Tetrahedron, 1963, Vol. 19, pp. 1359 to 1369. Pergamon Press Ltd. Printed in Northern Ireland

CONSTITUENTS OF *HELENIUM* SPECIES—XV

THE STRUCTURE OF MEXICANIN C., RELATIVE STEREOCHEMISTRY OF ITS CONGENERS[1,2]

W. HERZ[3], A. ROMO DE VIVAR[4], J. ROMO[4] and N. VISWANATHAN[3]
Department of Chemistry, The Florida State University, Tallahassee, Florida
and
The Instituto de Quimica de la Universidad Nacional Autónoma de México, México 20, DF

(*Received* 4 *March* 1963)

Abstract—The gross structure of mexicanin C is shown to be III. The relative stereochemistry of dihydroisotenulin, dihydroalloisotenulin, tetrahydrohelenalin, dihydromexicanin C, tetrahydrobalduilin and desacetyltetrahydrobalduilin A is defined.

THE sesquiterpene lactone mexicanin C was isolated from *Helenium mexicanum* H.B.K.[5] and correlated[6] with helenalin (H-I)[7] and balduilin (B-II), two other sesquiterpene lactones of *Helenium* and related species,[8] at a time when incorrect structures were assigned to this group of compounds. In this paper we show that mexicanin C has the formula III and define the stereochemical relationships among helenalin, tenulin, balduilin, mexicanin C and a number of their derivatives. In view of the recent determination of the relative stereochemistry of bromoisotenulin by X-ray analysis,[9] the relative stereochemistry of its congeners is therefore also defined.

The properties of mexicanin C, $C_{15}H_{20}O_4$, m.p. 251–252°, $[\alpha]_{20}$ −80°, have not previously been discussed in detail. The U.V. spectrum (λ_{max} 226 mμ, ε 8600) suggested the presence of conjugation which because of the I.R. bands at 1705 and 1585 cm^{-1} was ascribed to a cyclopentenone chromophore. I.R. absorption at 1760 cm^{-1} indicated the presence of a γ-lactone function. A hydroxyl group was also present because of an I.R. band at 3400 cm^{-1} and conversion to mexicanin C acetate (MC-IV). The latter exhibited the same U.V. absorption as mexicanin C and had I.R. bands at 1763 (γ-lactone), 1732 (acetate), 1710 and 1580 cm^{-1} (cyclopentenone).

Mexicanin C absorbed one mole of hydrogen on catalytic hydrogenation. The product, dihydromexicanin C (MC-V), was a hydrocyclopentanone lactone (I.R. bands at 3390, 1770 and 1740 cm^{-1}). That the hydroxyl group was secondary was shown by conversion of mexicanin C and its reduction product to the ketones dehydromexicanin

[1] Publication No. 153 from the Instituto de Química de la Universidad Nacional Autónoma de México. Work at the Florida State University supported in part by a grant from the National Science Foundation (NSF-G 14396).

[2] Previous paper, J. Romo, A. Romo de Vivar and W. Herz, *Tetrahedron*, in press (1963).

[3] Department of Chemistry, The Florida State University.

[4] Instituto de Química de la Universidad Nacional Autónoma de México.

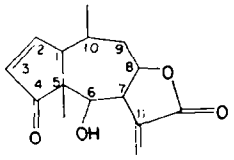
[5] A. Romo de Vivar and J. Romo, *Chem. & Ind.* 882 (1959); *Ciencia, Mex.* **21**, (1), 33 (1961).

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

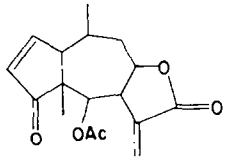
[7] Gross structures are indicated by Roman numerals. The initials H, B, T, MA and MC refer to members of the helenalin, balduilin, tenulin, mexicanin A and mexicanin C series.

[8] For a recent summary, see W. Herz, *J. Org. Chem.* **27**, 4043 (1962).

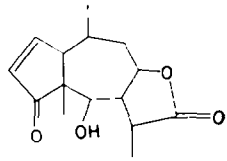
[9] D. Rogers and Mazhar-ul-Haque, *Proc. Chem. Soc.* **92**, (1963). We wish to thank Dr. Rogers for informing us of his results prior to publication.



