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CONSTITUENTS OF *HELENIUM* SPECIES—XIX

FURTHER TRANSFORMATIONS OF HELENALIN AND ITS CONGENERS. THE 1-EPIHELENALIN AND 1-EPIAMBROSIN SERIES[1,2]

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Abstract—The inversion of the asymmetric center at C_1 of helenalin and ambrosin is described. The isomerization of helenalin is accompanied by lactone ring reorientation. The ORD curves of the 1-epi derivatives and their transformation products do not correspond to those of analogous 14β-17-ketosteroids. The remaining ambiguity in the stereochemistry of ambrosin, parthenin and coronopilin has been removed. Previously deduced relationships between tetrahydrohelenalin, dihydromexicanin C, dihydroisotenulin, tetrahydrobalduilin A and tetrahydrobigelovin have been confirmed through a reaction permitting inversion of the asymmetric center at C_6, which has also led to the complete elucidation of the stereochemistry of tetrahydrobigelovin and thurberilin.

Hydrogen chloride–chloroform converts helenalin (IVa) into mexicanin A (VII).[7] In the previous paper[2] we were able to provide evidence for the formulation of VII and described[2] the isomerization of isotenulin (I) to IIb and the further conversion of IIb to 1-epiisotenulin (IIIb). Since the optical and chemical properties of III and its transformation products are unusual, we have investigated the action of hydrogen chloride–methanol on helenalin and ambrosin (XXIV) in the hope of preparing new *cis*-fused pseudoguaianolides which might be related to sesquiterpene lactones of as yet undetermined stereochemistry. The results are described in the present paper, together with related material pertaining to inversions at C_6 of the pseudoguaianolide carbon skeleton.

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[1] Work at Florida State University supported in part by grants from the National Science Foundation (GP-1962) and the U.S. Public Health Service (GM-05814). Work at the University of Texas was supported by the Robert A. Welch Foundation.

[2] Previous paper, W. Herz, M. V. Lakshmikantham and R. N. Mirrington, *Tetrahedron* 22, 1709 (1966).

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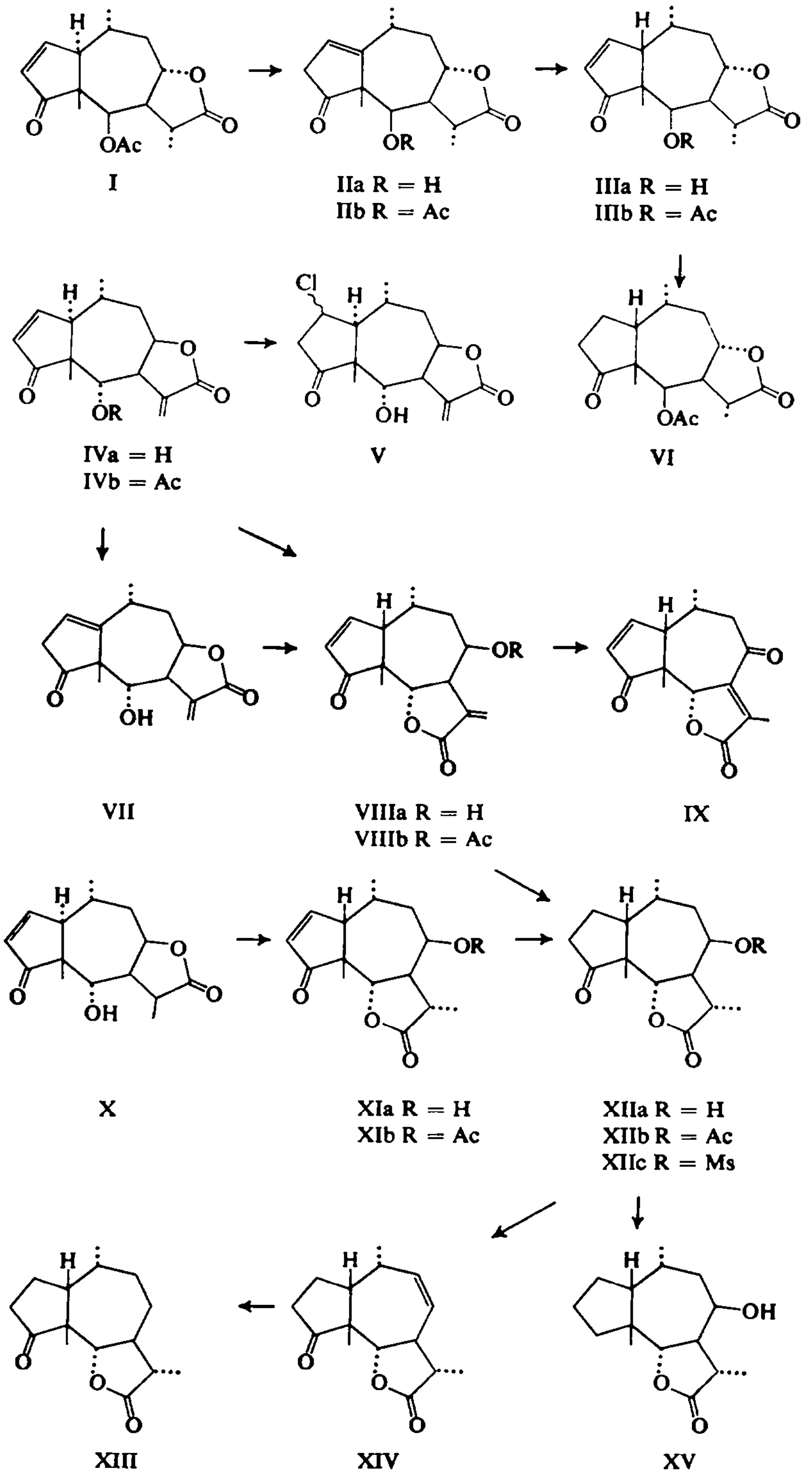
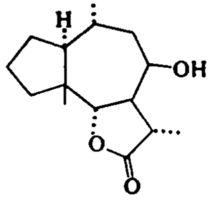
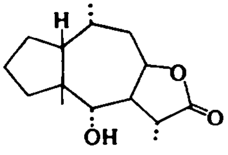
[7] W. Herz, A. Romo de Vivar, J. Romo and N. Viswanathan, *J. Amer. Chem. Soc.* 85, 19 (1963).

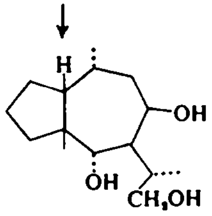

I
IIa R = H
IIb R = Ac
IIIa R = H
IIIb R = Ac
IVa = H
IVb = Ac
V
VI
VII
VIIIa R = H
VIIIb R = Ac
IX
X
XIa R = H
XIb R = Ac
XIIa R = H
XIIb R = Ac
XIIc R = Ms
XIII
XIV
XV



XVI



XVII



XVIII

Exposure of helenalin (IVa) to conc. HCl resulted only in addition of hydrogen chloride to the double bond of the α,β-unsaturated ketone function and formation of V. This material was unstable and regenerated IVa. However, treatment of IVa or VII with HCl–MeOH produced 1-epiallohelenalin (VIIIa) which had retained the two chromophores present in helenalin (cyclopentenone and unsaturated γ-lactone), but the lactone ring had undergone reorientation. This was evident from the NMR spectrum (Table 1) which exhibited a sharp doublet at 4·8 ppm (J = 9) ascribable to the proton *alpha* to the lactone ether oxygen, because it remained stationary on acetylation of VIIIa to VIIIb, and a multiplet at 4·3 ppm identifiable with the proton on carbon carrying the free hydroxyl group, because it displayed the characteristic downfield shift on conversion to VIIIb.

