Tetrahedron, 1963, Vol. 19, pp. 2317 to 2322. Pergamon Press Ltd. Printed in Northern Ireland

CONSTITUENTS OF *HELENIUM* SPECIES XIV

THE STRUCTURE OF MEXICANIN E[1]

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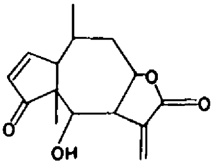
(*Received* 24 *April, in revised form* 27 *May* 1963)

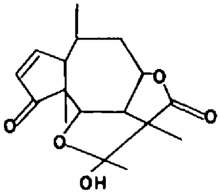
Abstract—The structure of the norsesquiterpene lactone Mexicanin E is shown to be IV.

Mexicanin E, a constituent of a variety of *Helenium mexicanum* H.B.K. found in the valley of Mexico[4] and more recently isolated from *H. ooclinium* Gray[5], has the formula $C_{14}H_{16}O_3$ and is the first representative of the new class of norsesquiterpene lactones.

We have demonstrated recently[1,6] that other constituents of *Helenium* species, such as helenalin (I), tenulin (II), mexicanin A and mexicanin C, contain an "abnormal" carbon skeleton which can be derived formally from that of a regularly constituted isoprenoid guaianolide (III) by invoking a methyl group migration during biogenesis. It appeared that congeneric norsesquiterpene lactones might plausibly be formed through loss of this methyl group and that revision of the structure previously suggested[7] for mexicanin E would be in order. In the present communication we show the correctness of this hypothesis and prove that mexicanin E is represented by formula IV.



I



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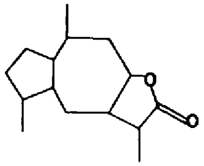

III

It has been shown previously[7] that mexicanin E is an α,β-unsaturated cyclopentenone and, like helenalin (I), contains an exocyclic methylene group conjugated with a γ-lactone function. Partial reduction to dihydromexicanin E (V) and complete

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[1] Publication No. 152 from the Instituto de Quimica de la Universidad Nacional Autonoma de Mexico. Work at the Florida State University supported in part by a grant from the United States Public Health Service (RG-5814). Previous paper, W. Herz, A. Romo de Vivar, J. Romo and N. Viswanathan, *J. Amer. Chem. Soc.*, **85**, 19 (1963).

[2] Instituto de Quimica de la Universidad Nacional Autonoma de Mexico.

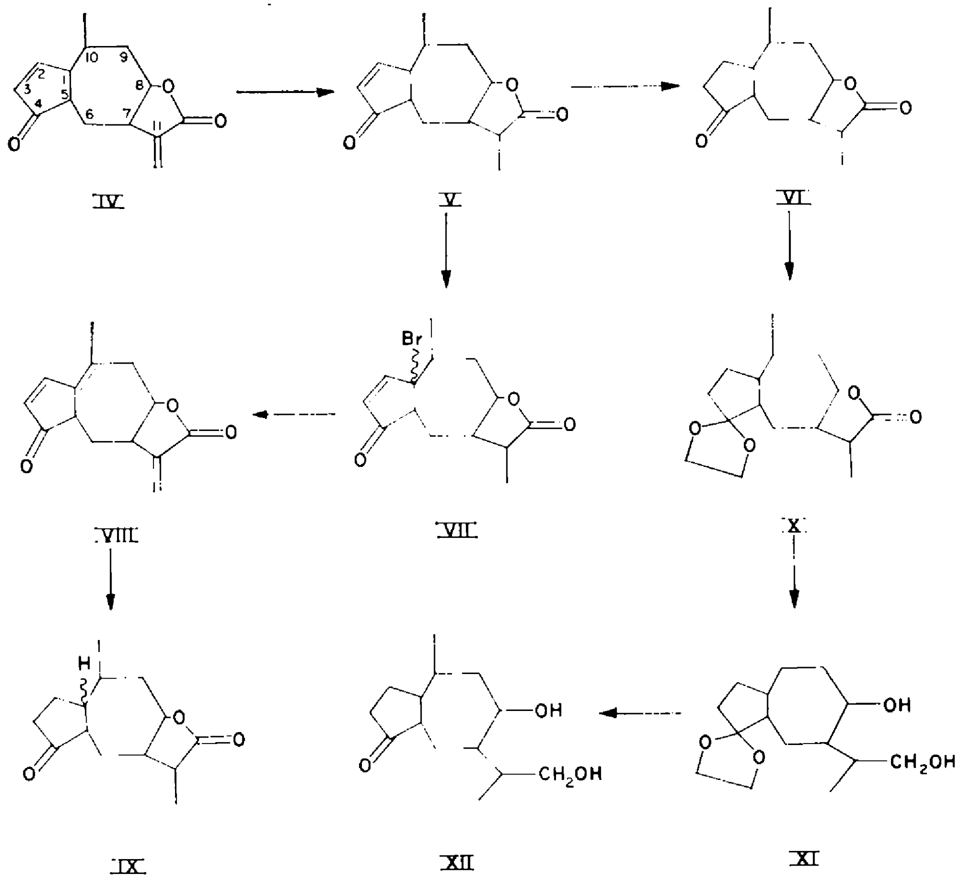
[3] Department of Chemistry, The Florida State University.