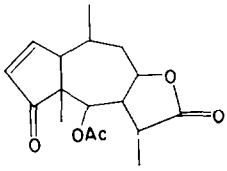
I



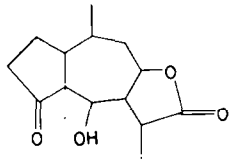
II



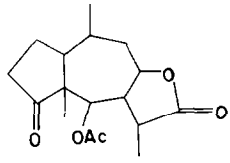
III



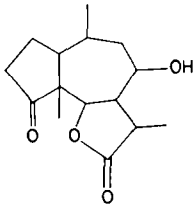
IV



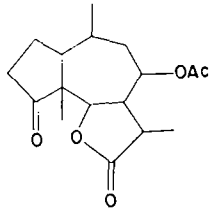
V



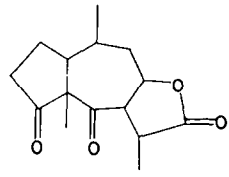
VI



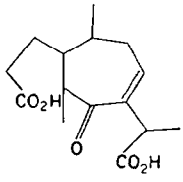
VII



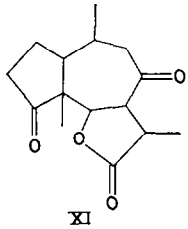
VIII



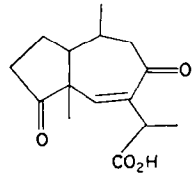
IX



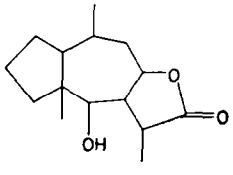
X



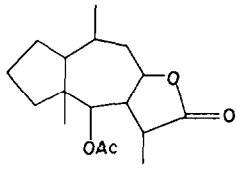
XI



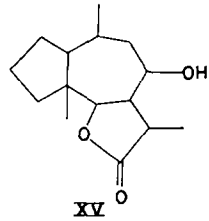
XII



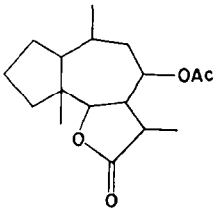
XIII



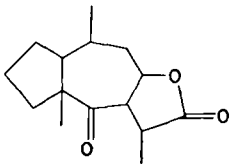
XIV



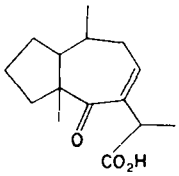
XV



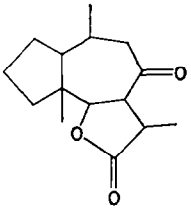
XVI



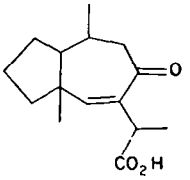
XVII



XVIII



XIX



XX

C (λ_{max} 231 mμ, ε 6600, I.R. bands at 1765, 1730, 1700 and 1575 cm^{-1}) and dehydrodihydromexicanin (MC-IX) which exhibited I.R. absorption at 1753 (double strength-acetate and cyclopentanone) and 1700 cm^{-1} (cycloheptanone). The band at 1700 cm^{-1} due to the new carbonyl group was relatively weak, as has been observed previously in the tenulin and helenalin series (normal lactone ring orientation).

As has been mentioned briefly in an earlier communication,[6] dehydrodihydromexicanin C (MC-IX) was identical with a substance prepared from tetrahydrohelenalin (H-V) by isomerization with sodium carbonate and subsequent oxidation of the new isomer with chromium oxide. In the interval it has been possible to demonstrate that dihydromexicanin C (MC-V) is itself identical with the tetrahydrohelenalin isomer. Since the structure of helenalin is now settled,[10] this establishes the carbon skeleton of mexicanin C and the locus of its oxygen functions, the remaining problems involving the lactone ring orientation[10] and the stereochemistry.

It was originally believed that the isomerization of tetrahydrohelenalin to dihydromexicanin C (then called allotetrahydrohelenalin) involved a change in lactone ring orientation, i.e. to a compound H-VII. For reasons to be discussed now, this conclusion was invalid.[11]

The N.M.R. spectra of mexicanin C acetate (MC-IV), dihydromexicanin C (MC-V) and dihydromexicanin C acetate (MC-VI), like those of all other sesquiterpene lactones of *Helenium* species, exhibit two signals whose chemical shift corresponds to hydrogen on carbon linked to oxygen. One of these, at 4·1 p.p.m. in the alcohols and 5·2–5·3 p.p.m. in the acetates, is a broad singlet or doublet which disappears on oxidation.[12] Hence it is assigned to H_6 which is spin coupled to only one proton, that

[10] W. Herz, W. A. Rohde, K. Rabindran, P. Jayaraman and N. Viswanathan, *J. Amer. Chem. Soc.* **84**, 3857 (1962); [b] W. Herz, A. Romo de Vivar, J. Romo and N. Viswanathan, *Ibid.* **85**, 19 (1963).

[11] The name allotetrahydrohelenalin should therefore be reserved for the as yet unknown substance H-VII which differs from tetrahydrohelenalin only in lactone ring orientation. The desoxo derivative H-XV of this compound, however, is known (*vide infra*).

[12] N.M.R. spectra were run on a Varian A-60 spectrometer in deuteriochloroform solution with tetramethylsilane serving as internal reference. The spectrometer at the Florida State University was purchased with the aid of a grant from the National Science Foundation.

at C_7, and which, because of its behavior, must be associated with the hydrogen on carbon carrying the hydroxyl or acetate function.

This requires lactone ring closure to C_8 and agrees with the multiplicity of the relatively invariant second signal near 4·8 p.p.m. the appearance of which indicates spin coupling to three hydrogens in the now familiar manner.[10] Other bands require no further discussion and are detailed in the Experimental section.

The N.M.R. spectrum of desacetyltetrahydrobalduilin A(B_2-V) which on oxidation is converted to dehydrodihydromexicanin C (MC-IX) further supports these assignments, lactone closure to C_8 being indicated by the usual complex triplet at 4·79 p.p.m. and H_6 by a doublet at 4·43 p.p.m. ($J = 3·5$ c.p.s.).[13] Hence B_2-V and MC-V are C_6-epimers and the formation of B_2-V from tetrahydrobalduilin (B-VI) does not involve lactone ring reorientation, but epimerization.[6] Desacetyltetrahydrobalduilin B,[6] the minor hydrolysis product of B-VI, was no longer available, but its previously unreported oxidation product differed from all other isomeric diketolactones in m.p. and I.R. spectrum.