Catalytic hydrogenation of VIIIa furnished XIIa comparison of whose NMR spectrum with that of the acetate XIIb (Table 1) reinforced the conclusions reached earlier about the orientation of the lactone ring. The same compound was also obtained by HCl–MeOH isomerization of dihydrohelenalin (X) to XIa and subsequent reduction. Desulfurization of the thioketal of XIIa led to XV which differed from desoxoallotetrahydrohelenalin (XVI).[8,9] LAH reduction of XV gave a crystalline triol (XVIII) which differed from the C_{11}-epimeric triols produced from XVI or desoxodihydromexicanin C (XVII).[9] Hence the transformation IV → VIIIa was accompanied by epimerization at one or more of the asymmetric centers C_1, C_5, C_6, C_7, C_8 or C_{10}.

The conversion of isomexicanin A (XIX)[7] to the triol XVIII by the route outlined below clearly shows that, since mexicanin A has the same stereochemistry as helenalin at C_5, C_6, C_7 and C_8[2,10], 1-epiallohelenalin (VIIIa) must have the same stereochemistry as helenalin at C_5, C_6 and C_8. However, the situation at C_7 needs further clarification. The method of correlation of VIIIa and XIX, *via* XX and XXI, could at least in theory have resulted in a triol whose stereochemistry at C_7 differs from that of helenalin, because one of the steps involved hydrogenation of a C_7–C_{11} double bond.

Now the configuration of triol XVIII and its precursors XV and XXIII at C_{11} is fixed because of the correlation with dihydrohelenalin (X, C_{11}-methyl β). If we then assume *cis*-hydrogenation of the double bond of XXI, the configuration at C_7 of XXIII is the same as that of helenalin and must have remained unaltered during the process IV → VIIIa → XVIIIa. That this conclusion was correct was confirmed by converting

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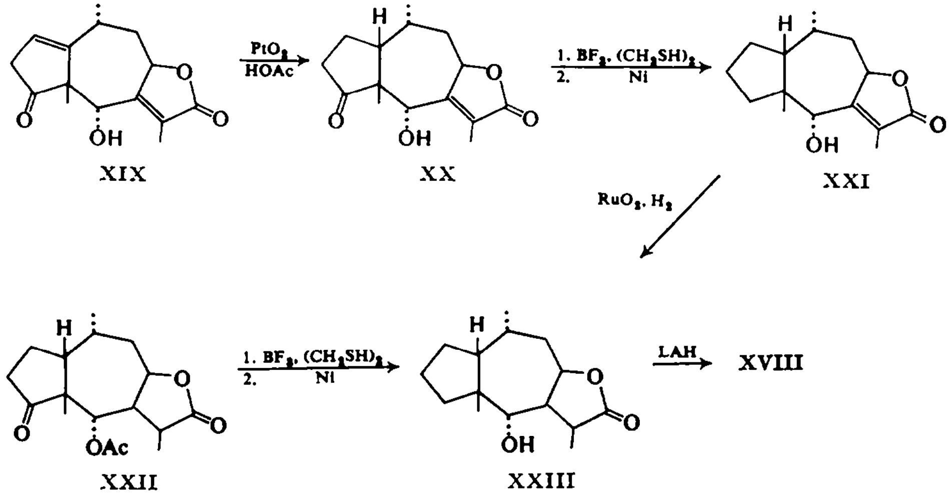
[8] W. Herz and R. B. Mitra, *J. Amer. Chem. Soc.* **80**, 4876 (1958).

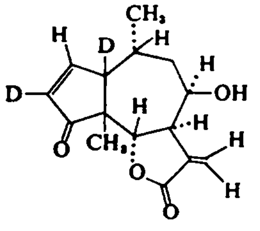
[9] W. Herz, A. Romo de Vivar, J. Romo and N. Viswanathan, *Tetrahedron* **19**, 1359 (1963).

[10] That the configuration of mexicanin A at C_{10} was the same as that of helenalin was assumed earlier[1] on excellent, though not incontrovertible, grounds and will be clearly demonstrated in the sequel.

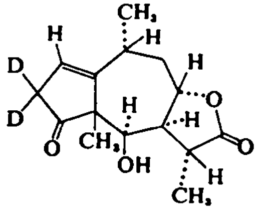
acetyltetrahydromexicanin A (XXII)[2,7] to XVIII *via* XXIII without isolation of intermediates, albeit in poor yield.



With the configuration of VIIIa at C_5, C_6, C_7 and C_8 securely established as shown in the formula, the nature of the asymmetric centers at C_1 and C_{10} remained to be defined. The problem was solved very simply by carrying out the isomerization of helenalin in DCl–CH_3OD. The NMR spectrum of the product A showed clearly that deuterium had attached itself to C_1 and C_3, but not to C_6, C_7 or C_{10}. Signals of VIIIa due to H_1 (multiplet at 3·5 ppm) and H_3 (doublet of doublets at 6·35 ppm) had disappeared and the H_2 doublet of doublets at 7·90 ppm had collapsed to a singlet. The vinyl hydrogens at 5·67 and 6·35 ppm were still coupled to H_7 (multiplet at 2·5 ppm) and most significantly, the signal of the C_{10}-methyl group had remained a doublet which indicated that no deuterium had been introduced at C_{10}. Hence the transformation IV → VIIIa solely involves epimerization at C_1, aside from reorientation of the lactone ring.



A



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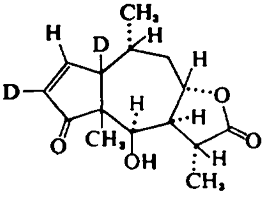
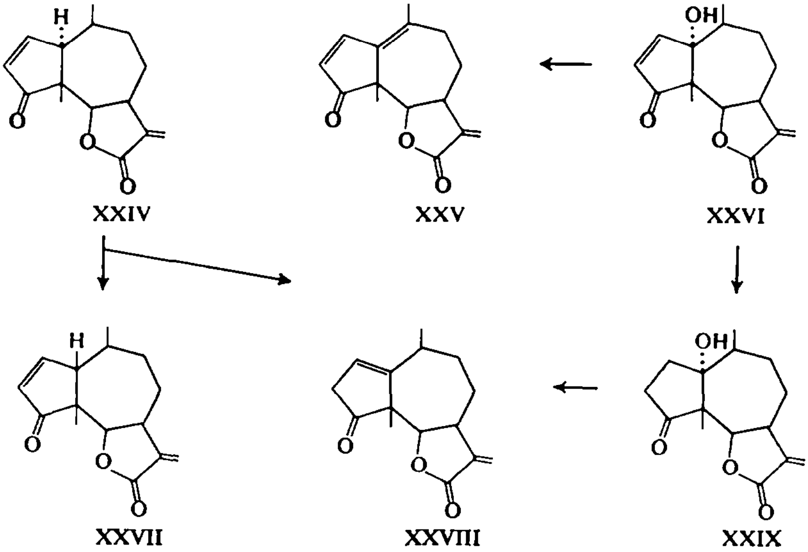