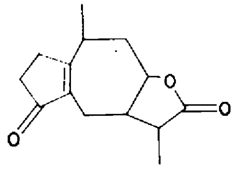
[4] A. Romo de Vivar and J. Romo, *Ciencia, Mex.*, **21**, No. 1, 33 (1961). This variety also yields helenalin and mexicanins A-D and F-H. A collection of *H. mexicanum* from Oaxaca State furnished helenalin and mexicanin I.

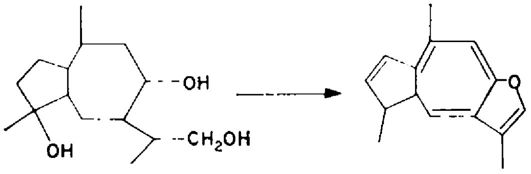
[5] W. Herz, *J. Org. Chem.*, **28**, 4043 (1962).

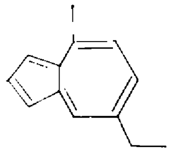
[6] W. Herz, W. A. Rohde, K. Rabindran, P. Jayaraman and N. Viswanathan, *J. Amer. Chem. Soc.*, **84**, 3857 (1962).

[7] A. Romo de Vivar and J. Romo, *J. Amer. Chem. Soc.*, **83**, 2326 (1961).




XVIII

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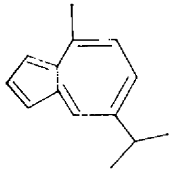
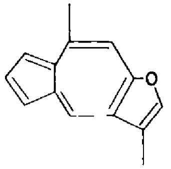
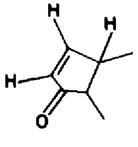

XVI

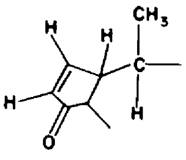

XVII

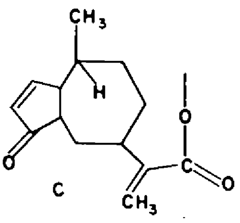
reduction to tetrahydromexicanin E (VI) could be effected. Sodium borohydride reduction followed by dehydrogenation furnished three unidentified azulenes of empirical formula $C_{13}H_{14}$, $C_{14}H_{16}$ and $C_{14}H_{14}O$ which indicated the presence of a perhydroazulene nucleus.