Finally, dehydrotetrahydromexicanin C (MC-IX) on treatment with sodium carbonate solution was cleaved to a crystalline dicarboxylic acid (MC-X). The mechanism of this transformation has been discussed previously[10] and requires lactone ring closure to C_8. The I.R. spectrum of the acid suggested identity with the dicarboxylic acid (T-X) from dehydrodesacetyldihydroisotenulin (T-IX) and indeed, when a freshly prepared sample of the latter was seeded with it, crystallization occurred. Comparison established complete identity; the N.M.R. spectrum (one vinyl proton at 6·77 p.p.m., three secondary methyl groups) supports the previously assigned[10] structure.

It is now necessary to reexamine the evidence which led us to conclude earlier[6] that the lactone ring of dihydromexicanin C was closed to C_6. Dihydromexicanin C, now known to be MC-V, was converted[6] to an oily thioketal A which apparently isomerized on chromatography over alumina to thioketal B. Desulfurization of thioketal A gave an oily hydroxylactone A which on oxidation with chromic acid furnished a presumably homogeneous viscous ketolactone A, whereas the hydroxylactone B from thioketal B was crystalline. Oxidation of the crystalline substance yielded a gummy ketolactone B not readily distinguishable from ketolactone A. Since both ketolactones gave positive Zimmermann tests it was erroneously assumed that the keto group was located at C_8 in both compounds and that the lactone ring was closed to C_6.

In fact, the N.M.R. spectrum of "hydroxylactone B" clearly shows that the lactone ring is still closed to C_8 and that it must be represented by formula MC-XIII. That no rearrangement or isomerization was involved in its formation was confirmed by carrying out the deoxygenation on acetyldihydromexicanin C (MC-VI). The crystalline thioketal was stable to alumina and on desulfurization with Raney nickel afforded a crystalline acetate (MC-XIV, lactone ring closed to C_8 by N.M.R. spectrum) whose stereochemistry at all centers was identical with that of "hydroxylactone B" since acetylation of the latter furnished MC-XIV. Hydrolysis of MC-XIV with potassium

[13] These assignments may be made with confidence, since in the entire series of *Helenium* constituents and their derivatives the H–C–OH proton signal is never found at lower field than the signal due to hydrogen on carbon carrying the lactone ether oxygen.

hydroxide regenerated "hydroxylactone B" which therefore possesses the thermodynamically stable lactone ring orientation and configuration at C_{11}.[14]

This sequence of reactions clearly eliminates the possibility that the conversion MC-V to MC-XIII is attended by epimerization at C_5 or C_{11} and shows that "hydroxylactone B" is truly desoxodihydromexicanin C. The thioketal from which "hydroxylactone A" was prepared earlier[6] must have been impure and probably contained some C_5 epimer produced from MC-V under the influence of boron trifluoride which was removed by chromatography. Indeed treatment of MC-V with boron trifluoride etherate alone yielded a gum from which only 80 per cent of MC-V could be recovered. Also repetition of the work reported earlier,[6] i.e. direct desulfurization of the thioketal without prior chromatography, now furnished crystalline "hydroxylactone B", though in somewhat lower yield.

Oxidation of desoxodihydromexicanin C yielded an oily ketolactone (MC-XVII) with the properties described previously.[6] This substance on treatment with methanolic potassium carbonate underwent the usual cleavage reaction. However, perhaps because of slightly different conditions, the reaction now yielded the lactol XXI[10] directly, instead of the precursor T-XVIII isolated previously.[10]

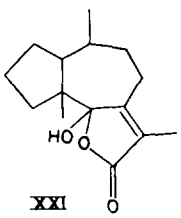
Since it has been confirmed that MC-XVII gives a positive Zimmerman test, it must be concluded that the test has no diagnostic value when applied to ketolactones of type XVII and XIX. Presumably the alkaline conditions of the test can induce the cleavage reaction so characteristic of the ketolactones of this series and a positive test may well result under favourable steric circumstances due to the now vinylogous active methylene group even if the lactone ring is oriented toward C_8. Also, a negative test is no guarantee that the lactone ring is closed to C_8.[10]

Examination of the N.M.R. spectra of desoxotetrahydrohelenalin (H-XIII) and the isomer H-XV obtained from it by chromatography or base treatment[15] showed that lactone ring reorientation had occurred during the base treatment, a conclusion which was already implied in the previously reported[15] conversion of the derived ketolactone, now known to be H-XIX, to the keto acid T-XX obtained from the ketolactone T-XIX of the alloisotenulin series.

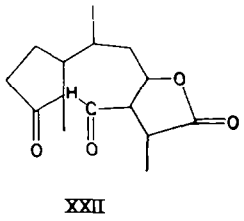
We are now ready to consider the relative stereochemistry at the various asymmetric centers. Since all series have been interrelated by reactions which cannot epimerize C_1 and C_{10}, C_1 and C_{10} must have the same configuration throughout. As for C_5, the following conversions have been effected under conditions which cannot epimerize C_5: T-XIII to T-XV,[10] B-XIV through B-XV to T-XIX[6,11] and H-XV through H-XIX to T-XX.[15] Since T-XIII, B-XIV and H-XV were prepared from tenulin, balduilin and helenalin, respectively, under conditions which were shown not to involve epimerization at C_5, the three compounds helenalin, tenulin and balduilin must have the same configuration at this asymmetric center, in spite of the opportunity provided for epimerization at C_5 (and thereby at C_6, C_7 and conceivably at C_8 through elimination and readdition of the carboxylate ion) by way of an intermediate XXII.