C

In a similar manner treatment of isotenulin (I) with DCl–CH$_3$OD established conclusively that the previously reported[3] conversion to II and III had resulted in epimerization at C$_1$, but not at C$_{10}$ (formulae B and C) which confirms the conclusions reached earlier.[2,11]

With a practical route to *cis*-fused pseudoguaianolides related to isotenulin and helenalin available, it was of interest to extend the study to ambrosin (XXIV). This compound and its congeners parthenin (XXVI)[12] and coronopilin (XXIX)[13,14] differ from the sesquiterpene lactones of *Helenium* species not only in orientation of the lactone ring, but also in configuration at C$_{10}$.[12] The relative stereochemical features assigned[12,14] to ambrosin have been confirmed by X-ray analysis[15] and if the correlation of ambrosin with parthenin through hydrogenation of anhydroparthenin (XXV) has not resulted in epimerization at C$_{10}$,[16] the absolute stereochemistry of ambrosin must be as indicated since the absolute configuration of parthenin at C$_{10}$ has been determined independently (C$_{10}$-methyl β).[12] We have been able to settle this one remaining ambiguity by correlating coronopilin and ambrosin through reactions which do not involve C$_{10}$ and at the same time afford an entry to *cis*-fused pseudoguaianolides of the ambrosin series.



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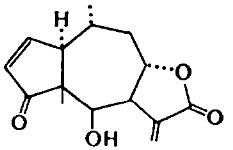
[11] The acid-catalyzed isomerization of mexicanin I (i) proceeded in poor yield and gave products whose structure could not be documented satisfactorily. Details are given in the Experimental.



i

[12] W. Herz, H. Watanabe, M. Miyazaki and Y. Kishida, *J. Amer. Chem. Soc.* **84**, 2601 (1962).

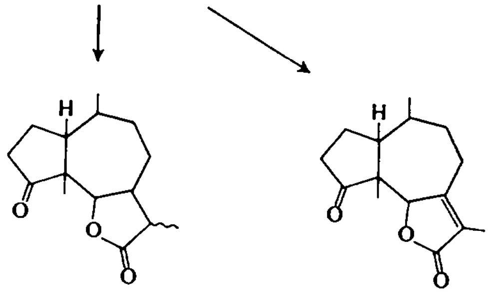
[13] W. Herz and G. Högenauer, *J. Org. Chem.* **26**, 5011 (1961).

[14] T. A. Geissman and R. J. Turley, *J. Org. Chem.* **29**, 2553 (1964).

[15] M. T. Emerson, C. N. Caughlan and W. Herz, to be published.

[16] Correspondence in the ORD curves of tetrahydroambrosin and tetrahydroparthenin was taken to indicate that the stereochemistry of the ring fusion was identical and *trans*, with H$_1\alpha$.

XXVII



XXX XXXI

Treatment of ambrosin with HCl–$CHCl_3$ furnished a mixture which was separated by fractional crystallization. The more soluble component was a β,γ-unsaturated ketone which was assigned formula XXVIII by analogy with the other isomerizations and on the basis of its NMR spectrum (Table 1).[17] The second substance obtained in better yield by treatment of ambrosin with HCl–MeOH, was an α,β-unsaturated ketone and had to be epimeric with ambrosin at C_1, C_{10} or both. Catalytic hydrogenation resulted in formation of XXX and XXXI which differed from analogous compounds prepared by hydrogenation of ambrosin. Repetition of the isomerization with DCl–CH_3OD resulted in incorporation of deuterium at C_1 and C_3, but not at C_{10}; hence the new compound must be formulated as 1-epiambrosin (XXVII). As was therefore to be expected, XXX differed from XIII, prepared from XIIc by treatment with collidine and reduction of the resulting XIV,[18] in configuration at C_{10} and certainly at C_6.

Compound XXVIII which, as could be demonstrated, represents an intermediate in the conversion of XXIV to XXVII could also be prepared by dehydration of coronopilin (XXIX) with thionyl chloride-pyridine.[19] This affords incontestable evidence for the previous assumption that the C_{10}-methyl groups of parthenin, coronopilin and ambrosin have the same orientation and completes the structure proof for these compounds and other sesquiterpene lactones derived from them, such as the psilostachyins.[20–22]

The ORD curves of VIIIa and VIIIb (Experimental) exhibit negative Cotton effects (a −33·1 and −48·9) which, because of the difference in orientation of the lactone ring, should perhaps not be compared with the ORD curves of IVa (a −45·9)[23]

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[17] The properties of this compound differed from those of a substance obtained[13] by zinc dust reduction of anhydroparthenin (XXV) for which structure XXVIII (devoid of stereochemistry) was postulated provisionally. It is possible that the previously-prepared compound has an α-C_{10}-methyl group.

[18] cf. the conversion of desacetyldihydroisotenulin to a substance epimeric with XIV at C_1 and C_6 described in Ref. 7.

[19] The conditions are critical (Experimental) which undoubtedly explains earlier failures[13,14] to obtain analyzable products from this reaction.

[20] H. E. Miller, H. B. Kagan, W. Renold and T. J. Mabry, *Tetrahedron Letters* 3397 (1965); T. J. Mabry, H. E. Miller, H. B. Kagan and W. Renold, *Tetrahedron* **22**, 681 (1966); *Tetrahedron* **22**, 1139 (1966).

[21] T. J. Mabry, W. Renold, H. E. Miller and H. B. Kagan, *J. Org. Chem.* **31** (1966).

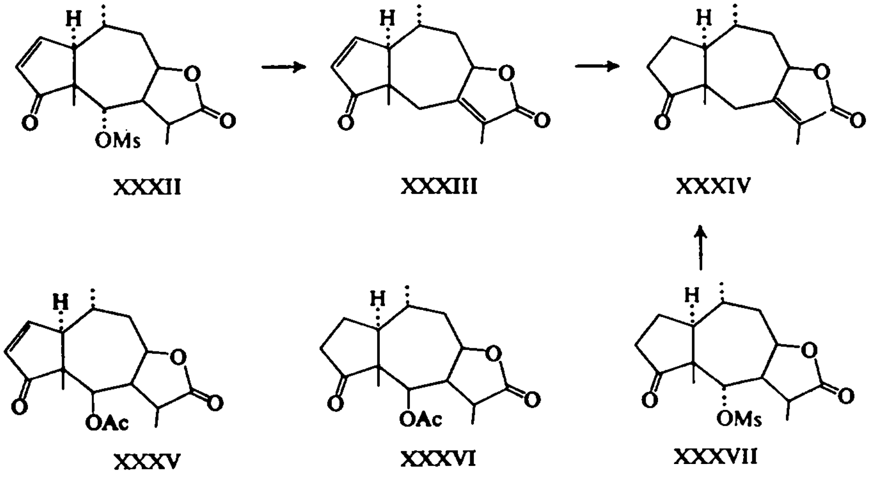
[22] H. B. Kagan, H. E. Miller, W. Renold, M. V. Lakshmikantham, L. R. Tether, W. Herz and T. J. Mabry, *J. Org. Chem.* **31**, 1629 (1966).

