Phytochemistry, 1972, Vol. 11, pp. 1803 to 1808. Pergamon Press. Printed in England.

TERPENOIDS OF *PEREZIA HEBECLADA**

P. Joseph-Nathan, Ma. P. González and V. M. Rodríguez

Departamento de Química del Centro de Investigación y de Estudios Avanzados,
Instituto Politécnico Nacional, P.O. Box 14–740, México 14, D.F., México

(*Received* 19 *October* 1971)

Abstract—Perezone (I), hydroxyperezone (IIa), hydroxyperezone monoisovalerate (IIb), α- (IIIa) and β-pipitzols (IVa) and the new compounds α- (Va), β- (VIa) and γ-perezols (Ve) were found in the roots of *P. hebeclada*. The structures and stereochemistry of the perezols were established by chemical evidence and comparison of their spectral properties with those of the known α- (IIIa) and β-pipitzols (IVa).

In continuing studies on perezone and related terpenoids of *Perezia adnata* (Compositae),[1–9] we examined the roots of an unidentified *Perezia* species from the local market and obtained three new perezols. Extracts of the roots of *Perezia hebeclada* (A. Gray) collected locally also furnished a crystalline mixture (m.p. 128–132°) of the same perezols, together with perezone (I), hydroxyperezone (IIa) hydroxyperezone[10] monoisovalerate (IIb), α-pipitzol (IIIa)[7] and β-pipitzol (IVa).[7]

Fractional crystallization of the colorless crystalline mixture m.p. 128–132° gave a mixture of α- and β-perezols m.p. 156–158°, and pure γ-perezol m.p. 182–184°.

The structure of γ-perezol, $C_{15}H_{20}O_4$, was easily determined after comparing its spectral properties with those of the known[7] α-pipitzol (IIIa). Both compounds gave $FeCl_3$ colours, showed UV absorption at 242 and 280 nm (ϵ 4000 and 7800 for α-pipitzol and ϵ 3400 and

---

* An abstract of this work appeared recently. See Ref. 1.

[1] P. Joseph-Nathan and Ma. P. González, *XXIII International Congress of Pure and Applied Chemistry* Abstracts of Papers p. 140, Boston (1971).

[2] Leopoldo Río de la Loza, *Disertación presentada a la Academia de Medicina*, Mexico City, October 30, (1852).

[3] M. Martínez, *Las Plantas Medicinales de México* (edited by Botas), p. 258, Mexico City (1959).

[4] M. C. Wild, *Ann.* **95,** 188 (1855); F. Mylius, *Chem. Ber.* **18,** 480 (1885); **18,** 936 (1885); R. Anschütz, *Chem. Ber.* **18,** 709 (1885); R. Anschütz and W. Leather, *Chem. Ber.* **18,** 715 (1885); J. McC. Sanders, *Proc. Chem. Soc.* **22,** 134 (1906); F. G. P. Remfry, *J. Chem. Soc.* **103,** 1076 (1913); Fr. Fichter, M. Jetzer and R. Leepin, *Ann.* **395,** 1 (1913); F. Kögl and A. G. Boer, *Rec. Trav. Chim.* **54,** 779 (1935); K. Yamaguchi, *J. Pharm. Soc. Japan* **62,** 491 (1942); D. Arigoni and O. Jeger, *Helv. Chim. Acta* **37,** 881 (1954).

[5] F. Walls, J. Padilla, P. Joseph-Nathan, M. Salmón and J. Romo, *Bol. Inst. Quím. Univ. Nal. Autón. Méx.* **17,** 3 (1965).

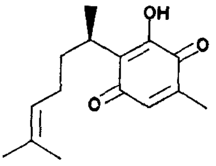
[6] (a) D. A. Archer and R. H. Thomson, *Chem. Commun.* 354 (1965); (b) R. B. Bates, S. K. Paknikar and V. P. Talacher, *Chem. & Ind.* 1793 (1965); (c) E. R. Wagner, R. D. Moss, R. M. Brooker, J. P. Heeschen, W. J. Potts and M. L. Dilling, *Tetrahedron Letters* 4233 (1965).