The N.M.R. spectrum of mexicanin E demonstrated the presence of *four* vinyl protons, thus disproving the previously derived structure[7]. The vinyl protons exhibited the same chemical shifts and splitting characteristics as the four vinyl protons of helenalin[6]. Two cyclopentenone vinyl proton signals at 7·75 (β-hydrogen) and 6·19 p.p.m. (α-hydrogen)[8] were split into quadruplets by spin coupling to each other ($J = 6$) and to a γ-hydrogen atom ($J = 2$) as required by partial formula A. Part of the high field quartet was superimposed on one of the two doublets characteristic of the exocyclic methylene group[9] which appeared at 6·15 and 5·64 p.p.m. ($J = 1·5$). Justification for these assignments was provided by comparison with the N.M.R. spectrum of V which retained the vinyl proton signals of the cyclopentenone chromophore, but had lost the exocyclic methylene group and contained two methyl doublets.

Equally significant was the observation that the N.M.R. spectrum of mexicanin E exhibited the presence of *only one methyl group*. Since this was secondary (doublet at 1·13 p.p.m., $J = 5·5$), it was obvious that the tertiary methyl group at C_5, so characteristic of constituents of *Helenium* species, was missing and that the original assumption to explain the genesis of mexicanin E was probably correct.


A


B


C

The following reaction sequence permitted expansion of partial structure A to B. Dihydromexicanin E (V) was converted to a bromo derivative VII by treatment with N-bromosuccinimide. VII retained the cyclopentenone chromophore (λ_{max} 220 mμ, ε_{max} 8170, infrared bands at 1760, 1710 and 1580 cm^{-1}). Treatment of VII with potassium acetate yielded a dienone whose properties were in accord[1,6] with formula VIII (λ_{max} 299 mμ, ε 12700, infrared bands at 1760 and 1680 cm^{-1}). The N.M.R. spectrum of VIII had no additional vinyl proton signals but exhibited only one methyl doublet at 1·12 p.p.m. ($J = 7$) due to the C_{11} methyl group and a new vinyl methyl singlet at 2·01 p.p.m. Hence the lone methyl group of mexicanin E is *delta* to the cyclopentenone carbonyl. Catalytic hydrogenation converted VIII to a new substance IX, epimeric with VI at C_1 or C_{10} or both.

Partial formula B, coupled with the formation of azulenes on dehydrogenation, suggested C for mexicanin E where the side chain was placed at C_7 for biogenetic reasons. Inspection of the N.M.R. spectrum did not permit a decision between the

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

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

two possible lactone ring orientations. A signal near 4·6 p.p.m. whose chemical shift was characteristic of hydrogen on carbon carrying a lactone ether oxygen did not resemble the complex triplet characteristic of lactone ring closure to C_8[1,6] in compounds of the helenalin and tenulin series, but at the same time was more complex than was to be expected if the lactone ring were closed to C_8.

Attachment of the side chain to C_7 and lactone ring closure to C_8 was definitely proved in the following manner. The ethylene ketal (X) of VI was reduced with lithium aluminum hydride and the resulting ketal diol XI cleaved to the ketodiol XII. Treatment of XII with acid or base did not result in the appearance of α,β-unsaturated ketone absorption, an observation which suggested that the lactone ring was closed to C_8. Similarly, dinitrophenylhydrazone formation was not accompanied by dehydration. Positive proof for lactone ring closure to C_8 was obtained as follows. Reaction of XII with methylmagnesium bromide followed by dehydrogenation with palladium charcoal yielded linderazulene (XIV), not artemazulene which would have been obtained had the lactone ring been closed to C_6. Hence mexicanin E is IV.

The three azulenes previously isolated are undoubtedly 4-methyl-7-ethylazulene (1-norchamazulene, XV), 4-methyl-7-isopropylazulene (1-norguaiazulene, XVI) and 3,8-dimethylfuro(3,2-*f*)azulene (1-norlinderazulene, XVII) and the isomeric cyclopentenone obtained by alkali treatment of dihydromexicanin E must be XVIII.

The optical rotatory dispersion curves of VI, its C_5 epimer and XI offer no clue to the absolute stereochemistry. VI and IX, which must differ at C_1 or C_{10} or both, exhibit multiple positive Cotton effect curves of very similar shape and amplitude. This suggests that the asymmetric center at C_1 has been preserved. The oily, stable C_5-epimer of VI surprisingly enough exhibits a greatly enhanced positive Cotton effect curve. An inversion of the curves would have been expected if comparisons of mexicanin E derivatives with appropriate steroids had been valid[10].