[23] C. Djerassi, J. Osiecki and W. Herz, *J. Org. Chem.* **22**, 1361 (1957).

or with that of III (positive Cotton effect, amplitude uncertain). The Cotton effect of XXVII is also negative (amplitude uncertain) and of the same sign as that of XXIV (a −23·2). The reduced compounds XIIa and XIIb display moderately strong negative Cotton effects comparable to that of VI,[2] while that of tetrahydro-1-epiambrosin (XXX) is weakly positive (a −9·0). These observations serve to reinforce our earlier conclusion[2] that comparison of the ORD curves of *cis*-fused pseudoguaianolides with those of 14β-17-ketosteroids is not warranted, due to conformational factors in the 7-membered ring.

We conclude by mentioning the results of some experiments which had as their aim the interconversion of pseudoguaianolides by epimerization of the asymmetric center at C_6. In the helenalin series this led to elimination rather than displacement. Thus, dihydrohelenalin mesylate (XXXII) on treatment with AcONa–AcOH furnished isoaromatin (XXXIII), whose structure was established by hydrogenation to the dihydroderivative XXXIV,[24] rather than dihydrobalduilin (XXXV), and tetrahydrohelenalin mesylate (XXXVII) furnished XXXIV rather than tetrahydrobalduilin[9,25] (XXVI). Dihydromexicanin C[9] mesylate (XXXVIII) underwent partial displacement, the product being a mixture of XXXIV, the C_8-epimer previously[26] prepared from tenulin and tetrahydrobalduilin A XXXIX.[9,25] Desacetyldihydroisotenulin mesylate (XL)[26] furnished tetrahydrobigelovin (XLII)[27-29] by displacement. These transformations afford further proof for the stereochemistry assigned to aromatin, tetrahydrobalduilin A and bigelovin.

The conversion XL → XLII establishes the previously unknown configuration of tetrahydrobigelovin at C_{11} as H β, methyl α and thereby solves the remaining uncertainty at C_{11} in the stereochemistry of thurberilin[28] which has been correlated with it. Thurberilin must be XLI (C_{11}-methyl α).



XXXII XXXIII XXXIV

XXXV XXXVI XXXVII

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[24] J. Romo, P. Joseph-Nathan and F. Diaz A., *Chem. & Ind.* 1839 (1963); *Tetrahedron* **20**, 79 (1964).

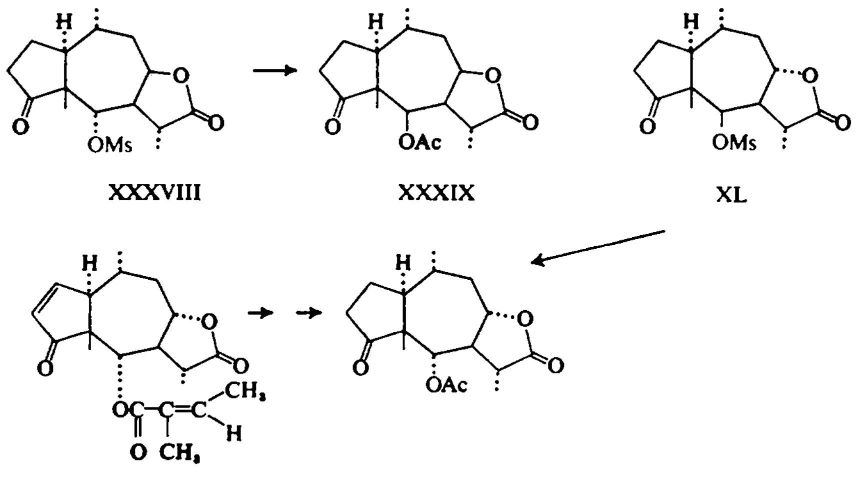
[25] W. Herz, R. B. Mitra and P. Jayaraman, *J. Amer. Chem. Soc.* **81**, 6061 (1959).

[26] W. Herz, W. A. Rohde, K. Rabindran, P. Jayaraman and N. Viswanathan, *J. Amer. Chem. Soc.* **84**, 3857 (1962).

[27] B. A. Parker and T. A. Geissman, *J. Org. Chem.* **27**, 4127 (1962).

[28] W. Herz and M. V. Lakshmikantham, *Tetrahedron* **21**, 1711 (1965).

[29] We are unable to account for our previous failure[26] to carry out this reaction.



XXXVIII XXXIX XL

XLI XLII

EXPERIMENTAL[20]

2,3-*Dihydro-2-chlorohelenalin* (V)

When IVa (1 g) was allowed to stand with conc. HCl (10 ml) at room temp for 6 hr, a crystalline product separated. It was filtered and washed with cold water, yield 1·03 g, m.p. 143–145° (dec), IR bands at 3600, 1765, 1750 (sh) and 1660 cm^{-1}. Attempts at recrystallization resulted in formation of helenalin. (Found: C, 60·15; H, 6·51; O, 21·20; Cl, 11·67. Calc. for $C_{15}H_{19}O_4Cl$: C, 60·29; H, 6·41; O, 21·42; Cl, 11·86%.)

1-*Epiallohelenalin* (VIIa)

(a) A solution of IVa (10 g) in MeOH (200 ml) and conc. HCl (200 ml) was refluxed for 1 hr, the solvent removed at red. press., the residue diluted with water and the mixture extracted with chf. The extracts were washed, dried and evaporated. The residue was crystallized from acetone–diisopropyl ether, yield 6·0 g of VIIIa, m.p. 180–182°. Recrystallization from acetone–hexane furnished the analytical sample, m.p. 181–182°, $[\alpha]_D$ +37·3° (*c*1) IR bands at 3600 (—OH), 1755 and 1655 (unsaturated γ-lactone), 1700 and 1590 cm^{-1} (cyclopentenone), λ_{max} 220 and 328–333 mμ (log ε 4·19 and 1·85), ORD curve[21] (MeOH, *c* 0·0354) $[\alpha]_{460}$ −150° (first reading), $[\alpha]_{362.5}$ −400°, $[\alpha]_{310}$ +865°, $[\alpha]_{295}$ +835°, $[\alpha]_{240}$ +12400°, $[\alpha]_{230}$ 0° (last reading). (Found: C, 68·43; H, 7·10; O, 24·47. Calc. for $C_{15}H_{18}O_4$: C, 68·68; H, 6·92; O, 24·40%.) Occasionally the yield of VIIIa was reduced. Chromatography of the mother liquors then furnished VII, m.p. 139–140°, undepressed on admixture of an authentic sample.

Repetition of the experiment with IVa (0·2 g), CH_3OD (4 ml) and 38% DCl (4 ml) furnished 1-epiallohelenalin-1,3-d_2 (0·15 g), m.p. 179–180°, NMR signals at 7·90 (H_2), 6·35 d (3·5) and 5·67 d (3, exocyclic methylene group), 4·84 d (9, H_6), 4·3 c (H_8), 3·13 (OH, removed by exchange with D_2O), 2·55 c (H_7 and H_{10}, $w_{1/2}$ 20 c/s), 1·42 (C_5-methyl) and 1·24 d (7, C_{10}-methyl). The spectrum was consistent with the introduction of deuterium at C_1 and C_3, but not at C_{10}.

(b) A solution of VII (0·4 g) in MeOH (5 ml) and conc. HCl (5 ml) was refluxed for 1 hr. The gummy product was chromatographed over alumina. Elution with benzene–AcOEt (4:1) gave VIIIa, yield 0·165 g, m.p. 178–181°.

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[20] M.p's are uncorrected. IR spectra, chf, UV spectra, 95% EtOH, rotations in chf, unless otherwise specified. Petroleum ether boiled at 30–60°.

