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Constituents of Helenium Species. XIII. The Structure of Helenalin and Mexicanin A[1]

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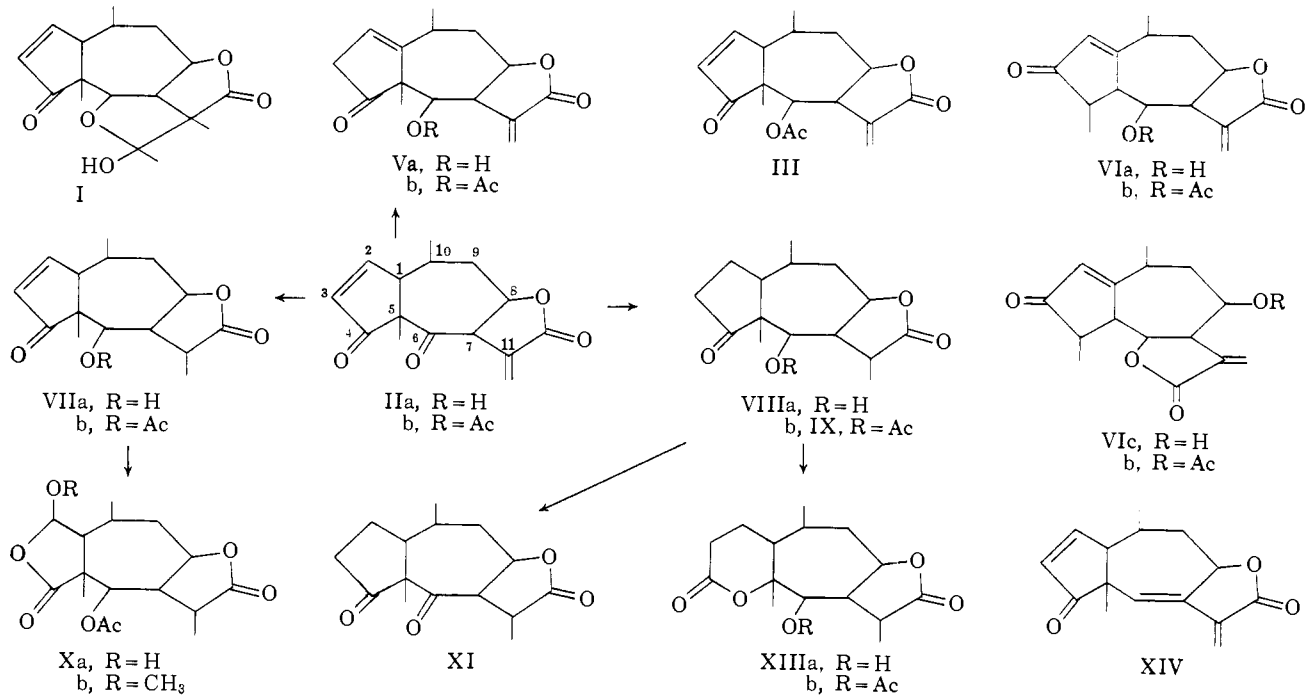
Structures of the sesquiterpene lactones helenalin, balduilin, mexicanin A and neohelenalin (mexicanin D) have been established.

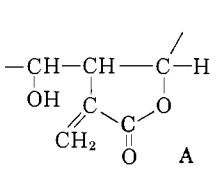
Structure I has recently[4] been deduced for tenulin, the main sesquiterpene lactone of *Helenium amarum* (Raf.) and several other Helenium species.

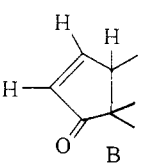
Somewhat earlier[5] tenulin had been correlated with helenalin, the main constituent of the common sneezeweed *Helenium autumnale* L.,[6] several other Helenium species[7-10] and *Balduina angustifolia* (Pursh) Robins,[5] which in turn had been correlated[11] with balduilin, a sesquiterpene lactone from *Balduina uniflora* Nutt. balduilin as III. Mexicanin A, a constituent of *H. mexicanum* H.B.K.,[12] is shown to possess the structure Va. Mexicanin D[12] has been identified with neohelenalin[10] whose structure is revised to XXIIa.

Instead of reviewing in detail earlier work, we merely note that helenalin has been shown to be a cyclopentenone[7] and to contain the partial grouping A which is part of a six-membered or larger ring.[7,8] Because of the formation of guaiazulene on reduction and dehydrogenation,[8,13] it was assigned formula VIa, the orientation of the lactone ring being based on chemical and spectroscopic evidence. For reasons which need not be amplified here, balduilin was assigned formula VIb or VId (lactone ring reorientated).



These correlations indicate that the previously postulated[8] structure for helenalin is in error and that helenalin and balduilin possess the same "abnormal" carbon skeleton as tenulin (I). Since *a priori*, a rearrangement during the reactions leading from helenalin or tenulin to a common intermediate[5] cannot be completely excluded, we present in this paper detailed evidence for the formulation of helenalin as IIa and





High resolution n.m.r. spectra of helenalin and balduilin (Table I) clearly disprove these proposals, since *four*, not three, vinyl protons betray their presence and since one singlet and one doublet methyl signal are observed instead of the two doublets required by VIa and VIb. It is possible to deduce complete structures for helenalin and balduilin by considering the n.m.r. spectra and the chemical transformations

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(4) W. Herz, W. A. Rohde, K. Rabindran, P. Jayaraman and N. Viswanathan, *J. Am. Chem. Soc.*, **84**, 3857 (1962).

(5) W. Herz and R. B. Mitra, *ibid.*, **80**, 4876 (1958).

(6) E. P. Clark, *ibid.*, **58**, 1982 (1936); **61**, 1836 (1939); **62**, 597 (1940). *H. macrocephalum* listed by Clark as a source of helenalin is obviously a misprint for *H. microcephalum*, since no such Helenium species is recorded in the botanical literature.

(7) R. Adams and W. Herz, *J. Am. Chem. Soc.*, **71**, 2546, 2551, 2554 (1949).

(8) G. Büchi and D. Rosenthal, *ibid.*, **78**, 3860 (1956).

(9) W. Herz, R. B. Mitra, K. Rabindran and W. A. Rohde, *ibid.*, **81**, 1481 (1959).

(10) W. Herz, P. Jayaraman and H. Watanabe, *ibid.*, **82**, 2276 (1960).

(11) W. Herz, R. B. Mitra and P. Jayaraman, *ibid.*, **81**, 6061 (1959).

(12) A. Romo de Vivar and J. Romo, *Chemistry & Industry*, 882 (1959); *Ciencia (Mex.)*, **21**, (1) 33 (1961). This species is also a good source of helenalin and other sesquiterpene lactones which can be isolated in variable amounts at different stages of its growth cycle.

(13) V. Herout, M. Romanuk and F. Sorm, *Coll. Czechoslov. Chem. Commun.*, **21**, 1359 (1956).

in detail, as has been done with tenulin,[4] but in the interest of brevity, we merely show how formulas IIa and III accord with the chemical and spectroscopic evidence.

In the n.m.r. spectra, two cyclopentenone vinyl proton signals near 6 (α-hydrogen) and 7.5 p.p.m. (β-hydrogen) are split into quadruplets by spin coupling to each other (J = 7 c.p.s. in helenalin, 6 in balduilin) and to the γ-hydrogen atom ($J_{H_1H_2}$ = 2 c.p.s. in helenalin, 1.5 in balduilin, $J_{H_1H_3}$ = 2.5) as required by partial formula B. This assignment is justified by comparison with the n.m.r. spectra of dihydrohelenalin acetate (VIIb),[7] which retains the cyclopentenone chromophore and the appropriate vinyl proton signals, and the cyclopentanone derivatives tetrahydrohelenalin (VIIIa) and tetrahydrobalduilin (IX), which are transparent in this region.

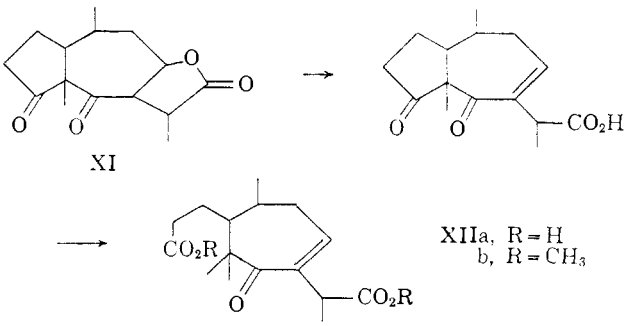
Ozonolysis of VIIb in the manner previously described for its C_6-epimer isotenulin[4,14] furnished corroborative chemical evidence. The product, a lactol $C_{16}H_{22}O_7$ (Xa), in accordance with the postulated formula gave a positive Tollens test and yielded a methyl ether Xb. The n.m.r. spectrum of this ether exhibited signals in the 5 p.p.m. region characteristic of H_6 and H_8 (*vide infra*) and an additional doublet near 5.3 p.p.m. as expected from a product resulting from ozonolysis of partial structure B.