[14] In a similar way it was shown that the deoxygenation of tetrahydrobalduilin (B–VI) was not attended by lactone ring orientation and yielded B–XIV (N.M.R. spectrum). We recall, however, that hydrolysis of B–XIV is accompanied by lactone ring reorientation and yields B–XV.[6]

[15] W. Herz and R. B. Mitra, *J. Amer. Chem. Soc.* **80**, 4876 (1958). This substance was previously referred to as desoxoepitetrahydrohelenalin, a name which must now be changed to desoxoallotetrahydrohelenalin (H–XV).



XXI



XXII

The remaining compound, mexicanin C, has not yet been related to helenalin, tenulin or balduilin through reactions in which blocking or removal of the cyclopentanone carbonyl clearly prevents the retroaldol cleavage exemplified by XXII, although we concluded earlier[10] that the stereochemistry at C_5 was probably the same as in the other constituents of *Helenium* species (optical rotatory dispersion curve of dihydromexicanin C). The following argument establishes this point unambiguously.

Basic hydrolysis of tetrahydrobalduilin (B-VI) yields[6] desacetyltetrahydrobalduilin A(B_2-V, lactone ring orientation established by N.M.R. spectroscopy). This reaction involves epimerization of at least one asymmetric center since reacetylation of B_2-V does not regenerate B-VI.[6,16] Now B_2-V differs from MC-V only in configuration at C_6[6] and MC-V in turn may be obtained from H-V by treatment with base. If the conversions B-VI → B_2-V and H-V → MC-V involved an intermediate of type XXII, the formation of *two* substances epimeric at C_6 only is a violation of chemical principles. Hence configuration at C_5 is maintained throughout and mexicanin C joins helenalin, tenulin and balduilin in what we may arbitrarily call the + configuration at this site. The conversion of mexicanin C to the lactol XXI also obtained from tenulin supports this conclusion. We adopt a similar convention for the remaining asymmetric centers C_6, C_7, C_8 and C_{11} in that order and arbitrarily adopt the representation + + + + + for isotenulin.

Lithium aluminium hydride reduction of T-XIII and the corresponding allo compound T-XV yields different triols[10] which can differ from each other only at C_{11}. Hence the allo lactone of the tenulin series should be written as + + + + −.

By contrast, hydrolytic conversion of H-XIII to the allo isomer H-XV does not change the C_{11} configuration since lithium aluminium hydride reduction of H-XIII and H-XV results in the same triol.[15] Now H-XV may be transformed via H-XIX to T-XX. Hence H-XIII and H-XV have the − configuration at C_{11}. Since H-XIII is prepared from tetrahydrohelenalin (H-V) without epimerization at any asymmetric center, C_{11} is − in H-V also. The conversions of H-IX to H-X, and H-VII to H-XVIII, which can differ from T-X and T-XVIII at C_{11} only, confirm this conclusion.

B-VI is transformed through B-XIV (no change in stereochemistry) to B-XV which is the C_8 epimer of T-XV.[6,17] Hence B-VI may be designated as + + + − ? where the C_{11} configuration remains temporarily unassigned. But since the hydrolysis of B-VI to B_2-V does not proceed via XXI (*vide supra*), B_2-V whose acetylation results in

[16] The structure of desacetyltetrahydrobalduilin B may be either V or VII.

[17] The conversion of B-XV to T-XIX which establishes this fact is reversible. This disposes of the possibility that the oxidation of B-XV, and therefore the correlation of balduilin with tenulin, might have involved epimerization at C_7. Since balduilin has been correlated with mexicanin C and helenalin under conditions which do not allow for epimerization of the C_7 side chain, all lactones discussed in this paper have the same configuration at C_7.

B_2-VI, not B-VI,[6] must be the C_{11}-epimer of B-V and has the configuration + + + − − since it can be transformed to T-X. Hence B-VI is + + + − − and M-V, the C_6-epimer of B_2-V (*vide supra*) is + − + − +.

The conversion of tetrahydrohelenalin (H-VI) for which we have deduced the − configuration at C_{11} to M-V therefore involves epimerization at C_{11} only and its full stereochemistry is expressed in the symbol + − + − −.

The stereochemical relationships deduced in this manner are tabulated in Table 1 and are entirely self-consistent. It is gratifying to note that the stereochemistry at C_7 turns out to be the same throughout.