[21] Kindly determined by Dr. Lin Tsai (Cary Model 60 recording spectropolarimeter).

TABLE 1[a]. NMR SPECTRA OF HELENALIN AND AMBROSIN DERIVATIVES

Compound	H_2	H_3	H_6	H_8	H_{13}	C_5–Me	C_{10}–Me	C_{11}–Me	Misc.
VIIIa	7·90 dd(6,2)	6·35 dd(6,2)	4·84 d(9)	4·3 br[b]	6·35 d(3·5) 5·67 d(3)	1·42	1·24 d(7)	—	2·5 c(w$_{1/2}$20)[c] 3·13[d], 3·5 m[e]
VIIIb	7·85 dd(6,2)	6·33 dd(6,2)	4·71 d(9)	5·4 br[b]	6·20 d(3·5) 5·50 d(3)	1·46	1·22 d(7)	—	2·8c[c], 2·02[f], 3·5 m[e]
XIa	7·80 dd(6,2)	6·28 dd(6,2)	4·8 d(9)	3·98 br[b]	—	1·37	1·22 d(7) and 1·12 d(7)		
XIIa	—	—	4·63 d(9)	4·02 br[b]	—	1·37	1·19 d(7) and 1·06 d(7)		
XII*b	—	—	4·55 d(9)	5·17 q	—	1·38	1·19 d(7) and 1·05 d(7)		2·12[f]
XIII	—	—	4·12 d(10)	—	—	1·35	1·15 d(5) and 1·04 d(7)		
XIV	—	—	4·23 d(11)	5·5 br[g]	—	1·35	1·25 d(7) and 1·25 d(7)		
XV	—	—	4·63 d(10)	4·0 br[b]	—	1·22	1·20 d(7) and 0·99 d(7)		
XX	—	—	5·20 dd(5,2)	4·5	—	0·96	1·09 d(7)	1·83 d(1)	
XXI	—	—	5·10 dd(6,2)	4·9	—	0·90	0·98 d(6)	1·70 d(1.5)	
XXVII	7·84 dd(6,3)	6·16 dd(6,2)	4·90 d(9·5)	—	6·31 d(3·8) 5·64 d(3·3)	1·12	1·10[i]	—	3·34 c[h], 2·6 c[e]
XXVIII	5·98 t(2)	2·95 dd(9,2)[j]	4·40 d(9)	—	6·18 d(3) 5·50 d(3)	1·15	1·15 d(7)	—	3·4 c[h]
XXX	—	—	4·70 d(9)	—	—	1·22	1·2 d and 1·1 c		
XXXI	—	—	5·05 br[k]	—	—	0·88	1·17	1·82 d(1)	
XXXIII	7·70 dd(6, 1·5)	6·21 dd(6,3)	—	5·1 c	—	1·20	1·38 d(6)	1·9 d(1·5)	

[a] Spectra in (CDCl$_3$ soln; Varian A-60 spectrometer using TMS as internal standard). Chemical shifts in ppm: d doublet, t triplet, q quartet, br broadened singlet, c complex signal whose center is given. Unmarked signals are singlets. Figures in parentheses are apparent coupling constants in c/s.

[b] w$_{1/2}$ 9, [c] H$_7$ and H$_{10}$, [d] H$_1$, removed by exchange with D$_2$O, [e] H, [f] acetate, [g] intensity 2 protons, combined with H$_8$, [h] H$_7$, [i] coupling uncertain, [j] intensity two protons, [k] w$_{1/2}$5.

Acetyl-1-*epiallohelenalin* VIIIb

Acetylation of VIIIa with pyridine–Ac_2O and recrystallization of the crude product from MeOH–Et_2O gave VIIIb, m.p. 182–184°, [α] +27·3° (*c* 1), IR bands at 1760 and 1660 (unsaturated γ-lactone) 1735 (acetate) and 1710 cm^{-1} (cyclopentenone), λ_{max} 215 and 326–332 mμ (log ε 4·17 and 1·83), ORD curve[21] (MeOH, *c* 0·0226) $[\alpha]_{450}$ +328° (first reading), $[\alpha]_{372.5}$ +40°, $[\alpha]_{367}$ +31° (infl.), $[\alpha]_{362.5}$ +19°, $[\alpha]_{312.5}$ +1640°, $[\alpha]_{292.5}$ +1570°, $[\alpha]_{238}$ +10,650°, $[\alpha]_{225}$ +3300°, $[\alpha]_{222}$ +4000°, $[\alpha]_{217}$ 0° (last reading). (Found: C, 66·86; H, 6·85; O, 26·40. Calc. for $C_{17}H_{20}O_5$: C, 67·05; H, 6·62; O, 26·29%.)

Dehydro-1-*epiallohelenalin* IX

To a solution of VIIIa (0·2 g) in AcOH (5 ml) was added at 0° a sol of chromic acid (0·2 g) in water (2 ml) and AcOH (1 ml). The mixture was allowed to stand at room temp for 1 hr, diluted with water and extracted with chf. The washed and dried extract was evaporated and the residue recrystallized from acetone–hexane, m.p. 178–180°, IR bands at 1755 (γ-lactone), 1705 and 1590 (cyclopentenone), 1680 and 1620 cm^{-1} (cross-conjugated α,β-unsaturated γ-ketolactone), NMR signals at 7·68 d and 6·20 d (=CH_2), 5·35 s (H_6), 2·1 s (C_{11}-methyl), 1·5 s (C_5-methyl) and 1·25 d (C_{10}-methyl), λ_{max} 225 mμ (log ε 4·26). (Found: C, 69·10; H, 6·44; O, 24·99. Calc. for $C_{15}H_{16}O_4$: C, 69·21; H, 6·20; O, 24·59%.)

Dihydro-1-*epiallohelenalin* (XIa)

A solution of (X) (3·5 g) in MeOH (100 ml) and conc. HCl (100 ml) was refluxed for 1 hr. The gummy product was crystallized from acetone–isopropyl ether, yield of XIa 1·28 g, m.p. 165–170°. Recrystallization from acetone–hexane raised the m.p. to 174–176°, $[\alpha]_D$ +50·1° (*c* 1), IR bands at 3600, 1765 (γ-lactone), 1700 and 1590 cm^{-1} (cyclopentenone), λ_{max} 222 and 328–330 mμ (log ε 3·98 and 1·85). (Found: C, 68·41; H, 7·58; O, 24·43. Calc. for $C_{15}H_{20}O_4$: C, 68·16; H, 7·63; O, 24·21%.) The acetyl derivative XIb could not be induced to crystallize.

Treatment of dihydroisohelenalin, m.p. 210–212°, and tetrahydrohelenalin with MeOH-HCl resulted in recovery of starting material.

Tetrahydro-1-*epiallohelenalin* XIIa

(a) Catalytic hydrogenation of VIIIa (3 g) with PtO_2 in EtOH gave 2·5 g of XIIa, m.p. 180–186°. Recrystallization from ether raised the m.p. to 194–196°, $[\alpha]_D$ −103·4° (*c* 1), IR bands at 3600, 1770 and 1740 cm^{-1}, λ_{max} 229–302 mμ (log ε 1·56) ORD curve[22] (dioxan, *c* 0·1) $[\alpha]_{700}$ −44°, $[\alpha]_{589}$ −160°, $[\alpha]_{600}$ −280°, (sh), $[\alpha]_{332.5}$ −184°, $[\alpha]_{330}$ −1750°, $[\alpha]_{325}$ −1870°, $[\alpha]_{312.5}$ −860° (last reading). (Found: C, 67·70; H, 8·45; O, 24·14. Calc. for $C_{15}H_{22}O_4$: C, 67·64; H, 8·33; O, 24·33%.)