Partial structure A is represented by the characteristic doublets of the conjugated methylene group[4,15] (absent in VIIb and all tetrahydro derivatives which instead exhibit a second methyl doublet) and by two signals whose chemical shift corresponds to hydrogen on carbon linked to oxygen. One of these, at 4.2–4.4 p.p.m., is a broad singlet (in most compounds of the helenalin series) or doublet (in the balduilin series, J = 3 c.p.s.) which moves to lower field on acetylation and disappears on oxidation. Hence it is traceable to H_8 which is spin coupled to only one proton, that at C_7.

Lactone ring closure to C_8 is consonant with the multiplicity of the signal near 4.8 p.p.m. whose appearance indicates spin coupling to three hydrogens. In the helenalin series, two of these are relatively large (J = 6–8 c.p.s.) while one is small (J = 1–2), thus producing a triplet with smaller doubling as in the tenulin series. In the balduilin series, the situation is somewhat more complex and can be interpreted most simply by assuming one large (J = 9), one medium (J = 5) and one small (J = 1–3) coupling constant.

Because the lactone ring is closed to C_8 in helenalin and its derivatives, the base-catalyzed conversion of dehydrotetrahydrohelenalin (XI) to a dibasic α,β-unsaturated keto acid[8,16] may now be interpreted as involving the cleavage of a β-diketone. In accordance with the postulated scheme, the n.m.r. spectrum of the product (as the dimethyl ester XIIb) exhibited a vinyl proton triplet at 6.60 p.p.m. (J = 8) and two methoxyl singlets at 3.12 p.p.m. There was no vinyl methyl resonance. The signals in the 1 p.p.m. region could be interpreted most simply by assuming the presence of three secondary methyl groups and the absence of a tertiary methyl group. The appearance of a new secondary methyl group during this transformation provides conclusive proof for attaching the tertiary methyl group of helenalin to C_5, between the two carbonyl groups of XI.

If more evidence were needed, it is provided by the peracetic acid oxidation of tetrahydrohelenalin (VIIIa)



XI

XIIa, R = H
b, R = CH_3

to the hydroxydilactone XIIIa. The n.m.r. spectrum of its acetate XIIIb had no new signals in the 3.5–5.5 p.p.m. region, which shows that C_5 is quaternary. In passing we note the remarkable chemical shift of the C_5–methyl singlet, undoubtedly the effect of the adjoining lactone oxygen and acetate groups.[17]

We have had occasion previously[10] to comment on the ultraviolet spectrum of anhydrohelenalin. This substance was obtained in poor yield on treatment of helenalin mesylate with base and should, on the basis of the previous discussion, be represented by XIV. This is difficult to reconcile with the ultraviolet maxima (207, 222 and 328 mμ) unless the cross-conjugated system were to exhibit anomalous features. Molecular weight determinations have now shown "anhydrohelenalin" to be a dimer, evidently a Diels–Alder self adduct of XIV.[18]

We are now ready to consider the structure of mexicanin A, $C_{15}H_{18}O_4$, whose properties have not previously been described in detail. The nature of the four oxygen atoms of this substance was established earlier[12] on spectroscopic grounds and they were shown to be distributed in a γ-lactone, a ketone (probably in a five-membered ring) and a free hydroxyl group capable of forming an acetate. The spectroscopic data also indicated the presence of a methylene group conjugated with the lactone function and an isolated double bond.

Mexicanin A contains two methyl groups and yielded formaldehyde on ozonolysis. Hydrogenation with palladium–charcoal afforded dihydromexicanin A (XVa) which exhibited no strong ultraviolet absorption at 212 mμ, indicating that the conjugated exocyclic methylene group had been saturated. This assumption was supported by the infrared spectrum (double strength band at 1755 cm.$^{-1}$) which no longer contained the characteristic band at 1652 cm.$^{-1}$. Although the second double bond was still present (weak band at 1635 cm.$^{-1}$), efforts to hydrogenate XVa further in neutral solution were unsuccessful. However, chemical evidence for the double bond was provided by the formation of an epoxide XVI and both double bonds were saturated when the medium was acetic acid and the catalyst platinum oxide, the product being XVIIa.

Chromatography of the mother liquors of XVa afforded isomexicanin A (XVIIIa) whose ultraviolet (λ_{max} 221 mμ, ϵ 13800) and infrared spectrum (hydroxyl at 3300 cm.$^{-1}$, combined lactone and cyclopentanone at 1740, double bonds at 1675 and 1628 cm.$^{-1}$) indicated that the exocyclic double bond of V had isomerized in the manner previously observed as occurring during the hydrogenation of parthenin.[19] Incidentally, similar isomerizations accompany the hydrogenation of helenalin and neohelenalin. The

(14) D. H. R. Barton and P. de Mayo, *J. Chem. Soc.*, 142 (1956).

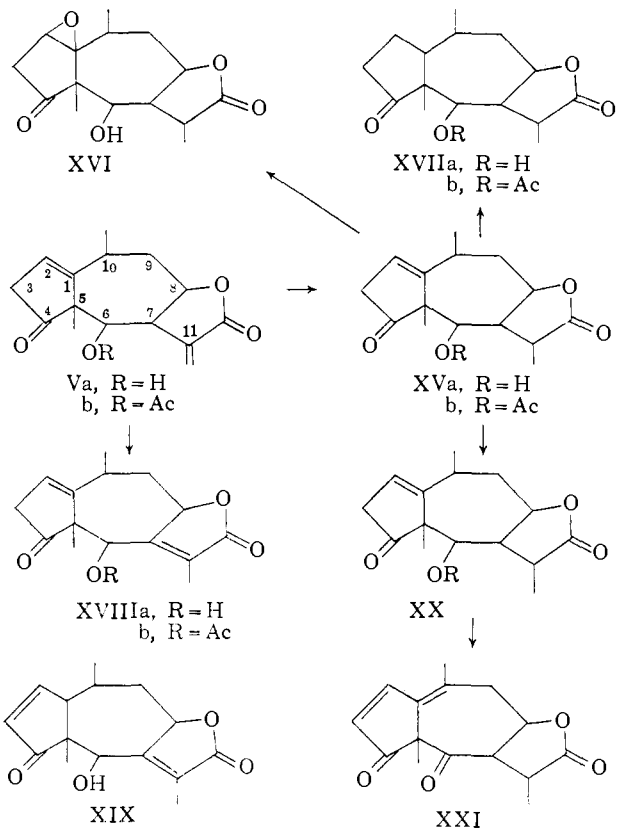
(15) W. Herz and G. Högenauer, *J. Org. Chem.*, **27**, 905 (1962).

(16) B. H. Braun, W. Herz and K. Rabindran, *J. Am. Chem. Soc.*, **78**, 4423 (1956).

(17) Compared with the n.m.r. spectrum of the corresponding dilactone of the tenulin series,[4] this signal is shifted downfield by an additional 0.16 p.p.m.

(18) E. A. Braude and F. A. Evans, *J. Chem. Soc.*, 3238 (1956).

(19) W. Herz, H. Watanabe, M. Miyazaki and Y. Kishida, *J. Am. Chem. Soc.*, **84**, 2601 (1962).



products, isohelenalin (XIX)[20] and isoneohelenalin (XXIII), are described in the Experimental section.

Chromic oxide oxidation of XVa furnished dehydrodihydromexicanin A (XX) whose infrared spectrum demonstrated the presence of a new carbonyl group (maxima at 1770, 1755, 1710 and 1628 cm.$^{-1}$). The new ketone group was not conjugated with the double bond, but the intensity of the n→π^*-transition (λ_{max} 300–302 mμ, ϵ 140) suggested that XX might be a β,γ-unsaturated ketone.[21]

That mexicanin A was closely related to helenalin was first deduced when it was observed that treatment of its dihydro derivative XVa with methanolic potassium bicarbonate resulted in isomerization to dihydroneohelenalin (XXIVa).[22] Moreover, under these conditions dihydrohelenalin (VIIa) furnished approximately the same yields of dihydroneohelenalin which argued for the belief that helenalin and mexicanin A differed from each other only in the position of one easily isomerizable double bond. It was discovered that hydrogen chloride–chloroform converts helenalin fairly smoothly into a mixture of mexicanin A and neohelenalin (XXIIa). This observation leads to structure V for mexicanin A when its physical properties and chemical behavior are considered.