TABLE 1

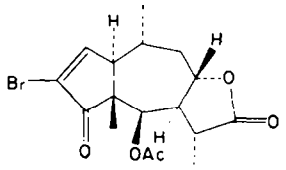
	C_5	C_6	C_7	C_8	C_{11}
Dihydroisotenulin	+	+	+	+	+
Dihydroalloisotenulin	−	−	+	−	−
Tetrahydrohelenalin	+	−	−	−	−
Dihydromexicanin C	+	−	+	−	+
Tetrahydrobalduilin	+	+	+	−	−
Tetrahydrobalduilin A	+	+	+	−	+

In a previous communication[10b] we discussed briefly the stereochemistry of tetrahydromexicanin A ((MA-V) which must be epimeric with the compounds described so far in this paper at C_1 or C_5 or both. That the configuration at C_5 was different was suggested by the optical rotatory dispersion curve. We have now transformed tetrahydromexicanin A into its dehydro derivative (MA-IX) and cleaved the latter with sodium carbonate to a ketodicarboxylic acid (MA-X). This substance differed from the previously isolated T-X and H-X which are epimeric at C_{11}. Since equilibration at C_5 must occur under the reaction conditions, MA-X is a C_1-epimer of T-X and H-X and tetrahydromexicanin A differs from tetrahydrohelenalin at C_1 and probably also at C_5.

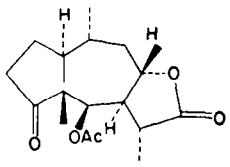
The results of an X-ray analysis of bromoisotenulin (XXIII or its mirror image) by Rogers and Mazhar-il Haque[9] confirm the biogenetically abnormal skeleton which we have deduced for the sesquiterpene lactones of *Helenium* species. The stereochemical relationships listed in Table 1 allow us to formulate the relative stereochemistry of the more important compounds as follows (based on XXIII which representation we tentatively favor because of the optical rotatory dispersion evidence discussed previously[10]). Dihydroisotenulin is XXIV, tetrahydrohelenalin is XXV, dihydromexicanin C is XXVI and tetrahydrobalduilin XXVII.

T-XIII and T-XV on reduction furnish two triols epimeric at C_{11}.[10] An attempt to apply to this transformation the Hudson-Klyne rule[18] as modified by Sykora and Romanuk[19] foundered completely and hence could not be used in support of the

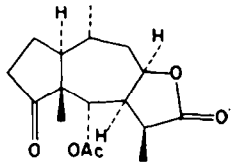
[18] W. Klyne, *Chem. & Ind.* 1198 (1954).
[19] V. Sykora and Romanuk, *Coll. Czech. Chem. Comm.* **22**, 1099 (1957).



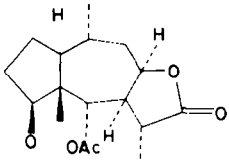
XXIII



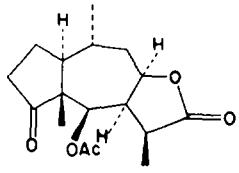
XXIV



XXV



XXVI



XXVII

absolute configurations suggested tentatively in the preceding paragraph. Comparison of the molecular rotations of T-XIII, T-XV and the two triols would have led to the conclusion that H_6 and H_8 of tenulin are both α. This is of course contradicted by the X-ray analysis which shows that either H_6 or H_8 is β. Similarly, comparison of the molecular rotations of H-XIII and H-XV with that of the triol[15] produced from both suggests that H_6 and H_8 of helenalin are α which is not in harmony with the relative configurations at C_6 and C_8 deduced in this paper.

EXPERIMENTAL[20]

Mexicanin C (MC-III). Mexicanin C was isolated from *Helenium mexicanum* H.B.K. from the valley of Mexico by extensive chromatography of the chloroform extract.[6] It exhibited m.p. 251–252°, $[\alpha]_D^{20}$ −80°, λ_{max} 226 mμ, ε 8600, I.R. bands at 3400, 1760, 1705 and 1585 cm^{-1}. It gave a weak Legal and Zimmerman test. The limited solubility prevented determination of the N.M.R. spectrum. (Found: C, 68·29; H, 7·50; O, 24·39; Calc. for $C_{15}H_{20}O_4$: C, 68·16; H, 7·63; O, 24·21%).

Mexicanin C *acetate* (MC-IV). Acetylation of mexicanin C with pyridine–acetic anhydride and crystallization of the product from acetone–ether afforded prisms, m.p. 181–182°, $[\alpha]_D^{20}$ −129°, I.R. bands at 1763, 1732, 1410 and 1580 cm^{-1}, N.M.R. signals[21] at 7·70 dd (J − 6, 2·5, H_8), 6·10 dd (6, 2·5, H_8), 5·30 br (H_6), 4·9 c (H_8), 1·91 (acetate), 1·41 d (5) and 1·32 d (6, C_{10}- and C_{11}-methyl), 1·25 (C_5-methyl). (Found: C, 66·51; H, 7·16; O, 26·01; acetyl, 14·37; Calc for $C_{17}H_{22}O_5$: C, 66·65; H, 7·24; O, 26·11; acetyl, 13·70%).

Dehydromexicanin C. A solution of 0·2 g mexicanin C in 8 ml acetic acid was allowed to stand at room temp for 1 hr with 0·15 g chromium trioxide in 0·5 ml water and 6 ml acetic acid. Dilution with water, extraction with chloroform, washing of the chloroform layer, drying, concentration at red. press. and crystallization of the residue from chloroform–ether yielded 0·11 g, m.p. 170–173°. Several crystallizations from acetone–ether raised the m.p. to 186–188°, $[\alpha]_D^{20}$ −235·4°, λ_{max} 231 mμ, ε 6600, I.R. bands at 1756, 1730, 1700 and 1575 cm^{-1}. (Found: C, 68·68; H, 7·23; O, 24·18; Calc. for $C_{15}H_{18}O_4$: C, 68·68; H, 6·98; O, 24·40%).