The acetyl derivative XIIb, prepared with Ac_2O–pyridine was recrystallized from acetone–hexane, m.p. 191–192°, $[\alpha]_D$ −115°, (*c* 1), IR bands at 1770, 1735 and 1705 cm^{-1} (double strength), ORD curve[22] (dioxan, *c* 0·1) $[\alpha]_{700}$ −120°, $[\alpha]_{589}$ −165°, $[\alpha]_{600}$ −266° (sh), $[\alpha]_{332.5}$ −1570° (sh), $[\alpha]_{325}$ −1717°, $[\alpha]_{310}$ −698° (last reading). (Found: C, 66·35; H, 7·76; O, 25·90. Calc. for $C_{17}H_{24}O_5$: C, 66·21; H, 7·84; O, 25·95%.)

The mesylate XIIc, prepared with methanesulfonyl chloride–pyridine was recrystallized from acetone–hexane, m.p. 197–198°, $[\alpha]_D$ −88·8° (*c* 1). (Found: C, 55·77; H, 6·84; O, 28·01; S, 9·38. Calc. for $C_{16}H_{24}O_6S$: C, 55·77; H, 7·02; O, 27·91; S, 9·30%.)

(b) Hydrogenation of XIa (0·4 g) in AcOEt with prereduced 10% Pd-C resulted in absorption of one mole equiv. of H_2. Filtration, evaporation and recrystallization of the residue from AcOEt afforded XIIa (0·375 g), m.p. 194–196°.

(c) A sol of VIIIa (1·5 g) in dry benzene (60 ml), piperidine (2·5 ml) and benzyl mercaptan (3 ml) was refluxed for 6 hr, cooled, poured into water and extracted with benzene. The neutral fraction was concentrated and the residue was dissolved in EtOH, refluxed with Raney Ni overnight, filtered and evaporated at red. press. The solid residue, (1 g), was recrystallized from acetone–hexane, m.p. 192–194°.

Anhydrotetrahydro-1-*epiallohelenalin* XIV

A mixture of XIIc (0·5 g) and collidine (50 ml) was refluxed for 7 hr, cooled, diluted with water and extracted with chf. The neutral fraction was chromatographed over neutral alumina. Elution

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[22] Determined in the Syntex Laboratories, Mexico City, on a Rudolph recording spectropolarimeter.

with benzene afforded solid XIV which was recrystallized from acetone–hexane, m.p. 113–114°, $[\alpha]_D$ −165° (*c* 1), IR bands (CCl_4) at 1780 and 1750 cm^{-1}, no UV absorption. (Found: C, 72·29; H, 7·88; O, 19·52. Calc. for $C_{15}H_{20}O_3$: C, 72·55; H, 8·12; O, 19·33%.)

8-*Desoxytetrahydro*-1-*epiallohelenalin* (XIII)

A solution of XIV (40 mg) in EtOH was reduced with Pd-$CaCO_3$ (20 mg). The product was recrystallized from isopropyl ether–hexane, m.p. 131–132°, $[\alpha]_D$ −73·3°, (*c*, 1), IR bands at 1770 and 1735 cm^{-1}. (Found: C, 71·75; H, 8·69; O, 19·50. Calc. for $C_{15}H_{22}O_3$: C, 71·97; H, 8·86; O, 19·17%.)

Desoxotetrahydro-1-*epiallohelenalin* (XV)

A mixture of XIIa (0·79 g), ethane dithiol (1 ml) and BF_3- etherate (2 ml) was allowed to stand for 1 hr at room temp, poured onto ice and extracted with AcOEt. The washed and dried extract was concentrated at red. press. and the residue recrystallized from benzene–hexane. The thioketal, (0·85 g), melted at 135–136°. (Found: C, 59·59; H, 7·55; O, 13·94; H, 7·55; O, 13·94. Calc. for $C_{17}H_{26}O_3S_2$: C, 59·65; H, 7·60; O, 14·01; S, 18·73%.)

A sol of the thioketal (0·8 g) in EtOH was refluxed with Raney Ni (8 g) for 24 hr, filtered, evaporated and the solid residue (0·58 g), m.p. 170–177°, recrystallized from acetone–hexane, m.p. 180–181°, $[\alpha]_D$ −42·0 (*c* 0·1), IR bands at 3650 and 1765 cm^{-1}. (Found: C, 71·17; H, 9·58; O, 19·26. Calc. for $C_{15}H_{24}O_3$: C, 71·39; H, 9·59; O, 19·02%.)

Triol XVIII

(a) To a solution of XV (1 g) in anhydrous THF (40 ml) was added LAH (2 g). After 6 hr at reflux, the excess of hydride was destroyed with AcOEt and sat Na_2SO_4aq. The sol was filtered, evaporated and the residue crystallized from ether–hexane, yield 0·4 g, m.p. 135–140. The analytical sample of the triol melted at 149–150°, $[\alpha]_D$ −20° (*c* 1·11), broad OH and no carbonyl bands. (Found: C, 70·17; H, 10·86; O, 19·19. Calc. for $C_{15}H_{28}O_3$: C, 70·27; H, 11·01; O, 18·72%.)

(b) A mixture of XXII (0·6 g),[7] ethane dithiol (1·5 ml) and BF_3- etherate (5 ml) was left at room temp for 3 hr, poured into ice water and immediately extracted with AcOEt. The organic layer was washed, dried and evaporated. The oily thioketal was dissolved in EtOH (80 ml), refluxed for 16 hr with Raney Ni (5 g), filtered and evaporated to dryness. The gummy residue (XXIII; 0·38 g), which could not be induced to crystallize, was dissolved in THF (60 ml), and refluxed for 16 hr with LAH. The crude product was chromatographed over 12 g alumina and the solid eluates combined and recrystallized from ether–isopropyl ether, yield 20 mg, m.p. 149–151°, undepressed on admixture of XVIII. The IR spectra were superimposable.

Dihydroisomexicanin A (XX)

A solution of XIX (1·01 g)[7] in AcOEt (75 ml) was hydrogenated with PtO_2 (0·2 g) until absorption of H_2 ceased. Filtration, evaporation and crystallization from ether–hexane afforded 0·59 g of XX, m.p. 185–188°. The analytical sample melted at 192–194°, $[\alpha]_D$ −47·9° (*c* 0·96), IR bands at 3610, 1740 (double strength) and 1675 cm^{-1}. (Found: C, 68·38; H, 7·86; O, 24·15. Calc. for $C_{15}H_{20}O_4$: C, 68·16; H, 7·63; O, 24·24%.)

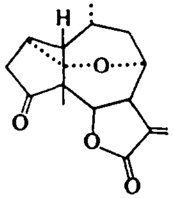
Desoxodihydromexicanin A XXI

A mixture of XX (0·54 g), ethane dithiol (1 ml) and BF_3- etherate (2 ml) was kept at room temp for 1 hr, and the crude thioketal desulfurized by refluxing with Raney Ni (6 g) in EtOH (60 ml) for 24 hr. The catalyst was filtered off, the solvent evaporated and the solid residue recrystallized from acetone–hexane, yield 0·37 g, m.p. 168–170°, $[\alpha]_D$ −96·2° (*c* 1·06), IR bands at 1740 and 1680 cm^{-1}. (Found: C, 71·66; H, 8·93; O, 19·13. Calc. for $C_{15}H_{22}O_3$: C, 71·97; H, 8·86; O, 19·17%.)