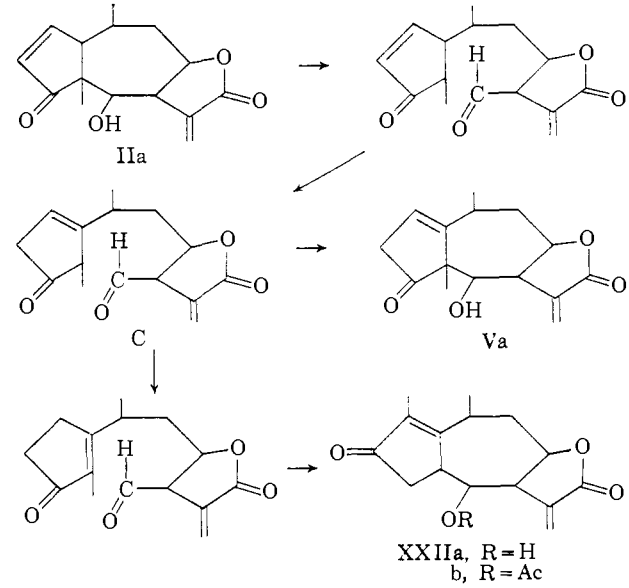
The formulation of mexicanin A as the 1,2-double bond isomer of helenalin is rendered secure by an examination of the n.m.r. spectra of Vb and its derivatives (Table I). We draw attention to the presence of a vinyl proton signal near 6 p.p.m. (in Vb a narrowly split triplet superimposed on one of the two vinyl proton doublets of the exocyclic methylene group) and of a complex multiplet, intensity two protons,[23] near 3 p.p.m. These signals are associated with the single vinyl proton at C_2 and the two protons of the α-methylene group at C_3. They are strikingly similar to signals in the n.m.r. spectra of pyrotenulin[4] and parthenin derivatives[19] which have the same general structure.

The remaining signals indicate, in the now familiar manner, that the lactone ring of mexicanin A is closed toward C_8 and that the hydroxyl (or acetate) group is attached to C_6. Evidence for the structure previously assigned to isomexicanin A is the appearance of a slightly split vinyl methyl signal at 1.96 p.p.m. in place of the two vinyl proton doublets of the exocyclic methylene group.

We have carried out one additional transformation in the mexicanin A series which is worthy of note. Treatment of XX with selenium dioxide in acetic acid resulted in the formation of a dienone, λ_{max} 300 and 210–222 mμ (ϵ 9400 and 5800), which must be formulated as XXI. The n.m.r. spectrum (Table I) was fully in accord with this, since it displayed the typical α- and β-vinyl proton signals of the cyclopentenone chromophore, but no others. The significant feature of the spectrum is the appearance of a vinyl methyl singlet at 1.60 p.p.m. Hence one of the methyl groups of helenalin, tenulin and their congeners can be assigned unequivocally to C_{10}. This assignment previously rested on the isolation of 1,4,7-trialkylsubstituted azulenes through procedures requiring a dehydrogenation and, while justifiable on biogenetic grounds, could not be said to be completely rigorous.

Mexicanin D[12] was identified with neohelenalin[10] (XXIIa) by direct comparison and by comparison of its dihydro derivative with dihydroneohelenalin (XXIVa). The latter could also be obtained by isomerization of dihydrohelenalin or dihydromexicanin A with potassium bicarbonate in methanol.

Definition of helenalin and mexicanin A as IIa and Va, respectively, requires that the previously postulated structure of neohelenalin be revised. The simplest hypothesis is that neohelenalin and dihydroneohelenalin are formed from helenalin and dihydrohelenalin by a sequence of reactions analogous to those invoked to explain the isomerization of tenulin to desacetylneotenulin (Scheme I). Under acid conditions an alternate pathway is provided leading from intermediate C to mexicanin A (*vide infra*).



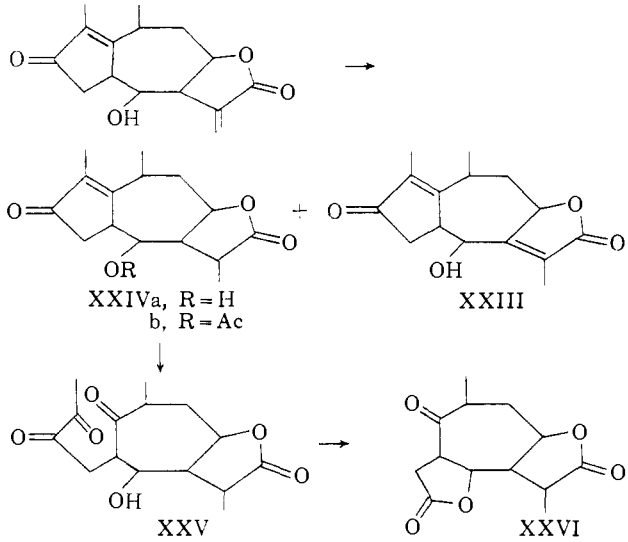
(20) This substance was first encountered by Büchi and Rosenthal[8] as a constituent of *H. microcephalum* DC.

(21) R. C. Cookson and N. S. Waryar, *J. Chem. Soc.*, 2302 (1956); S. F. Mason, *Quart. Revs.*, **15**, 287 (1961).

(22) The experiment was suggested by the base-catalyzed conversion of tenulin to desacetylneotenulin,[4,14] but the yields were considerably lower in the helenalin series.

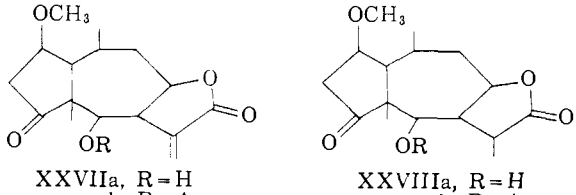
(23) In some of the reduced compounds, the intensity and complexity of this multiplet is such as to lead to the belief that it includes the signal for the C_{11}-hydrogen.

The experimental evidence is completely in accord with the new structure XXIIa. Physical and chemical results cited previously[10] apply equally well to XXIIa and to the old structure, but the n.m.r. spectra (Table I) are only compatible with XXIIa. The only vinyl proton signals are those of the exocyclic methylene protons in XXIIa; H_6 appears as an unresolved triplet in XXIIa, as a triplet at much lower field in XXIIb and XXIVb and as a broad singlet at relatively low field (allylic hydrogen) in XXIII. The multiplicity of the lactone ether hydrogen signal indicates lactone ring closure to C_8. In the methyl region are found two normally split methyl doublets (one doublet and one narrowly split vinyl methyl signal in the case of XXIII) and one slightly split vinyl methyl resonance which replaces the methyl singlet found in the n.m.r. spectra of helenalin and all of its derivatives.



The results of an oxidative degradation of dihydroneohelenalin (XXIVa) exactly parallel those obtained with desacetylneotenulin[4] and corroborate the assigned structures. Ozonolysis of XXIVa furnished a non-crystalline triketone XXV which was oxidized with periodic acid to a crystalline ketodilactone of formula $C_{13}H_{16}O_5$. Its infrared spectrum (bands at 1780—double strength, two γ-lactones—and 1706 cm.$^{-1}$—cycloheptanone) was compatible with XXVI. Reasoning of the sort previously used in the tenulin series therefore requires XXIIa for neohelenalin.

Reference has been made in a preceding paragraph to the observation that hydrogen chloride–chloroform converts helenalin to a mixture of neohelenalin and mexicanin A. Mexicanin A and helenalin acetate were the products when helenalin was subjected to the action of concd. hydrochloric acid in acetic acid, but isomerization could not be brought about under acid conditions with IIb or VIIb. This indicates that a free hydroxyl group is necessary for the conversion of helenalin to neohelenalin and mexicanin A and supports the scheme suggested earlier in this paper for the formation of these compounds. Instead, methanolic hydrochloric acid converted IIb and VIIb to 2-methoxydihydrohelenalin acetate (XXVIIb) and 2-methoxytetrahydrohelenalin acetate (XXVIIIb).