EXPERIMENTAL[11]

Mexicanin E. Mexicanin E was isolated from *Helenium mexicanum* H.B.K. (Valley of Mexico) as described previously.[4,7] Its ORD curve (dioxane, *c*, 0·0725) exhibited the following characteristics: $[\alpha]_{700}$ −45°, $[\alpha]_{689}$ −62°, $[\alpha]_{367.5}$ −385°, $[\alpha]_{365}$ −300° shoulder), $[\alpha]_{270}$ −7°, $[\alpha]_{280}$ −1390° (no minimum), N.M.R. spectrum[12] 7·75 dd (6, 2, H_2) 6·19 dd (6, 2, H_3), 6·15 d and 5·64 d (1·5. $=CH_2$), 4·6 c (H_8), 1·135 d (5·5, C_{10}-methyl).

Dihydromexicanin E (*V*). This substance was prepared as described previously[7], N.M.R. spectrum 7·78 dd (6, 2, H_2), 6·18 dd (6, 2, H_3), 4·58 c (H_8), 1·15 d (5) and 1·13 d (7, C_{10}- and C_{11}-methyl).

Ozonolysis of Dihydromexicanin E.[13] Ozonolysis of V. paralleled the results in the helenalin[1] and tenulin[6] series and confirmed the presence of the cyclopentenone chromophore, but the yields of the lactol XVIII were disappointingly small. A solution of 0·2 g of V in 25 ml of chloroform was ozonized at −10° for 1·5 hr. The chloroform solution was shaken with 25 ml of water overnight. The chloroform layer was dried, evaporated and the residual gum extracted by stirring with sodium carbonate solution for 6 hr. The aqueous extract was extracted with chloroform. Acidification of the aqueous alkaline layer followed by extraction with chloroform gave the lactol XIX, yield 0·015 g,

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[10] N. L. Allinger, R. B. Hermann, C. Djerassi, *J. Org. Chem.*, **25**, 922 (1960); J. F. Bielmann and G. Ourisson, *Bull. soc. chim. Paris* 331 (1962).

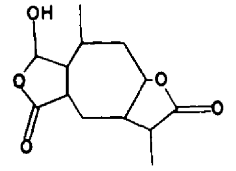
[11] M.P.'s and b.p.'s are uncorrected. Analyses by Dr. F. Pascher, Bonn, Germany. Rotations in chloroform unless specified otherwise.

[12] Singlets are unmarked, multiplets are described as follows: d, doublet; dd, doublet of doublets; t, triplet; q, quartet; c, complex band whose center is given.

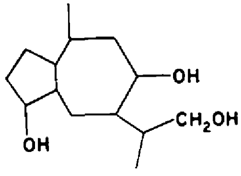
[13] This experiment was carried out by Dr. N. Viswanathan.

m.p. 192–194° (from chloroform–petroleum ether), infrared bands (KBr pellet) at 3500, 3300, 1765 and 1755 cm^{-1}.

Anal. Found: C, 61·78; H, 7·64 O, 31·36. Calcd. for $C_{13}H_{18}O_5$: C, 61·40; H, 7·14; O, 31·46



XIX



XX

1-*Bromodihydromexicanin E* (*VII*). A solution of 0·5 g of dihydromexicanin E, 0·4 g of N-bromosuccinimide, 0·003 g of benzoyl peroxide and 30 ml of carbon tetrachloride was refluxed for 30 min (irradiation with a flood lamp), cooled, filtered, washed, dried and concentrated at reduced pressure. The residue was recrystallized from ether, yield 0·435 g, m.p. 117–119° (dec.). The analytical sample, long prismatic needles, melted at 128–130° (dec.) and decomposed slowly on standing which caused analytical difficulties, $[\alpha]_D^{20}$ +223°, (C, 0·8) λ_{max} 220 mμ, ϵ 8170, infrared bands at 1760 (γ-lactone), 1710 and 1580 cm^{-1} (cyclopentenone).