A sol of XXI (0·3 g) in EtOH (25 ml) was hydrogenated with ruthenium dioxide (60 ml) at 2000 psi and 50° for 24 hr. The product XXIII, (0·25 g) could not be induced to crystallize and was reduced with LAH in boiling THF for 6 hr. The product was isolated and chromatographed over neutral alumina. Triol XVIII crystallized in the fractions eluted with benzene, yield 35 mg, m.p. 149–151°, no depression on admixture of an authentic sample, IR spectra superimposable.

Isomerization of mexicanin I

A sol of mexicanin I[23] (0·79 g) in MeOH (20 ml) and conc. HCl (20 ml) was refluxed for 1 hr. The gummy product was chromatographed over neutral alumina. Benzene eluted 60 mg of solid material, m.p. 103–110°, which was recrystallized from benzene–hexane, m.p. 110–115°, IR bands (CCl_4) at 1780 and 1750 cm^{-1} (no —OH), NMR signals (deuteriodimethyl sulfoxide) at 5·95 d (J = 2·5) and 5·45 d (J = 2·5, conjugated exocyclic methylene), 4·9 d (6, H_6), 4·0 c (2 protons, H_2 and H_8), 1·5 (C_5-methyl) and 0·95 d (7, C_{10}-methyl). The physical properties suggested formula ii. (Found: C, 68·34; H, 6·63. Calc. for $C_{15}H_{18}O_4$: C, 68·68; H, 6·92%.) The material eluted with other solvents could not be crystallized.



II

Refluxing of mexicanin I (0·2 g) with MeOH (10 ml) and conc. HCl (0·5 ml) for 1 hr gave, after chromatography over alumina, 40 mg of an isomer, possibly 1-epiisomexicanin I, m.p. 256–258° after recrystallization from acetone–hexane (depression on admixture of mexicanin I), IR bands (KBr) at 1745, 1670 and 1630 cm^{-1}. (Found: C, 68·60; H, 6·77; O, 24·64. Calc. for $C_{15}H_{18}O_4$: C, 68·68; H, 6·92; O, 24·40%.) Catalytic hydrogenation in MeOH with Pd-C resulted in a substance, m.p. 231–235° after recrystallization from acetone–hexane, IR bands (KBr) at 1750, 1670 and 1620 cm^{-1}. (Found: C, 67·91; H, 8·37; O, 24·27. Calc. for $C_{15}H_{22}O_4$: C, 67·64; H, 8·33; O, 24·03%.)

Isomerization of isotenulin

A solution of I (0·8 g) in conc. HCl (16 ml) and MeOH (16 ml) was refluxed for 2 hr. The solvents were removed at red. press., the residue taken up in chf, washed, dried and evaporated. The crude yellow gummy residue was chromatographed over 100 g of silica gel (chf). Chf eluted 0·15 g of unidentified oily material followed by several crystalline fractions which were combined to give IIa (0·11 g) of as a low melting solid which could not be crystallized satisfactorily. NMR signals at 5·98 tbr (H_2, $w_{1/2}$ = 6), 4·72 m (H_8), 4·27 br (H_6, $w_{1/2}$ = 3), 3·1–2·8 m (2 protons, H_3), 1·28 d and 1·12 d (J = 7, C_{10}- and C_{11}-methyls) and 1·18 ppm (C_5-methyl).

Elution with chf–Et_2O (9:1) gave IIIa (0·35 g) which crystallized from chf–Et_2O as colorless needles, m.p. 113–115°, NMR signals at 7·99 dd (J = 2·6, H_2), 6·38 dd (J = 2·5, 6, H_3), 4·50 m (H_8), 4·02 br ($w_{1/2}$ = 3·5, H_6), 1·24 d and 1·06 d (J = 7, C_{10}- and C_{11}-methyls) and 1·20 ppm (C_5-methyl). The analysis showed that the material was a hydrate which decomposed on attempted drying. The structure was confirmed by acetylation which gave IIIb, identical with an authentic sample.[2] (Found: C, 64·38; H, 7·94; O, 28·13. Calc. for $C_{15}H_{22}O_5$: C, 68·81; H, 7·85; O, 28·33%.)

When the above experiment was repeated with isotenulin (0·2 g) using 38% DCl and MeOD, IIa and IIIa were isolated in approximately the same yield, but both had incorporated deuterium. The NMR spectrum of IIa-d_2 exhibited a *singlet* at 5·98 (H_2) and no H_3-multiplet between 3·1 and 2·8 ppm. The signal of H_{10} at 3·5 ppm appeared somewhat simplified, indicating that it might have experienced long range coupling with one or both of the protons at C_3 of undeuterated IIa. However, no incorporation of deuterium at C_{10} was observed. The NMR spectrum of IIIa-d_2 exhibited a *singlet* at 7·99 (H_2), but no signal at 6·38 ppm (H_3). The complex set of signals in the range 2·9–2·6 integrated for one less proton, due to incorporation of deuterium at C_1, but the remainder of the spectrum was completely identical with that of undeuterated IIIa.

Isomerization of ambrosin

(a) A sol of XXIV (5 g) in chf (100 ml) was saturated with dry HCl at ice temp and then refluxed for 5 hr. The solvent was removed and the residue chromatographed over deactivated alumina (200 g) using benzene. Benzene (200 ml) eluted 3·4 g of gum which on rubbing with ether gave

[23] E. Dominguez and J. Romo, *Tetrahedron* 19, 1415 (1963).

XXVII (1·13 g), m.p. 152° and 2·19 g of gummy material from the ether washings. Benzene-chf (20:1) eluted an additional XXVII (0·23 g), chf eluted unchanged ambrosin.

Recrystallization of XXVII from acetone–pet. ether raised the m.p. to 160°, mixed m.p. with XXIV 100–105°, $[\alpha]_D$ +27·1 (*c* 1·07), IR bands at 1770 (γ-lactone), 1710 (cyclopentenone), 1660 and 1600 cm^{-1} (double bonds), ORD curve[34] (MeOH, *c*, 0·0375) $[\alpha]_{600}$ +21° (first reading), $[\alpha]_{374}$ −600°, $[\alpha]_{370}$ −585°, $[\alpha]_{348}$ −640°, $[\alpha]_{345}$ −535°, $[\alpha]_{334}$ −750°, $[\alpha]_{300}$ +3060 (sh), $[\alpha]_{267}$ +4050° (last reading). (Found: C, 72·89; H, 7·16; O, 19·71. Calc. for $C_{15}H_{18}O_3$: C, 73·14; H, 7·37; O, 19·49%.) The previously unrecorded ORD curve of XXIV had the following values[34] (MeOH, *c*, 0·0589) $[\alpha]_{600}$ −182°, $[\alpha]_{589}$ −234°, $[\alpha]_{333}$ −1200°, $[\alpha]_{306}$ −138°, $[\alpha]_{300}$ −228° (last reading).