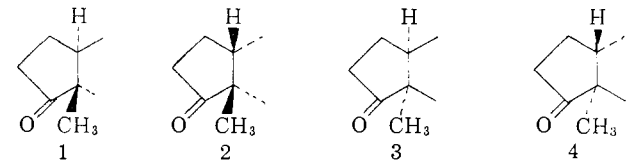


Evidence for these structures are the n.m.r. spectra and the cleavage of these compounds to IIb and VIIb with aqueous hydriodic acid. The latter, while unable to cause isomerization of IIa and VIIa, may be employed to convert IIa and VIIa to XXVIIa and XXVIIIa in methanol.

We now discuss briefly some stereochemical aspects. The correlations established earlier[5,11] were taken to indicate that helenalin, tenulin and balduilin possess common stereochemistry at the ring junction since, on the basis of the old structures such as VIa and VIc, there was no mechanism for epimerization at C_5 during the reactions used to interrelate these substances. The concatenation of functional groups actually present does afford such an opportunity. Treatment of VIIIa with base, or hydrolysis of IX, might cause inversion at C_5 by way of a retroaldol cleavage followed by aldol condensation. This sequence of reactions could of course be accompanied by epimerization at C_6 and C_7 as well. Alternatively, the configuration at C_5 might be maintained, but that at C_6 could be inverted.[24]

Despite this uncertainty we consider it likely, in view of the optical rotatory dispersion curves, that tetrahydrohelenalin (VIIIa),[25] dihydroisotenulin,[25] allodihydroisotenulin,[25] tetrahydrobalduilin (IX) and allotetrahydrohelenalin (see Experimental) possess the same stereochemistry at the ring junction and that the reactions used to interrelate them did not involve epimerization at C_5. Each of these compounds exhibits a moderately strong Cotton effect, the amplitude varying from about 1700° in IX to more than 3300° in dihydroisotenulin.[26,27] Deacetylation is accompanied by an increase in amplitude although all other features are preserved.

Even if this view were correct and assuming that comparisons with appropriate steroids were valid, an attempt to distinguish between absolute configuration 1 (strong positive Cotton effect[28]) and 2 (relatively weak positive Cotton effect[28,29]) would at best be highly



tentative. However, a C_5-α-configuration (partial structures 3 and 4) would seem to be excluded since such compounds should exhibit a negative Cotton effect.

In spite of the ease with which helenalin can be converted to mexicanin A, tetrahydromexicanin A (XVIIa) is not identical with tetrahydrohelenalin (VIIIa), nor is its acetate identical with tetrahydrobalduilin (IX). The simplest explanation would be to assume that hydrogenation of the C_1–C_2 double bond of mexicanin A (V) leads to a substance whose stereochemistry differs from that prevailing in compounds of the helenalin, tenulin and balduilin series. While this may well be true, it cannot be the sole point of difference because comparison of the optical rotatory dispersion curves previously discussed with the optical rotatory dispersion curve of tetrahydromexicanin A

(24) The revision in the structures of helenalin, tenulin and balduilin also renders invalid previous conclusions[5,11] about configurational similarities and differences at C_6 and C_8. This problem is now being re-examined.

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

(26) This is a minimum value since readings could not be taken down to the wave length of the trough.

(27) The optical rotatory dispersion curve of balduilin (see Experimental) exhibits the general features of that of isotenulin.

(28) F. Sondheimer, S. Burstein and R. Mechoulam, *J. Am. Chem. Soc.*, **82**, 3209 (1960).

(29) C. Djerassi, R. Riniker and B. Riniker, *ibid.*, **78**, 6362 (1956).

TABLE I

N.M.R. PEAKS OF HELENALIN AND BALDUILIN DERIVATIVES[a]

Compound	H_2	H_3	H_6	H_9[b]	H_{13}	C_5–Me	C_{10}–Me and/or C_{11}–Me	Misc.
IIa	7.72dd(7.5, 2)	5.90dd(7, 2.5)	4.46br	4.96t(8)	6.24d(3) 5.78d(3)	0.98	1.26d(6) — —	
IIb	7.66dd(6, 1.5)	6.06dd(6, 2.8)	5.36br	4.86t(6)	6.42d(2.8) 6.11d(2.8)	0.98	1.25d(5.6)	1.99[c]
III	7.50dd(6.5, 1.5)	6.14dd(6.5, 3.5)	6.00d(3)	4.72c	6.33d(2) 5.80d(2)	1.13	1.27d(7)	2.02[c]
Vb	5.90t(1.8)[d]	2.86t(1.8)[e]	5.16d(5.5)	4.80t(7)	6.35d(1.9) 5.91d(1.9)	1.00	1.29d(7)	1.97[c]
VIIb	7.77dd(6, 1.6)	6.05dd(6, 3)	5.61br	4.71t(6)		1.02	1.23d(7), 1.49d(7)	1.92[c]
VIIIa			4.21d(6.5)	4.69t(6)		0.74	0.99d(5), 1.27d(6.5)	
VIIIb			5.35br	4.71t(6)		.87	1.17d(5), 1.40d(6.5)	1.98[c]
IX			5.70d(2)	4.81t(6)		.89	1.13d(8), 1.15d(6)	2.08[c]
Xb	5.32d(5)		5.24d(4)	4.70c		1.39	1.15d(6), 1.58d(7)	2.16,[c] 3.52[l]
XI				4.80c		1.25	1.24d(7), 1.44d(7)	
XIIIb			5.21br	4.48c		1.52	0.94d(4), 1.25d(6)	2.10[c]
XVb	5.97d	2.90br[e]	5.26d(2)	4.61c		1.13	1.36d(6), 1.51d(6)	2.00[c]
XVIIa		2.94c[f]	3.68d(9)	4.51dd(6, 5)		1.35	1.06d(6.5) 1.41d(6)	
XVIIb		3.0c[f]	5.20d(4)	4.64dd(5, 5)		1.03	1.06d(6.5), 1.27d(6)	2.03[c]
XVIIIa	5.95t	3.0br	5.12	5.33c		1.06	1.27d(6), 1.96d(2)	
XX	5.16dd	3.13t		4.71dd(5, 5)		1.35	1.23d(7.5), 1.41d(8.5)	
XXI[g]	8.15d(6)	6.47d(6)		5.05c		1.60	2.30, 1.37d(7)	4 protons in range 2.2–3.6
XXIIb			5.65t(2.5)	5.00q(7.5)	6.30d(2) 5.77d(2)		1.26d(7.5)	1.71[h] 1.92[c]
XXIIa			4.24br	5.01q(7.5)	6.18d(3) 5.71d(3)		1.23d(7)	1.68d(2)[h]
XXIIIa	3.33c, 3.56[i]		4.86br	5.24c			1.40d(8), 1.99d(1.5)	1.76[h]
XXIVb			[j]	[j]			1.23d(7.5), 1.39d(7)	1.77d(2)[h]
XXVIIa	3.92t(3.5)	2.30t[e]	4.25br	4.90t(7)	6.21d(2) 5.61d(2)	0.92	1.11d(5)	2.52[k] 3.32[l]
XXVIIb	3.90t(3.5)	2.92t[e]	5.20d(2)	4.76t(4.5)	6.07d(3) 6.40d(3)	0.96	1.14d(5.5)	2.00[c] 2.54[k] 3.25[l]

[a] Spectra determined by Mr. Fred Boerwinkle on a Varian HR-60 spectrometer in deuteriochloroform solution. Values given in p.p.m. relative to tetramethylsilane as internal standard. All signals in first five columns correspond to one proton, all signals in last four to three, unless otherwise specified. Singlets are unmarked, multiplets are described as follows: d doublet, dd doublet of doublets, t triplet, q quartet, br somewhat broadened singlet or ill-defined doublet, c complex signal whose center is given. Numbers in parentheses denote coupling constants in c.p.s. [b] Each of the triplet components is split again, generally into a doublet, except in XIV–XVIIIa. [c] Acetate. [d] Superimposed on one of the methylene protons. [e] Two protons. [f] Intensity three protons, probably includes H_{11}. [g] Taken in trifluoroacetic acid. [h] C_3-methyl. [i] H_4 and H_5 protons. [j] Not recognizable because of high dilution. [k] H_7?. [l] Methoxyl.

reveals a remarkable contrast. The latter exhibits a relatively weak *negative* Cotton effect whose amplitude of about 900° almost doubles on acetylation.