Anal. Found: C, 54·56; H, 5·68; O, 15·08, Br, 24·77. Calcd. for $C_{14}H_{17}O_3Br$: C, 53·68; H, 5·46; O, 15·32; Br, 25·51.

1,10-*Dehydrodihydromexicanin C* (*VIII*). A solution of 0·21 g of VII, 15 ml of acetic acid and 1·5 g of freshly fused potassium acetate was refluxed for 2 hr, cooled, diluted with water and extracted with chloroform. The extract was washed, dried and concentrated, the oily residue taken up in benzene–hexane (1:5) and chromatographed over 10 g of alumina. The crystalline fractions eluted with benzene–hexane (1:4, 1:3 and 1:2) were combined and recrystallized from acetone–hexane. There was obtained 0·07 g of needles, m.p. 148–150°, $[\alpha]_D^{20}$ −785°, (*C*, 0·6) λ_{max} 299 mμ, 12700, infrared bands at 1760 (γ-lactone and 1680 (cyclopentenone), N.M.R. signals at 7·94 d (*J* 5·5 c/s, H_2), 6·13 d (5·5, H_3), 4·55 (C, H_6), 2·01 (C_{10}-methyl), 1·12 d (C_{11}-methyl).

Anal. Found: C, 72·39; H, 6·99; O, 20·54. Calcd. for $C_{14}H_{16}O_3$: C, 72·39; H, 6·94; O, 20·67.

Catalytic reduction of VIII. A solution of 0·175 g of VIII in 30 ml of ethyl acetate was reduced with 0·03 g of pre-reduced 10% palladium-on-charcoal. Hydrogen uptake ceased after absorption of 2 mol. equivs. The solution was filtered and evaporated to dryness. The residue on crystallization from ether–hexane afforded 0·12 g of needles, m.p. 140–143°. The analytical sample of this tetrahydromexicanin E epimer (IX) melted at 146–148°, $[\alpha]_D^{20}$ +34·4°, (*C*, 0·6) infrared bands at 1770 (γ-lactone) and 1735 cm^{-1} (cyclopentanone), ORD curve (in dioxane, C, 0·06425) $[\alpha]_{700}$ +64°, $[\alpha]_{589}$ +47, $[\alpha]_{332.5}$ +1483°, $[\alpha]_{315}$ +1066°, $[\alpha]_{312.5}$ +1097°, $[\alpha]_{277}$ −1332°, $[\alpha]_{265}$ −971°.

Anal. Found: C, 71·32; H, 8·76; O, 20·24. Calcd. for $C_{14}H_{20}O_3$: C, 71·16; H, 8·53; O, 20·31.

Tetrahydromexicanin E (*VI*). This substance was prepared as described previously[7], N.M.R. spectrum 4·48 c (H_6), 1·15 d (8) and 1·04 d (5, C_{10}- and C_{11}-methyl), optical rotatory dispersion curve (in dioxan, *c* 0·0645) $[\alpha]_{700}$ +39°, $[\alpha]_{589}$ +70°, $[\alpha]_{325}$ +1948, $[\alpha]_{317.5}$ +1520, $[\alpha]_{315}$ +1635°, $[\alpha]_{280}$ −1115° (no minimum). The epimer[7], prepared by alkaline treatment of V had the following optical rotatory dispersion curve (methanol, *c* 0·0177) $[\alpha]_{600}$ +500, $[\alpha]_{589}$ +690, $[\alpha]_{312.5}$ +9520, $[\alpha]_{270}$ −8640 (last reading).

The ethylene ketal of VI was prepared as follows. A solution of 0·8 g of VI and 0·08 g of p-toluene sulfonic acid in 50 ml of benzene and 10 ml of ethylene glycol was refluxed for 40 hr (water trap), cooled, washed, dried and the benzene removed *in vacuo*. The residue was recrystallized from ether–hexane, yield 0·26 g, m.p. 145–148°. The analytical sample of X melted at 149–150°, $[\alpha]_D^{20}$ −42°, (*C*, 0·8) infrared band at 1760 (γ-lactone).