The gummy material from the ether washings was recrystallized from ether–pet. ether, yield of XXVIII 1·2 g, m.p. 120°, IR bands at 1765 (double strength, combination of γ-lactone and β,γ-unsaturated cyclopentenone), 1665 and 1630 cm^{-1}. (Found: C, 72·90; H, 7·23; O, 19·73. Calc. for $C_{15}H_{18}O_3$: C, 73·14; H, 7·37; O, 19·49%.)

(b) A sol of ambrosin (2 g) in MeOH (40 ml) and conc. HCl (40 ml) was refluxed for 1 hr, evaporated *in vacuo*, diluted with water and extracted with AcOEt. The washed and dried extract was concentrated and the solid residue recrystallized from AcOEt–isopropyl ether, yield of XXVII 0·93 g, m.p. 159–161°.

Repetition of this experiment with ambrosin (0·2 g) in MeOD (4 ml) and 38% DCl (4 ml) furnished 1-epiambrosin-1,3-d_2, m.p. 155–157°, NMR bands at 7·84 (H_2), 6·31 d (3·8) and 5·64 d (3·3, exocyclic methylene group), 4·90 d (J = 9·5, H_6), 3·34 c ($w_{1/2}$ 25, H_7), 1·12 (C_5-methyl) and 1·05 d (J = 7, C_{10}-methyl). The NMR spectrum was consistent with introduction of deuterium at C_1 and C_3 only.

Dehydration of coronopilin

To a sol of coronopilin (0·195 g) in pyridine (5 ml) was added $SOCl_2$ (1 ml) at room temp. An exothermic reaction took place immediately and the reaction mixture darkened. Without delay the sol was taken to dryness at red. press. and room temp or below. The residue was dissolved in chf, the organic layer washed thoroughly with water until the washings were colorless, dried and evaporated. The residual oil (TLC revealed disappearance of starting material and formation of a single product) was filtered through a short column of silica gel, yield 0·110 g of chromatographically pure XXVIII which crystallized only on seeding. Recrystallization from AcOEt–isopropyl ether raised the m.p. to 119–121°, m.p. undepressed on admixture of authentic XXVIII, IR and NMR spectra superimposable.

The yield of XXVIII decreased dramatically as time elapsed between addition of $SOCl_2$ and work-up to the point that no XXVIII could be isolated when the mixture was allowed to stand in the refrigerator overnight. This observation probably explains earlier failures to obtain analyzable products from this reaction.

Reduction of 1-*epiambrosin*

A sol of XXVII (1·86 g) in EtOH was reduced with Pd-$CaCO_3$ (50 mg) at 40 lbs/in^2. The solution was filtered and concentrated at red. press.; the residue gave two spots on TLC. Chromatography over silicic acid (solvent and eluent chf) separated the components into the faster moving XXX and the slower-moving XXXI. The former was recrystallized from acetone–pet. ether, yield 0·5 g, m.p. 100°, $[\alpha]_D$ +18° (*c* 1·09), IR bands at 1770 and 1740 cm^{-1}, ORD curve[34] (MeOH, *c*, 0·148) $[\alpha]_{600}$ +22°, $[\alpha]_{589}$ +37°, $[\alpha]_{319}$ +281°, $[\alpha]_{285}$ −82°, $[\alpha]_{277}$ −59° (last reading). (Found: C, 72·26; H, 8·75; O, 19·33. Calc. for $C_{15}H_{22}O_3$: C, 71·97; H, 8·86; O, 19·17%.)

The slower-moving XXXI was recrystallized from acetone–pet. ether, wt. 0·9 g, m.p. 117°, $[\alpha]_D$ −41·6° (*c* 0·865), IR bands at 1755 and 1675 cm^{-1}. (Found: C, 72·85; H, 8·09; O, 19·09. Calc. for $C_{15}H_{20}O_3$: C, 72·55; H, 8·12; O, 19·33%.)

Compound XXX was prepared in somewhat better yield by treatment with benzyl mercaptan and subsequent desulfurization. A solution of XXVII (0·15 g) in dry benzene (20 ml) was refluxed with piperidine (1 ml) and benzyl mercaptan (0·5 ml) for 6 hr, cooled, poured into water and extracted with benzene. The neutral fraction was dried, evaporated and the gummy residue dissolved in EtOH and refluxed with Raney Ni overnight. Filtration, concentration and crystallization from acetone–pet. ether gave 0·1 g of XXX.

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[34] Determined by Dr. L. R. Tether on a Rudolph recording spectropolarimeter.

Isoaromatin XXXIII

The mesylate (XXXII) of X was prepared in the usual fashion but could not be obtained in crystalline form. A solution of XXXII (0·5 g) in AcOH (15 ml) was refluxed with anhydrous AcONa (2 g) for 3 hr, and the solvent removed *in vacuo*. The residue was diluted with water, extracted with chf and the washed and dried extract taken to dryness. The solid residue (0·2 g), m.p. 195–205°, was recrystallized from acetone–hexane, m.p. 208–210°, $[\alpha]_D$ $-150°$ (*c* 1·0), λ_{max} 220 and 320–324 mμ (log ε 4·44 and 1·82), IR bands at 1755, 1710, 1675 and 1590 cm^{-1}. (Found: C, 72·95; H, 7·42; O, 19·69. Calc. for $C_{15}H_{18}O_3$: C, 73·14; H, 7·37; O, 19·49%.)

Dihydroisoaromartin (XXXIV)

(a) A mixture of XXXVIII (2 g), of AcOH (50 ml) and anhydrous AcONa (10 g) was refluxed for 3 hr. After removal of solvent the residue was recrystallized from acetone–hexane to furnish dihydroisoaromatin (0·3 g), m.p. 141–143°, identical by mixed m.p., IR and NMR spectrum with an authentic sample.[24] The mother liquors were chromatographed over alumina. Elution with hexane–benzene (1:1) and recrystallization from acetone–hexane yielded 0·4 g of a mixture of lactones, m.p. 118–121°. Fractional crystallization from AcOEt–hexane afforded 0·2 g of material, m.p. 141–143°, (m.p. depression on admixture of dihydroisoaromatin), $[\alpha]_D$ $+168°$ (*c* 1·0), IR bands (CCl_4) at 1770, 1750 and 1670 cm^{-1}, λ_{max} 220 mμ (log ε 4·17). These properties were identical with those of anhydrodesacetyldihydroisotenulin.[26] Elution with benzene furnished 0·1 g of tetrahydrobalduilin A, m.p. 174–176°, identical with authentic material.

(b) Catalytic hydrogenation of XXXIII (0·1 g) with Pd–C furnished XXXIV (50 mg) (no depression on admixture of authentic material, IR spectra superimposable).

(c) Acetolysis of XXXVII (0·475 g)[25] afforded dihydroisoaromatin (0·115 g), m.p. 144–146°, identical by mixed m.p., IR and NMR spectrum with authentic material.

Tetrahydrobigelovin (XLII). A mixture of XL[26] (0·5 g), of AcOH (8 ml) and anhydrous AcONa (2 g) was refluxed for 5 hr. The crude product (0·16 g), m.p. 203–205°, was recrystallized from acetone–hexane, m.p. 208°, and proved to be identical with tetrahydrobigelovin by direct comparison. (Found: C, 66·37; H, 7·95; O, 25·55. Calc. for $C_{17}H_{24}O_5$: C, 66·21; H, 7·84; O, 25·95%.)

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[26] W. Herz, P. Jayaraman and H. Watanabe, *J. Amer. Chem. Soc.* **82**, 2276 (1960).