There can be little question that this striking inversion of the Cotton effect betokens a configurational change at C_5 in going from helenalin to mexicanin A. This is a strong argument for the belief that this isomerization is not simply a double bond migration, but involves the intermediate C postulated in Scheme I. In view of the relatively weak negative Cotton effect, configuration 3 would seem to be more probable for tetrahydromexicanin A than 4.

Experimental[30]

The helenalin used in this work was obtained from *H. mexicanum* H.B.K.[12] or *B. angustifolia* (Pursh) Robins.[5] Previously known compounds were prepared as described in the literature.

Ozonolysis of Acetyldihydrohelenalin.—A solution of 0.5 g. of VIIb in 25 ml. of chloroform was ozonized for 1.5 hr. at −10°, decomposed with water and allowed to stand overnight. The chloroform layer was dried, evaporated and the residue stirred with sodium bicarbonate solution for 15 hr. The aqueous extract was extracted with chloroform, acidified to congo red and re-extracted with chloroform. The second chloroform extract was washed, dried and evaporated. The residue was taken up in methanol, treated with a few drops of water and refrigerated. The crystalline product was recrystallized from methanol; yield 0.035 g. of lactol Xa, m.p. 257–259° (uncor.); infrared bands at 3340 (hydroxyl), 1780 and 1775 (γ-lactones) and 1718 cm.$^{-1}$ (acetate). It was not readily soluble in sodium bicarbonate solution and gave a positive Tollens test.

Anal. Calcd. for $C_{16}H_{22}O_7$: C, 58.89; H, 6.75; O, 34.36. Found: C, 58.94; H, 7.03; O, 34.18.

A solution of 0.04 g. of the lactol in 4 ml. of methanol was treated with diazomethane from 1 g. of EXR-101 and allowed to stand overnight. The solvent was removed and the residue recrystallized from benzene–petroleum ether; yield 0.022 g. of Xb, m.p. 219–221°.

Anal. Calcd. for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11; O, 32.91. Found: C, 59.67; H, 7.03; O, 32.76.

Peracid Oxidation of Tetrahydrohelenalin.—A solution of 2 g. of tetrahydrohelenalin in 15 ml. of acetic acid was allowed to stand for 4 days with 10 ml. of 40% peracetic acid in the presence of a few mg. of *p*-toluenesulfonic acid. The solution was concentrated to small volume, diluted with water, neutralized with sodium bicarbonate solution and extracted with chloroform. The washed and dried organic layer was concentrated *in vacuo;* yield 2 g. of viscous gum which was chromatographed over alumina (solvent and eluent benzene). The major portion, wt. 1.2 g., was eluted with benzene as a viscous gum (XIIIa) infrared bands at 3600 (hydroxyl), 1760 (γ-lactone) and 1700–1725 (δ-lactone). The characteristic 1410 cm.$^{-1}$ band (methylene α- to ketone) had disappeared. Acetylation with acetic anhydride–pyridine fur-

(30) M.p.'s were taken on the Kofler block and are corrected, unless otherwise specified. Ultraviolet spectra were run on a Beckman DK2 or Cary 14 spectrophotometer in 95% ethanol solution; infrared spectra in chloroform solution, unless noted otherwise, on Perkin–Elmer model 21 or infracord instruments. Rotations were determined in chloroform solution. Microanalyses by Dr. F. Pascher, Bonn, Germany; C–methyl determinations by Dr. J. M. L. Cameron, Department of Chemistry, University of Glasgow. The alumina used was washed with ethyl acetate and dried at 100° *in vacuo*.

nished an oil (XIIIb) which solidified after chromatography over alumina and was recrystallized from benzene–petroleum ether; m.p. 192–193° (uncor.), infrared bands at 1760 (γ-lactone and acetate) and 1725 cm.$^{-1}$ (δ-lactone).

Anal. Calcd. for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46; O, 29.60. Found: C, 63.46; H, 7.39; O, 29.35.

Dimer of Anhydrohelenalin.—Repetition of the previously[29] described experiment, using 0.855 g. of helenalin mesylate, yielded 0.092 g. of product after crystallization from benzene–petroleum ether; m.p. 289–293° (previously reported[10] no m.p. below 260°). The infrared spectrum was superimposable on that of the material prepared previously; maxima at 1752 (γ-lactone), 1705 and 1595 (cyclopentenone), 1660 (double bond conjugated with lactone) and 1570 cm.$^{-1}$ (third double bond, probably conjugated). The ultraviolet spectrum had maxima of 207, 222 and 328 mμ (ε 21600, 22600 and 138). The n.m.r. spectrum had two methyl singlets at 1.17 and 1.18 p.p.m. and two methyl doublets at 1.31 (J = 6) and 1.36 p.p.m. (J = 5.5). The vinyl proton region was difficult to interpret but suggested the presence of one methylene group (doublets at 5.59 and 5.96 p.p.m., J = 3) whose signals were superimposed on a broad absorption centered near 5.74 and what appeared to be a doublet of doublets at 5.99 (α-proton of cyclopentenone). Another doublet of doublets (β-proton) was centered at 7.46 at which frequency there was also a narrowly-split triplet (H_6-vinyl proton?). There was also a lactone ether proton signal centered at 5.12 p.p.m. These data suggest a structure resulting from a Diels–Alder condensation between the cyclopentenone group of one molecule and the diene half of a second, but lack of material precluded further chemical investigation.

Anal. Calcd. for $C_{30}H_{32}O_6$: mol. wt., 488. Found: mol. wt. (Kofler), 486.

Isohelenalin (XIX).—A solution of 3 g. of helenalin in 120 ml. of ethyl acetate was hydrogenated with 10% palladium-on-charcoal until one mole-equivalent of hydrogen was absorbed. The solvent was removed, the residue taken up in benzene–hexane (1:1) and chromatographed over 30 g. of alumina. Benzene–hexane (1:1 and 2:1) eluted dihydrohelenalin, m.p. 238–240° (from methanol), $[\alpha]_D$ −117°, λ_{max} 228 and 310–315 mμ (ε 6500 and 74); infrared bands at 3300 (hydroxyl), 1755 (γ-lactone), 1705 and 1580 cm.$^{-1}$ (cyclopentenone).

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; O, 24.21. Found: C, 67.88; H, 7.58; O, 24.61.

The acetate melted at 174–176°, $[\alpha]_D$ −114°, λ_{max} 227 and 310–315 mμ (ε 9100 and 95).

Anal. Calcd. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24; O, 26.11. Found: C, 66.89; H, 6.82; O, 26.73.

The crystalline fractions eluted with benzene–hexane (3:1, 4:1) and benzene were combined and recrystallized from acetone–ether; yield of XIX, 0.32 g., m.p. 243–247°. Further crystallization raised the m.p. to 268–270° (no depression on admixture of an authentic specimen[8]), $[\alpha]_D$ −183°, λ_{max} 220 mμ (ε 19600); infrared bands at 3380 (hydroxyl), 1765 (γ-lactone), 1670 (double bond), 1700 and 1580 (cyclopentenone).

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92; O, 24.40. Found: C, 68.76; H, 6.91; O, 24.35.

The acetate melted at 184–185°, $[\alpha]_D$ −156°, λ_{max} 219 and 310–315 mμ (ε 20000 and 86).

Anal. Calcd. for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62; O, 26.29. Found: C, 67.08; H, 6.64; O, 26.52.

The helenalin used for this hydrogenation was chromatographed over alumina prior to use and recrystallized from benzene and acetone–hexane to m.p. 178–180°. Hence the isohelenalin isolated from the reaction mixture was not a contaminant of starting material, as might conceivably be supposed.

Mexicanin A (Va). (a).—As obtained from the plant, mexicanin A (prisms from acetone–hexane) exhibited m.p. 138–140°, $[\alpha]_D$ −27°, λ_{max} 212 mμ (8400); infrared bands at 3400 (hydroxyl), 1750 (lactone), 1652 and 1630 cm.$^{-1}$ (double bonds); strong positive Legal and Tollens test.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92; O, 24.40; C-methyl (two groups), 11.45. Found: C, 68.78; H, 6.95; O, 24.59; C-methyl, 10.69.

The oxime (needles from ether–hexane) melted at 191–192° dec.

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 65.01; H, 7.42; N, 5.67.

