretical figures of 23·9 and 23·75% respectively.

Dehydrogenation of Lactucin.—Lactucin (2·0 g.) in " AnalaR " acetic acid containing 72% aqueous perchloric acid (5 drops) was hydrogenated over platinum (600 mg.). The gummy product (1·5 g.) was dehydrogenated in portions (200 mg.) by 10% palladised charcoal (200 mg.) for 15 min. under nitrogen at 320°. The combined batches were extracted with light petroleum and the blue solution was filtered through alumina (6 g.; Brockmann No. 5). Extraction into 80% phosphoric acid and further treatment in the usual way gave chamazulene (6 mg.), characterised as its trinitrobenzene adduct (m. p., mixed m. p., ultraviolet and visible absorption spectra).

Dienone from Tetrahydrolactucin.—Tetrahydrolactucin (300 mg.) in 95% ethanol (63 ml.)

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[15] Fieser, " Experiments in Organic Chemistry," 3rd Edn., Heath, Boston, 1955, p. 86.

[16] Pregl's " Quantitative Organic Micro-Analysis," Ed. J. Grant, 5th Edn., J. and A. Churchill Ltd., London, 1951, p. 202.

was treated with 5% ethanolic potassium hydroxide (7 ml.) at room temperature. The ultraviolet absorption of this solution developed a maximum at 305 mμ (measured against the appropriate control) which reached its highest intensity after 6 hr. Crystallisation of the neutral product, obtained *without* acidification, from acetone–light petroleum gave the *dienone* (VI) (171 mg.) as rectangular prisms, m. p. 207—209°, $[\alpha]_D$ −240° (*c* 0·56), $\lambda_{max.}$ 301 mμ (ε 12,300) (Found: C, 68·8; H, 6·75. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%). When this compound (35 mg.) was refluxed with zinc dust (750 mg.) in dry acetic anhydride (2·5 ml.) under nitrogen with good stirring for 10 min. it gave a product (20 mg.) showing no ultraviolet absorption at 303 mμ, but instead a band at 243 mμ.

Dienone from iso*Tetrahydrolactucin Diacetate.*—*iso*Tetrahydrolactucin diacetate (162 mg.) in 95% ethanol (9 ml.) was treated with 5% ethanolic potassium hydroxide (1·0 ml.) at room temperature for 30 min. The reaction was controlled spectrophotometrically as above, to give the optimum conditions. The acidic product was crystallised from chloroform or from acetone–light petroleum, to furnish the *dienone* (VIII) (72 mg. crude; 30 mg. pure), m. p. 200—205° after sintering at 190°, $[\alpha]_D$ +219° (*c* 0·90 in MeOH), $\lambda_{max.}$ 281 mμ (ε 14,000) (Found: C, 63·2; H, 6·6; Ac, 13·85. $C_{17}H_{22}O_6$ requires C, 63·35; H, 6·9; 1Ac, 13·35%). The compound effervesced briskly in sodium hydrogen carbonate solution.

Reduction of Dihydrolactucin Diacetate with Zinc Dust and Acetic Anhydride.—Dihydrolactucin diacetate (300 mg.) in dry acetic anhydride (6 ml.) was refluxed under nitrogen with dry zinc dust (3·0 g.; added in one portion) with vigorous stirring for 8—10 min. The oily product (269 mg.) was chromatographed over silica gel (20 g.). Elution with benzene (50 ml. portions) gave 12 fractions showing acetate infrared bands of reduced intensity (relative to the intensity of the γ-lactone carbonyl). Fractions 3—11 were combined (147 mg.) and crystallised from methanol, to afford *deoxydihydrolactucin acetate*, m. p. 188—190°, $[\alpha]_D$ +15° (*c* 0·92), $\lambda_{max.}$ 258 mμ (ε 15,000) (Found: C, 66·95; H, 6·7; *C*-Me, 14·4. $C_{17}H_{20}O_5$ requires C, 67·1; H, 6·6; 3*C*-Me, 14·8%). An acetyl determination showed Ac, 20·75 instead of the theoretical 14·15%. The excess of " acetyl " must again be due to the generation of formic acid (see above).

iso*Hexahydrolactucin and its Derivatives.*—Hexahydrolactucin (106 mg.) in 95% ethanol (5·5 ml.) was treated with ethanolic potassium hydroxide (5% w/v; 0·1 ml.) at room temperature in a polarimeter tube. After 5 min. $[\alpha]_D$ was −50°; after 3 hr. it was constant at −63°. The solution was poured into water (90 ml.) and, without acidification, was extracted with chloroform (10 × 25 ml.). The chloroform extract, after being washed with water (2 × 10 ml.) and dried (Na_2SO_4), afforded a neutral product (42 mg.) which did not crystallise. It is regarded as *iso*hexahydrolactucin on the basis of its physical properties {$[\alpha]_D$ −108° (*c* 2·50), no high-intensity ultraviolet absorption, infrared bands ($CHCl_3$) at 3340 (OH), 1760 (γ-lactone), and 1730 (*cyclo*pentanone) cm.$^{-1}$} and of its further chemical reactions (see below).

Treatment of the oily *iso*hexahydrolactucin (135 mg.) in redistilled benzaldehyde (0·6 ml.) on the steam-bath with 6N-aqueous hydrochloric acid (2 drops) for 2 min., followed by removal of excess of benzaldehyde at steam-bath temperature *in vacuo*, gave the iso*hexahydrolactucin* OO-*benzylidene derivative* (XIV). Recrystallised from acetone–light petroleum this (59 mg.) had m. p. (cubes) 266—268°, $[\alpha]_D$ −143° (*c* 0·86) (Found: C, 71·1; H, 6·95. $C_{22}H_{26}O_5$ requires C, 71·35; H, 7·1%). Hexahydrolactucin, itself, was recovered unchanged under the same conditions.

The condensation of benzaldehyde with *iso*hexahydrolactucin under alkaline conditions was also investigated. *iso*Hexahydrolactucin (390 mg.) in absolute ethanol (10 ml.) was treated with redistilled benzaldehyde (2·4 ml.) and ethanolic potassium hydroxide (5% w/v; 0·2 ml.) at room temperature for 23 hr. (spectrophotometric control using the band at 300 mμ). The neutral product was chromatographed over alumina (13 fractions). The (five) fractions showing the correct ultraviolet and infrared bands for a benzylidene derivative were combined. They showed $[\alpha]_D$ −11° (*c* 0·80), $\lambda_{max.}$ 300 mμ (ε 16,000), infrared bands at 3363 (OH), 1760 (γ-lactone), 1704 (*cyclo*pentenone), 1615 (strong *cisoid* C=C), and 1580 (aromatic C=C) cm.$^{-1}$ and consisted of essentially pure benzylidene derivative. This compound (90 mg.) in benzaldehyde (0·6 ml.) was heated on the steam-bath with 6N-aqueous hydrochloric acid (2 drops) for 2 min. Working up as in the comparable example above afforded the iso*hexahydrolactucin dibenzylidene derivative* (XIII). Recrystallized from acetone–light petroleum this formed rectangular prisms, m. p. 287—289°, $[\alpha]_D$ −72° (*c* 0·83), $\lambda_{max.}$ 300 mμ (ε 17,600) (Found: C, 76·1; H, 6·75. $C_{29}H_{30}O_5$ requires C, 75·95; H, 6·6%). Treatment of crude benzylidene compound gave the same dibenzylidene derivative without any difficulty. The dibenzylidene derivative could not be acetylated under normal conditions.

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The University, Glasgow, W.2.
Imperial College, London, S.W.7.

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