[20] M.p.'s and b.p.'s are uncorrected. Analyses by Dr. F. Pascher, Bonn, Germany. N.M.R. spectra were run on A-60 N.M.R. spectrometers in deuteriochloroform solution, tetramethylsilane serving as internal standard. The spectrometer at Florida State University was purchased with the aid of a grant from the National Science Foundation. I.R. spectra and rotations were run in chloroform unless otherwise specified, ultraviolet spectra in 95% ethanol.

[21] Singlets are unmarked, multiplets are described as follows: d, doublet, dd, doublet of doublets, t, triplet, br, broad singlet or ill-defined doublet, c, complex signal whose center is given. The triplet characteristic of H_8 is generally broadened or split further.

Dihydromexicanin C (MC-V). A solution of 0·3 g mexicanin C in 50 ml ethyl acetate was hydrogenated in the presence of 0·05 g prereduced platinum oxide. Hydrogen uptake ceased after the absorption of one mol-eqvt. Filtration followed by evaporation and crystallization from chloroform–ether yielded prismatic needles, m.p. 174–176°, yield 0·2 g. The analytical sample melted at 175–177°, $[\alpha]_D^{20}$ +119°, I.R. bands at 3390, 1770 and 1740 cm^{-1}, N.M.R. signals at 4·08 d (6, H_6-superimposed on —O—H signal at 4·00; this was established by exchange with deuterium oxide whereupon the hydroxyl proton signal disappeared), 4·82 (9, H_8), 1·37 d (7) and 1·09 d (5, C_{10}- and C_{11}-methyl), 1·03 p.p.m. (C_5-methyl). (Found: C, 68·24; H, 8·29; O, 24·07; Calc. for $C_{15}H_{22}O_4$: C, 67·64; H, 8·33; O, 24·03%).

This substance was identical with material prepared in 0·18 g yield by isomerization[6] of 0·5 g tetrahydrohelenalin (m.p. previously[5] reported as 166·5° from aqueous methanol–capillary, m.p. 174–175°–block–from ether–hexane, $[\alpha]_D^{20}$ +122°) by mixed m.p., I.R. spectrum and thin-layer chromatogram.

The method of choice for the preparation of MC-V from tetrahydrohelenalin consists in refluxing 0·5 g H-V with sodium methoxide (from approx. 0·1 g sodium) in 35 ml methanol for 30 min. The solvent is removed *in vacuo*, the residue is acidified with dil. hydrochloric acid, filtered and washed, yield 0·43 g MC-V of high purity.

Acetyldihydromexicanin C (MC-VI). Acetylation of 0·1 g dihydromexicanin C with pyridine–acetic anhydride furnished 0·65 g material from ether–hexane, m.p. 115–116°. The analytical sample melted at 119–120°, $[\alpha]_D^{20}$ +122°, I.R. band at 1750 (broad, containing peaks at 1760 and 1740 cm^{-1}. N.M.R. signals at 5·20 br (H_6), 4·85 t (7, H_8), 1·99 (acetate) 1·41 d (7) and 1·09 d (5, C_{10}- and C_{11}-methyl), 0·95 p.p.m. (C_5-methyl). (Found: C, 65·96; H, 7·73; O, 25·67; Calc. for $C_{17}H_{24}O_5$: C, 66·21; H, 7·84; O, 25·25%).

Dehydrodihydromexicanin C(MC-IX). Oxidation of 0·15 g of the preceding material with chromic acid afforded 0·09 g of the title compound, m.p. 170–172° (acetone–ether), $[\alpha]_D^{20}$ +48°, λ_{max} 295 mμ, ε 129, I.R. bands at 1753 (double strength) and 1700 cm^{-1}, N.M.R. signals at 5·00 t (10, H_8), 1·26 d (7) and 1·25 d (C_7, C_{10}- and C_{11}-methyl), 1·22 (C_5-methyl). 3·41 c and 3·29 c (2 protons, H_7 and H_{11}?). (Found: C, 68·53; H, 7·71; O, 24·04; Calc. for $C_{15}H_{20}O_4$: C, 68·16; H, 7·63; O, 24·21%).

This substance was also prepared by reduction of dehydromexicanin C (one mol-eqvt, of hydrogen uptake). It was identical in all respects (mixed m.p., I.R. spectrum, thin-layer chromatogram) with the substance previously[6] called dehydroallotetrahydrohelenalin.

Alkaline cleavage of dehydrodihydromexicanin C. A mixture of 0·14 g of the above, 0·3 g sodium carbonate and 3 ml of water was heated at 50–60° for 2 hr, cooled, acidified to congo red with dil. hydrochloric acid and left in the refrigerator overnight. The crystals (X) which had separated (wt. 0·05 g) were crystallized twice from ethyl acetate–petroleum ether, m.p. 113–115°, mixed m.p. with the dicarboxylic acid from dehydrotetrahydrohelenalin 97–104°, $[\alpha]_D^{23}$ +218° (*c*, 2·5), λ_{max} 235·5 and 320 mμ (ε 7800 and 56), I.R. bands (KBr pellet) 1720, 1710 and 1660 cm^{-1}, N.M.R. spectrum 6·67 t (6, H_8), 3·679 (H_{11}), 1·31 d (8), 1·20 d (7) and 1·18 d (6, C_5, C_{10} and C_{11}-methyls). (Found: C, 63·56; H, 8·18; O, 28·26; neut. equiv. 130; Calc. for $C_{15}H_{22}O_5$: C, 63·82; H, 7·86; O, 28·32%).