Anal. Found: C, 68·28; H, 8·41; O, 22·77. Calcd. for $C_{16}H_{24}O_4$: C, 68·54; H, 8·63; O, 22·83.

Lithium Aluminium Hydride Reduction of VI. A solution of 0·7 g of VI in 40 ml of tetrahydrofuran was refluxed with 0·7 g of $LiAlH_4$ for 6 hr, cooled, the excess hydride decomposed with ethyl acetate and 5 ml of water was added. The mixture was filtered, the precipitate washed with chloroform and the combined filtrate and washings were dried and evaporated to dryness. Crystallization from ether afforded prisms of triol XX, m.p. 163–164°, $[\alpha]_D^{20}$ −46·3 (*C*, 0·8) broad infrared band at 3280 cm^{-1}.

Anal. Found: C, 69·49; H, 10·76; O, 19·85. Calcd. for $C_{14}H_{26}O_3$: C, 69·38; H, 10·81; O, 19·81.

Lithium Aluminum Hydride Reduction of X. Reduction of 1·5 g of the ketal X in 40 ml of tetrahydrofuran with 1·5 g of $LiAlH_4$ in the manner described in the previous section yielded 0·82 g of the ketaldiol XI, m.p. 120–122° from ether–hexane. The analytical sample melted at 122–124°, $[\alpha]_D^{20}$ −24°, (*C*, 0·6) broad infrared band at 3250 cm^{-1}.

Anal. Found: C, 67·81; H, 9·54; O, 22·68. Calcd. for $C_{16}H_{28}O_4$: C, 67·57; H. 9·92; O, 22·51.

Hydrolysis of the ketaldiol XI, wt. 1 g, with 20 ml of methanol, 0·5 ml of conc. hydrochloric acid and 1 ml of water at room temperature for 4 hr, dilution with water, extraction with chloroform, drying and removal of solvent yielded an oil (XII) wt. 0·83 g, infrared bands at 3300 (broad) and 1730 cm^{-1} (cyclopentanone), λ_{max} 278–282 mμ (ε 80), $[\alpha]_D^{22}$ +107·3° (*c*, 4). The material did not develop a maximum corresponding to that of an α, β-unsaturated ketone after treatment with potassium hydroxide solution or dilute hydrochloric acid. The orange dinitrophenylhydrazone melted at 175° (methanol–ether), λ_{max} (chloroform) 368 mμ (ε 24000).

Anal. Found: C, 57·04; H, 6·43; N, 12·41; O, 23·50. Calcd. for $C_{20}H_{28}N_4O_6$: C, 57·13; H, 6·71; N, 13·33; O, 22·83.

Linderazulene. A solution of 0·7 g of XII in 40 ml of benzene was treated with 10 ml of a 3 M methyl magnesium bromide solution, refluxed for 8 hr and decomposed with ammonium chloride solution. The organic layer was dried and concentrated; the residual oil, wt. 0·66 g, did not exhibit a carbonyl band in the infrared. Dehydrogenation with 3 g of selenium at 385–390° for 20 min in a nitrogen atmosphere was followed by extraction with hexane. The hexane solution was chromatographed over 40 g of alumina; the blue fraction was concentrated, dissolved in 6 ml of 80% phosphoric acid, extracted with benzene and the red complex decomposed with ice water. The regenerated azulene was extracted with hexane. The hexane solution was dried and evaporated and the residual oil, wt. 0·045 g, converted to the trinitrobenzene complex, wt. 0·025 g, m.p. 150–151° after crystallization from ethanol.

Anal. Found: C, 59·73; H, 4·59; N, 9·30; O, 26·30. Calcd. for $C_{21}H_{17}N_3O_7$: C, 59·57; H, 4·05; N, 9·93; O, 26·45.

This material was identical in all respects (m.p., mixed m.p., chromatographic behavior) with an authentic sample of linderazulene kindly furnished by Dr. K. Takeda.