(b) **From Helenalin.**—A solution of 10 g. of helenalin (from *H. mexicanum* or *B. angustifolia*) was dissolved in 350 ml. of anhydrous chloroform saturated with hydrogen chloride. The solution was left at room temperature overnight, then refluxed for 35 minutes, washed with water, 5% sodium hydroxide, water, dried and concentrated to dryness *in vacuo*. The residue, wt. 9.4 g., was dissolved in 500 ml. of benzene and chromatographed over 200 g. of deactivated alumina. The benzene eluates crystallized. Combination and crystallization from acetone–ether furnished 2.45 g. of mexicanin A; benzene–ether and ether eluted oils. Fractions eluted with chloroform–ether (1:1, 2:1 and 3:1) and chloroform crystallized. Combination and recrystallization from acetone–ether furnished 0.44 g. of neohelenalin, m.p. 240–242°, undepressed on admixture of an authentic sample and of mexicanin D from the plant (*vide infra*), infrared spectra superimposable.

Another preparation in the course of which 3 g. of helenalin was refluxed with 30 ml. of acetic acid and 5 ml. of concd. hydrochloric acid for 30 minutes, cooled, diluted with water, extracted with chloroform and worked up in the usual manner yielded 0.89 g. of mexicanin A after chromatography over 60 g. of deactivated alumina (solvent and eluent benzene–hexane 4:1). Some of the fractions eluted with benzene crystallized and afforded 0.06 g. of helenalin acetate.

Ozonolysis of 0.2 g. of mexicanin A dissolved in 40 ml. of tetrahydrofuran for 30 minutes at 0° followed by steam distillation into an aqueous solution of dimedone furnished 0.025 g. of formaldehyde dimedone derivative, m.p. 188–189°, undepressed on admixture of an authentic sample.

Acetylmexicanin A (Vb).—Acetic anhydride–pyridine at room temperature furnished the acetate, prisms from methanol–ether, m.p. 149–150°, λ_{max} 214 mμ (ε 9100); infrared bands at 1745 (composite of γ-lactone and acetate), 1653 and 1638 cm.$^{-1}$ (double bonds). Vb was not changed by treatment with methanol–hydrochloric acid.

Anal. Calcd. for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.26; H, 6.72.

Hydrogenation of Mexicanin A.—A solution of 0.7 g. of the lactone in 80 ml. of ethyl acetate was hydrogenated with 10% palladium–charcoal until hydrogen absorption ceased. The solution was filtered and concentrated at reduced pressure. The gummy residue on crystallization from acetone–hexane afforded 0.31 g. of dihydromexicanin A (XVa), m.p. 148–149.5°, $[\alpha]_D$ −100°, λ_{max} 302 mμ (ε 45), λ_{max} in alkali 238 and 295 mμ (ε 12400 and 182); infrared bands at 3450 (hyroxyl), 1755 (γ-lactone) and 1635 cm.$^{-1}$ (double bond).

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; O, 24.21. Found: C, 68.27; H, 7.72; O, 24.13.

Material from the mother liquors was chromatographed over alumina. The initial benzene eluates yielded an additional 0.105 g. of XVa, m.p. 148–149°. Later fractions eluted isomexicanin A (XIIIa), wt. 0.6 g., m.p. 178–179° (plates from acetone–ether), $[\alpha]_D$ −83°, λ_{max} 221 mμ (ε 13800), λ_{max} in alkali 225 and 236 mμ (ε 14100 and 14000); infrared bands at 3300 (hydroxyl), 1740 (γ-lactone and cyclopentanone), 1675 (conjugated double bond) and 1628 cm.$^{-1}$ (isolated double bond).

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92; O, 24.40. Found: C, 68.93; H, 6.58; O, 24.90.

Dihydromexicanin A Acetate (XVb).—Acetylation of dihydromexicanin A with acetic anhydride–pyridine furnished small prisms from acetone–hexane, m.p. 142–143°, $[\alpha]_D$ −25°, infrared bands at 1750 and 1640 cm.$^{-1}$. The same substance was obtained in 65% yield by hydrogenation of Vb.

Anal. Calcd. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24; O, 26.11. Found: C, 66.49; H, 7.25; O, 26.66.

Dihydromexicanin A Oxide (XVI).—A solution of 0.1 g. of XVa in 5 ml. of chloroform was allowed to stand at 0° for 24 hr. with 2 ml. of 5% perbenzoic acid in chloroform. The solution was washed with 5% sodium hydroxide solution and water, dried and concentrated. The residue was recrystallized from ether–hexane; yield 0.035 g., m.p. 230–232°, $[\alpha]_D$ −71°, infrared band at 1755 cm.$^{-1}$ (combination of cyclopentanone and γ-lactone).

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19; O, 28.54. Found: C, 63.89; H, 7.13; O, 28.71.

Dehydrodihydromexicanin A (XX).—A solution of 0.25 g. of XVa in 8 ml. of acetic acid was allowed to stand for 1 hour with 0.2 g. of chromic acid in 5 ml. of 80% acetic acid. The mixture was diluted with water and extracted with chloroform. The organic layer was washed, dried and evaporated and the gummy residue recrystallized from ether; yield 0.09 g., m.p. 164–166°, $[\alpha]_D$ +44°, λ_{max} 300–302° mμ (ε 140); infrared bands at 1770 (γ-lactone), 1755 (cyclopentanone), 1710 (relatively weak cycloheptanone) and 1627 cm.$^{-1}$ (double bond).

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92; O, 24.40. Found: C, 68.29; H, 6.79; O, 24.70.

Selenium Dioxide Oxidation of XX.—A solution of 0.3 g. of XX in 30 ml. of acetic acid was refluxed with 150 mg. of sublimed selenium dioxide for 30 minutes, cooled, filtered, diluted with 100 ml. of chloroform, washed, dried and evaporated. The solid residue was taken up in benzene and passed through 3 g. of alumina. The eluate was concentrated and recrystallized from acetone–ether; yield of XXI, 0.14 g., m.p. 250–254°, $[\alpha]_D$ −73°, λ_{max} 300 mμ (ε 9400, plateau at 210–222, ε 5800); infrared maxima at 1782 (γ-lactone), 1725 (cycloheptanone), 1690 (cyclopentenone) and 1650 cm.$^{-1}$ (double bond).

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20; O, 24.59. Found: C, 68.79; H, 6.40; O, 24.70.

Tetrahydromexicanin A (XVIIa).—Hydrogenation of 0.8 g. of XVa in 50 ml. of acetic acid with 0.08 g. of prereduced platinum oxide until one equivalent of hydrogen was absorbed furnished 0.57 g. of XVIIa, m.p. 168–171°, which was recrystallized from acetone–hexane; m.p. 171–173°, $[\alpha]_D$ −19°; infrared bands at 3400 (hydroxyl), 1762 (γ-lactone) and 1722 cm.$^{-1}$ (cyclopentanone).

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33; O, 24.03. Found: C, 67.70; H, 8.33; O, 24.07.

The acetate XVIIb, prepared with pyridine–acetic anhydride, was recrystallized from ether–hexane; m.p. 121–122°, $[\alpha]_D$ −16.5°, infrared peaks at 1760 (γ-lactone) and 1738 cm.$^{-1}$ (cyclopentanone and acetate).

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84; O, 25.95. Found: C, 66.33; H, 7.68; O, 26.13.

Neohelenalin (Mexicanin D).—Neohelenalin as obtained from *H. mexicanum* H.B.K. had m.p. 252–253°, $[\alpha]_D$ +107°, λ_{max} 235 mμ (ε 17800), no depression on admixture of an authentic sample, infrared spectra superimposable.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92; C-methyl (two groups), 11.45. Found: C, 68.37; H, 6.92; C-methyl, 10.81.

The acetate XXIIb, prepared from acetic anhydride–pyridine, was recrystallized from acetone–methanol; m.p. 192–193°, $[\alpha]_D$ +129°, λ_{max} 230–232 and 304–310 mμ (ε 1900 and 263); infrared bands at 1760 (lactone), 1700 (cyclopentenone) and 1640 cm.$^{-1}$ (double bond).

Anal. Calcd. for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62; O, 26.29. Found: C, 67.35; H, 6.69; O, 26.15.

Hydrogenation of Mexicanin D.—A solution of 0.8 g. of the material obtained from the plant in 100 ml. of ethyl acetate was hydrogenated with 0.1 g. of 10% palladium–charcoal. The filtered solution was concentrated to small volume. Upon addition of ether, the dihydro derivative XXIVa crystallized, wt. 0.36 g., m.p. 280–283°. Further crystallization raised this to 306–308° dec. The substance proved to be identical with dihydroneohelenalin (*vide infra*). Its acetate XXIVb was prepared with acetic anhydride–sodium acetate; m.p. 155–157° from methanol, $[\alpha]_D$ −222°, λ_{max} 236 mμ (ε 20700); infrared bands at 1770 (γ-lactone), 1735 (acetate), 1695 and 1640 cm.$^{-1}$ (cyclopentenone).