The cleavage of dehydrodesacetyldihydroisotenulin reported previously was repeated. After one month at 5°, the product had not crystallized but crystallized on seeding with the acid obtained in the above paragraph, m.p. 116–117°, undepressed on admixture of the other sample. I.R. spectra were completely superimposable, $[\alpha]_D^{23}$ +218°. Noteworthy is the large change in rotation when ethanol was used as solvent, $[\alpha]_D^{23}$ +438° (ethanol, *c*, 1·8).

Acetyldesoxodihydromexicanin (MC-XIV). A solution of 2·0 g MC-VI in 4 ml boron trifluoride etherate and 2 ml of ethanedithiol was left at room temp for 3 hr, diluted with water and extracted with chloroform. The organic layer was washed, dried and evaporated. The solid residue was recrystallized from chloroform-hexane, yield 2·16 g, m.p. 215–217°, $[\alpha]_D$ −54·4°, I.R. bands at 1770 and 1750 cm^{-1}. (Found: C, 59·23; H, 7·43; O, 16·78; S, 16·38; Calc. for $C_{19}H_{32}O_4S_2$: C, 59·36; H, 7·34; O, 16·65; S, 16·65%).

The mercaptal was chromatographed over alumina (solvent 1 : 1 benzene–hexane). 85% of material with unchanged m.p., mixed m.p. undepressed, was recovered from the benzene–hexane, benzene and benzene–ether eluates.

A solution of 0·08 g of the mercaptal in 300 ml ethanol was treated with 10 g Raney nickel under reflux with stirring for 6 hr, filtered and concentrated *in vacuo*. The oily residue was recrystallized from acetone–hexane, yield 0·51 gm, m.p. 107–109°. The analytical sample melted at 109°, $[\alpha]_D$ +17°, I.R. bands at 1770 and 1745 cm^{-1}, N.M.R. signals at 5·15 d (10, H_6), 4·67 broad t (7, H_8), 1·29 d and

0·985 d (7 and 8, C_{10} and C_{11} methyls), and 0·915 p.p.m. (C_5-methyl). (Found: C, 69·26; H, 8·83; O, 21·99; Calc. for $C_{17}H_{26}O_4$: C, 69·36; H, 8·90; O, 21·74%.)

Desoxodihydromexicanin C (MC-XIII). A solution of 1·8 g MC-V in 5 ml boron trifluoride etherate and 2 ml ethanedithiol was converted to the oily mercaptal, wt. 1·96 g. A blank experiment using 0·36 g MC-V and 1 ml boron trifluoride gave a gummy product which on crystallization from methanol resulted in recovery of 0·28 g (80%) MC-V. There was an amporhous, methanol-insoluble fraction, wt. 0·05 g, which was uncrystallizable.

Raney nickel desulfurization of the oily thioketal, wt. 0·98 g, resulted in solid, wt. 0·71 g, m.p. 135–136°, I.R. bands as reported previously, $[\alpha] +12°$ ($CHCl_3$), N.M.R. bands at 4·72 td (10, H_8), 3·75 dd (12, 7, H_6), 2·82 d (H_{11}), 2·20 d (7, OH), 1·40 d and 1·07 d (C_{10}- and C_{11}-methyls), 0·99 p.p.m. (C_5-methyl). That the extra splitting of H_6 was due to spin coupling with OH was shown by running the N.M.R. spectrum after D_2O exchange. H_6 now appeared as a doublet at 3·94 (J = 12) and the signal at 2·20 p.p.m. had disappeared. (Found: C, 71·34; H, 9·49; O, 18·88; Calc. for $C_{15}H_{24}O_3$: C, 71·39; H, 9·59; O, 19·02%).

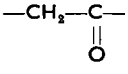
This substance was also prepared by hydrolysis of 0·4 g MC-XIV with 0·4 g potassium hydroxide in 2 ml water under reflux for 30 min. The solution was acidified, concentrated to small volume, extracted with chloroform and dried. The solid residue afforded needles from ether–hexane, m.p. 135–136°, undepressed on admixture of MC-XIII. Reacetylation of MC-XIII, wt. 0·15 g, with acetic anhydride–pyridine furnished 0·15 g material, m.p. 108–109°, undepressed on admixture of MC-XIV.

Chromatography of 0·98 g of the ketal over alumina gave 0·79 g of oily residues from the benzene–hexane and benzene eluates; these were combined and desulfurized. There was obtained 0·62 g MC-XIII, m.p. 134–136°, which on acetylation furnished authentic MC-XIV.

Dehydrodesoxodihydromexicanin C (MC-XVII). A solution of 0·4 g MC-XIII in 15 ml acetic acid was oxidized with 0·4 g chromic oxide in the usual fashion. The oily product has been described previously. Sublimation at 130–140° (04 mm) yielded material, which crystallized spontaneously, m.p. 57–58°, I.R. spectrum unchanged. (Found: C, 72·43; H, 8·96; O, 18·89; Calc. for $C_{15}H_{22}O_3$: C, 71·97; H, 8·86; O, 19·17%.)