Anal. Calcd. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24; O, 26.11. Found: C, 66.69; H, 7.20; O, 26.44.

The mother liquors of the hydrogenation crystallized from ether–hexane and furnished 0.39 g. of isonohelenalin (isomexicanin D, XXIII, m.p. 191–192° (needles from acetone–ether), $[\alpha]_D$ −28°, λ_{max} 230–231° and 304–306 (ε 24500 and 91); infrared maxima at 3300 (hydroxyl), 1740 (γ-lactone), 1685 and 1628 cm.$^{-1}$ (cyclopentenone).

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92; O, 24.40. Found: C, 68.84; H, 6.70; O, 24.70.

Hydrogenation of XXIIb, wt. 0.2 g., in 50 ml. of ethyl acetate with 10% palladium–charcoal until one equivalent of hydrogen was absorbed and crystallization of the residue from methanol yielded what is undoubtedly the C_{11}-epimer of XXIVb, wt. 0.12 g., m.p. 200–203°, $[\alpha]_D$ −33°, λ_{max} 234 and 308 mμ (ε 17000 and 70); infrared bands at 1770 (γ-lactone), 1750 (acetate), 1700 and 1640 cm.$^{-1}$ (cyclopentenone).

Anal. Calcd. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24; O, 26.11. Found: C, 66.22; H, 7.22; O, 26.70.

Dihydroneohelenalin was also obtained by isomerization of dihydromexicanin A. On refluxing 0.5 g. of the latter, dissolved in 30 ml. of methanol, with a solution of 0.5 g. of potassium bicarbonate in 10 ml. of water for 45 minutes, cooling, acidifying with acetic acid, and concentrating at reduced pressure, there was obtained a gum which was extracted with chloroform, washed and dried. Concentration to small volume followed by dilution with ether yielded XXIIa, wt. 0.1 g., m.p. after additional recrystallizations from chloroform–ether 303–305°,[31] $[\alpha]_D$ −34°, λ_{max} 238 mμ (ε 14800), no depression on admixture of an authentic specimen, infrared spectra superimposable.

Isomerization of 1 g. of dihydrohelenalin by the above procedure furnished 0.11 g. of dihydroneohelenalin. The mother liquors were chromatographed over alumina. The crystalline fractions eluted with benzene–hexane (2:1 and 3:1) were recrystallized from acetone–ether and furnished 0.18 g. of plates, m.p. 222–224°, identified as 2-methoxytetrahydrohelenalin (*vide infra*). The yield of XXVIIIa in this reaction was quite variable.

Attempts to isomerize XXIVa with *p*-toluenesulfonic acid in the manner successful with isotenulin resulted in recovery of starting material.

(31) The m.p., previously given as 270° (capillary), depends on the rate of heating.

Desoxotetrahydroneohelenalin.—A solution of 0.3 g. of XXIVa in 40 ml. of acetic acid and two drops of 70% perchloric acid was hydrogenated (A.R.) with 0.06 g. of platinum oxide until hydrogen absorption ceased. The solution was diluted with chloroform, washed, dried and the chloroform removed *in vacuo*. The residue was chromatographed over alumina. The crystalline fractions eluted with benzene were combined and recrystallized from acetone–hexane. This afforded needles, wt. 0.05 g., m.p. 175–176°, $[\alpha]_D$ +25°, infrared maxima at 3300 (hydroxyl) and 1770 cm.$^{-1}$ (γ-lactone).

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59; O, 19.12. Found: C, 71.40; H, 9.64; O, 19.10.

An isomeric substance was obtained by P. J. on hydrogenation of 0.4 g. of XXIVa in 50 ml. of 95% ethanol containing 2 ml. of ethanolic hydrogen chloride and 0.12 g. of platinum oxide in a Parr hydrogenator. Removal of solvent furnished a brown gum which was chromatographed over alumina (solvent benzene). Benzene–ether eluted 0.1 g. of an oil which slowly solidified. Recrystallization from benzene–petroleum ether furnished a solid, m.p. 151–152°, $[\alpha]^{25}_D$ −92.3°, infrared bands at 3500 (hydroxyl) and 1750 cm.$^{-1}$ (γ-lactone), no ultraviolet absorption.

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 71.39; H, 9.58. Found: C, 71.82; H, 9.69.

Hydrogenation of XXIVa thus results in reduction of the double bond after reduction and hydrogenolysis of the ketone function. This contrasts with results in the neotenulin series where the double bond remains unaffected.[4]

Ozonolysis of Dihydroneohelenalin.—A solution of 0.25 g. of XXIVa in a 3:2 mixture of acetic acid–ethyl acetate was ozonized at −10° for 2 hr. Most of the solvent was removed in an air stream, the remainder was diluted with ethyl acetate and reduced catalytically (0.14 g. of 10% palladium-on-charcoal) in a Parr hydrogenator. The filtered solution was concentrated. The residual gum exhibited infrared maxima at 1775 (γ-lactone) and 1710 cm.$^{-1}$ (shoulder at 1725 cm.$^{-1}$). It was dissolved in methanol and stirred for 12 hr. with a solution of 0.4 g. of sodium periodate in 20 ml. of water. After acidification with a little hydrochloric acid, it was extracted with chloroform. The chloroform extracted was washed, dried and evaporated. The residual froth partially crystallized on trituration with acetone–ether; crystallization from chloroform–petroleum ether (b.p. 35–60°) yielded 0.02 g. of the crystalline ketodilactone XXVI, m.p. 226–228° (uncor.), λ_{max} 289 mμ (ε 18), infrared bands at 1775–1780 (double strength, two γ-lactones) and 1706 cm.$^{-1}$ (cycloheptanone).

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39; O, 31.71. Found: C, 61.69; H, 6.25; O, 31.62.

2-Methoxydihydrohelenalin (XXVIIa).—A solution of 2 g. of helenalin in 100 ml. of methanol, 2.5 ml. of 47% hydriodic acid and 2.5 ml. of water was refluxed for 1 hour, concentrated to small volume and chilled. Prisms, wt. 0.77 g., separated. Recrystallization from acetone–ether furnished XXVIIa, m.p. 179–181°, $[\alpha]_D$ +136°, λ_{max} 208 mμ (ε 8000); infrared bands at 3550, 1755 (shoulder at 1740) and 1660 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{22}O_5$: C, 65.29; H, 7.54; O, 27.17; $-OCH_3$, 10.01. Found: C, 65.44; H, 7.43; O, 27.08; $-OCH_3$, 10.27.

2-Methoxydihydrohelenalin Acetate (XXVIIb).—A mixture of 2.8 g. of acetylhelenalin, 200 ml. of methanol, 10 ml. of concd. HCl and 10 ml. of water was refluxed, concentrated to small volume and diluted with water. The product, wt. 1.9 g., was recrystallized from ethyl acetate–ether; m.p. 221–223°, $[\alpha]_D$ +42°, λ_{max} 208 mμ (ε 8500), infrared bands at 1740 (broad) and 1755 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19; O, 28.54; C-methyl, 9.32; acetyl, 12.79. Found: C, 64.04; H, 7.03; O, 28.78; C-methyl, 9.30; acetyl, 12.58.

The substance was also prepared by acetylation of XXVIIa with acetic anhydride–pyridine.

Treatment of 0.5 g. of XXVIIa with 2 ml. of hydriodic acid at room temperature overnight followed by dilution with water regenerated 0.15 g. of recrystallized acetylhelenalin.

2-Methoxytetrahydrohelenalin (XXVIIIa).—Treatment of 0.9 g. of VIIa with hydriodic acid–methanol afforded 0.28 g. of XXVIIIa after recrystallization from methanol and acetone–ether; m.p. 219–221°, $[\alpha]_D$ +30°; infrared bands at 3450, 1770 and 1745 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16; O, 26.90. Found: C, 64.69; H, 8.31; O, 27.10.

This substance was also prepared in 70% yield by hydrogenation of XXVIIa (solvent ethyl acetate, catalyst palladium-on-calcium carbonate) and accompanied dihydroneohelenalin in the isomerization of VIIa (*vide supra*).