A solution of 0·32 g of this material in methanol was refluxed with 0·32 potassium carbonate in 5 ml water for 1 hr, acidified with acetic acid, concentrated and extracted with chloroform. The organic layer was washed, dried, concentrated and the residue crystallized from hexane, yield 0·81 g, m.p. 174–179°. Several recrystallizations raised the m.p. to 185°, λ_{max} 216 mμ (ε 8200), $[\alpha]_D^{20}$ +95·6°. This material (XXI) was identical with substance XLVIII of ref. 10b. (Found: C, 71·44; H, 8·84; O, 19·24; Calc. for $C_{15}H_{22}O_3$: C, 71·97; H, 8·86; O, 19·17%.)

Dehydrodesacetyltetrahydrobalduilin B. A solution of 0·1 g disacetyltetrahydrobalduilin B[6] was oxidized with chromium oxide in the usual manner. The product, 0·05 g, was a semicrystalline mass which was dissolved in a minimum of benzene and diluted with petroleum ether. On standing, a few crystals appeared which were separated, m.p. 134–136°, I.R. bands at 1760 (γ-lactone), 1740 (cyclopentanone), and 1710 (cyclopentanone) and 1400 $cm.^{-1}$



The fingerprint region differed from the fingerprint region of dehydrodesacetyldihydroisotenulin and its allo isomer, dehydrotetrahydrohelenalin and dehydrodihydromexicanin C. There was insufficient material for analysis.

Dehydrotetrahydromexicanin A (MA-IX). A solution of 0·5 g tetrahydromexicanin A (MA-V) in 10 ml acetic acid was mixed with 0·4 g chromic oxide in 2 ml water and 8 ml acetic acid at a temp below 15° (mechanical stirring). After 1 hr at room temp, the mixture was diluted with ice water and extracted with chloroform. The extract was washed, dried and evaporated and the residue recrystallized from ether, m.p. 134–136°, yield 0·46 g. The analytical sample melted at 136° (acetone–ether), I.R. bands at 1790 (γ-lactone), 1740 (cyclopentanone) and 1715 cm^{-1} (cycloheptanone). (Found: C, 68·33; H, 7·74; O, 24·38; Calc. for $C_{15}H_{20}O_4$: C, 68·16; H, 7·63; O, 24·21%).

Cleavage of MA-IX. A mixture of 0·26 g MA-IX, 0·6 g sodium carbonate and 6 ml water was heated for 4 hr at 70–80°. The solution was cooled, acidified and extracted with chloroform to yield the ketodiacid as an uncrystallizable gum, λ_{max} 238 mμ (ε 4600), I.R. bands at 1710 and 1670 cm^{-1}, $[\alpha]_D^{23}$ −11·9° (95% ethanol, *c* 6·55). Treatment with diazomethane gave the dimethyl ester as a colorless viscous liquid, b.p. 200–205° (1 mm), λ_{max} 237·5 mμ (ε 5000), I.R. bands at 1742 and 1680

cm^{-1}, $[\alpha]_D^{23}$ +24·4° (95% ethanol, *c* 3·24), N.M.R. signals at 6·15 (t, J = 5, H_8), 1·27 (d, 7), 1·16 (d, 7) and 0·995 (d, 7, C_9, C_{10}- and C_{11}-methyls). (Found: C, 65·43; H, 7·96; O, 26·29; Calc. for $C_{17}H_{24}O_5$ C, 65·58; H, 8·35; O, 25·72%).

N.M.R. *Spectra of previously reported compounds*

Desacetyltetrahydrobalduilin A (B_5-V). 4·79 td (7·5, 2·5, H_8), 4·34 d (4·5, OH, disappears on treatment with deuterium oxide), 4·18 dd (4·5, 3·5, H_6—becomes doublet on treatment with deuterium oxide), 3·08 qd (8, 3, H_{11}), 1·39 d (7·5) and 1·07 d (7, C_{10}- and C_{11}-methyls), 0·98 p.p.m. (C_5-methyl).

Desoxotetrahydrobalduilin (B-XIV). 5·06 br (H_6), 4·76 t (6, H_8), 2·83 c (2 protons, H_{11} + ?), 2·01 (acetate), 1·06 d (6·5, 6 protons, C_{10}- and C_{11}-methyls), 0·79 p.p.m. (C_5-methyl).

Desoxoallotetrahydrohelenalin (H-XIX). 4·15 d (12·5, H_6), 2·94 d (3, H_7 ?), 2·81 c, 2·02 c, 2·30 c (4 protons), 1·24 d (7) and 1·01 d (5, C_{10}- and C_{11}-methyls), 1·07 p.p.m. (C_5-methyl).

Desoxotetrahydrohelenalin (H-XIII). 4·8 c (H_8), 3·82 d (4, H_6), 3·3 (—OH, disappears on D_2O exchange), 2·9 c (2 protons, H_{11} + ?), 1·32 d (5) and 1·00 d (4, C_{10}- and C_{11}-methyl), 0·85 p.p.m. (C_5-methyl).

Dehydrodesoxotetrahydrohelenalin (H-XVII). 4·76 c (H_8), 4·00 (H_7 ?), 2·84 (H_{11} ?), 1·21 d (7) and 1·11 d (8, C_{10}- and C_{11}-methyl), 1·05 p.p.m. (C_5-methyl).