2-Methoxytetrahydrohelenalin Acetate (XXVIIIb).—Hydrogenation of 0.1 g. in ethyl acetate with palladium-on-calcium carbonate, followed by recrystallization from ethyl acetate–ether furnished prisms, m.p. 186–187°, $[\alpha]_D$ +43°, infrared bands at 1760 and 1738 cm.$^{-1}$.

Anal. Calcd. $C_{18}H_{26}O_6$: C, 63.88; H, 7.75; O, 28.37. Found: C, 63.79; H, 7.89; O, 28.15.

This substance was also prepared from VIIb by treatment with methanol, hydrochloric acid and water (yield 40%) and by acetylation of XXVIIIa. Hydriodic acid at room temperature regenerated VIIb in 50% yield.

2-Methoxydehydrotetrahydrohelenalin.—Oxidation of 0.15 g. of XXVIIIa in 5 ml. of acetic acid with 0.1 g. of chromium oxide in 0.5 ml. of water and 2 ml. of acetic acid at room temperature for 1 hour, dilution with water and extraction with chloroform yielded 2-methoxydehydrotetrahydrohelenalin from the organic layer after washing and drying; m.p. 166–167° (from acetone–hexane), $[\alpha]D$ −32.8°, λ_{max} 296 mμ (ε 109).

Anal. Calcd. for $C_{16}H_{22}O_5$: C, 65.29; H, 7.54; O, 27.17. Found: C, 65.13; H, 7.26; O, 27.19.

Rotatory Dispersion Curves.—Balduilin[32] (in dioxane, *c* 0.116): $(\alpha)_{700}$ +29, $(\alpha)_{589}$ + 43°, $(\alpha)_{360}$ −612°, $(\alpha)_{277.5}$ +2890°; tetrahydrobalduilin[32] (in methanol, *c* 0.0675): $(\alpha)_{700}$ −18°, $(\alpha)_{589}$ +28°, $(\alpha)_{315}$ + 903°, $(\alpha)_{280}$ −732, $(\alpha)_{264}$ −558°; allotetrahydrohelenalin[32] (in methanol, *c* 0.117). $(\alpha)_{700}$ +77°, $(\alpha)_{589}$ +126°, $(\alpha)_{315}$ +1985, $(\alpha)_{277.5}$ −1093°, $(\alpha)_{255}$ −488°; Neohelenalin[33] (in dioxane, *c* 0.679): $(\alpha)_{700}$ + 51°, $(\alpha)_{589}$ +131°, $(\alpha)_{332.5}$ +1048°, $(\alpha)_{312.5}$ +779°, $(\alpha)_{280}$ +1600°; tetrahydromexicanin A[33] (in dioxane, *c* 0.059): $(\alpha)_{700}$ −22°, $(\alpha)_{589}$ −8°, $(\alpha)_{500}$ +12°, $(\alpha)_{312.5}$ −471°, $(\alpha)_{270}$ +402°, $(\alpha)_{265}$ +380°; tetrahydromexicanin A acetate[33] (in dioxane, *c* 0.050): $(\alpha)_{700}$ +4°, $(\alpha)_{589}$ +10°, $(\alpha)_{320}$ −816°, $(\alpha)_{275}$ +822°, $(\alpha)_{265}$ +730°; 2-methoxydihydrohelenalin acetate[33] (in dioxane, *c* 0.054): $(\alpha)_{700}$ +53°, $(\alpha)_{589}$ +72°, $(\alpha)_{317.5}$ +1231°, $(\alpha)_{280}$ −931°, $(\alpha)_{270}$ −452°; 2-methoxydihydrohelenalin[33] (in dioxane, *c* 0.050): $(\alpha)_{700}$ + 42°, $(\alpha)_{589}$ +72°, $(\alpha)_{315}$ +1601°, $(\alpha)_{282.5}$ −428°, $(\alpha)_{270}$ +301°.

(32) We wish to express our appreciation to Dr. C. Djerassi and his group for determining these curves at Wayne State University.

(33) These curves were determined in the laboratories of Syntex S.A., Mexico, D.F.

[CONTRIBUTION FROM THE UNION CARBIDE RESEARCH INSTITUTE, UNION CARBIDE CORPORATION, TARRYTOWN, N. Y.]

The Conjugate Acids of 2,5-Dimethylpyrrole

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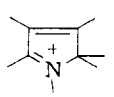
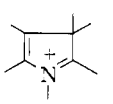
While protonation of methylpyrroles normally occurs in the α-position, competitive β-protonation can be observed in the n.m.r. spectra of 2,5-dimethylpyrrole (~30% β-protonation) and certain of its N-substituted derivatives. Separate bands can be identified in the electronic spectra of the isomeric salts in solution and used together with the n.m.r. data to determine pK_a's toward protonation at each site. Observation over a varying medium of the distribution ratio between two conjugate acids derived from the same base permits direct verification that both are subject to parallel indicator acidity functions over the entire range of composition in aqueous sulfuric acid. The order of C-protonation rates of the bases in strong acids is shown to be opposite from that of stability of the conjugate acids.

Previous studies[1] by proton magnetic resonance of the hydrochloride salts of alkylpyrroles show a general preference for α-protonation, and indicate that α-methyl groups direct protonation to the opposite α-position while β-methyl substitution orients protonation to the adjacent α-site.[2] Both orientations are associated with a base strengthening effect at the position cited.[1] β-Protonation of the indole ring occurs with high specificity[3] and methyl substitution in either the 1- or 2-positions is base strengthening.[4] In both ring systems methyl substitution decreases basicity on the carbon atom bearing the methyl group. Less direct evidence points to a substantial base strengthening at the 2-position due to 3-methyl substitution on the indole ring.[3] On the basis of the assumption that attached methyl groups stabilize in decreasing order carbonium ions, double bonds and tetrahedral carbon atoms, all of the above facts are consistent with the description of the conjugate acids in terms of the normal structures I or II and the "excited" structures III

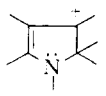


I

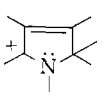


II

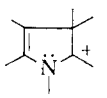
through V. The β-protonation of indole would be a first-order effect arising from the fact that two Kekulé



III



IV



V

structures can be written in a fused benzene ring only in the case of II. In pyrrole, the orientation is determined by the presence of two excited structures III and IV opposed to the single structure V. Since this involves higher order structures, the specificity is less than for indole. As the heteroatom electronegativity increases, the weighting of the excited structures relative to the normal becomes greater, and this plus the fact that more singly charged excited structures (five *vs.* two) can be written for the α-protonated isomer when a fused aromatic ring is present accommodates the observation that electrophilic substitution in benzofuran occurs preferentially in the α-position.[5]

The orientation rules for methyl substituents follow directly from the positions of the charge in I through V and of the double bonds in the uncharged structures for the bases. One would predict from this argument that addition of a 2-methyl group to pyrrole would favor protonation at the 3- and 5-positions, have little effect at the 4-position and decrease basicity at the 2-position. A second methyl group at the 5-position would similarly increase basicity at positions 2 and 4, not further alter position 3, and oppose 5-protonation. There would hence be some cancellation of opposing effects of the α-positions, but only a net increase in basicity at the β-positions. It would therefore follow that in 2,5-dimethylpyrrole the C-methyl groups would have their greatest tendency to oppose the normal preference for α-protonation in the pyrrole ring. N-Methyl substitution should result in a further increase in relative basicity at the β-position due to a greater weighting of the normal structure II than of I.

The proton magnetic resonance spectrum of a solution of 2,5-dimethylpyrrole in 12 *M* sulfuric acid is shown in Fig. 1.[6] The line positions indicated are

(1) R. J. Abraham, E. Bullock and S. S. Mitra, *Can. J. Chem.*, **37**, 1859 (1959).

(2) The directive effects are indicated by single examples in the original work, and some of the proton resonance lines are improperly assigned (see subsequent text). The chemical structures assigned are nevertheless the correct ones, and a more extensive study of the methylpyrrole conjugate acids in this Laboratory confirms the directivities.

(3) R. L. Hinman and E. B. Whipple, *J. Am. Chem. Soc.*, **84**, 2534 (1962).

(4) R. L. Hinman and J. Lang, A.C.S. Abstracts, Sept., 1961, p. 98 Q.

(5) M. W. Farrar and R. Levine, *J. Am. Chem. Soc.*, **72**, 4433 (1950).

(6) Abraham, Bullock and Mitra[1] reported a complex spectrum for hydrochloric acid solutions of this base. We observed similar patterns in sulfuric acid solutions unless air was excluded during sample preparation. With these precautions the patterns observed in Fig. 1 were stable over several days.