[7] F. Walls, J. Padilla, P. Joseph-Nathan, F. Giral and J. Romo, *Tetrahedron Letters* 1577 (1965); F. Walls, J. Padilla, P. Joseph-Nathan, F. Giral, M. Escobar and J. Romo, *Tetrahedron* **22,** 2387 (1966).

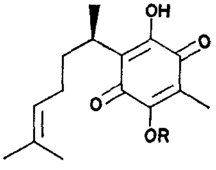
[8] D. A. Archer and R. H. Thomson, *J. Chem. Soc.* C, 1710 (1967); P. Joseph-Nathan, J. Reyes and Ma. P. González, *Tetrahedron* **24,** 4007 (1968).

[9] J. Padilla, J. Romo, F. Walls and P. Crabbé, *Rev. Soc. Quim. Méx.* **11,** 7 (1967); P. Joseph-Nathan, Ma. P. González and E. Díaz, *Rev. Soc. Quim. Méx.* **13,** 57 (1969); P. Joseph-Nathan and Ma. P. González, *Can. J. Chem.* **47,** 2465 (1969); P. Joseph-Nathan, Ma. P. González, L. F. Johnson and J. N. Shoolery, *Org. Magn. Res.* **3,** 23 (1971).

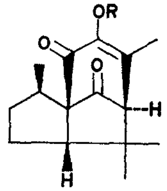
[10] T. García, E. Domíguez and J. Romo, *Bol. Inst. Quim. Univ. Nal. Autón. Méx.* **17,** 16 (1965).



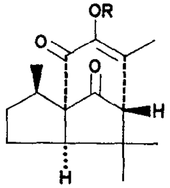
(I)



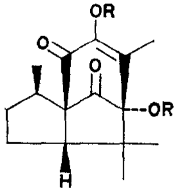
(II) a R = H
b R = $COCH_2CH(Me)_2$



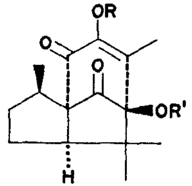
(III) a R = H
b R = Ac
c R = Bz



(IV) a R = H
b R = Ac
c R = Bz



(V) a R = H ; R' = Angelate
b R = Ac; R' = Angelate
c R = Bz; R' = Angelate
d R = H ; R' = COCH(Me)Et
e R = H ; R' = H



(VI) a R = H ; R' = Angelate
b R = Ac; R' = Angelate
c R = Bz; R' = Angelate
d R = H ; R' = COCH(Me)Et
e R = H ; R' = H

7400 for γ-perezol) and IR bands at 3450, 1760, 1670 and 1635 cm^{-1}. In addition γ-perezol showed a band at 3525 cm^{-1}, suggesting that the fourth oxygen is a hydroxyl group. The position of this last group is deduced from a comparison of the 60 MHz PMR spectra (Fig. 1) of α-pipitzol (IIIa) and γ-perezol. The important difference between the two spectra is the position of the singlet due to the proton at the junction of the five and six membered rings of γ-pipitzol (IIIa) which appears at 2·83 ppm. The singlet at 3·01 ppm in the spectrum of γ-perezol (Ve), which disappears after equilibration with D_2O, substantiates the presence of the fourth oxygen as a tertiary hydroxyl group at the ring junction. The stereochemistry of γ-perezol is deduced from its ORD curve, which is very closely similar to that of α-pipitzol (IIIa).[11] Both compounds provide strong positive Cotton effects in the 330 nm region. Therefore γ-perezol is adequately represented as Ve.

Although we were able[7] to resolve the α- and β-pipitzols mixture by fractional crystallization of their benzoates, several attempts to separate the mixture as such failed. Therefore the spectral properties of the crystalline fraction m.p. 156–158° ('perezol'), $C_{20}H_{26}O_5$, were compared with those of 'pipitzol', $C_{15}H_{20}O_3$, [the mixture[7] of α-(IIIa) and β-pipitzols (IVa)]. The new mixture showed UV absorption at 218 (α–β unsaturated ester) and 281 nm (diosphenol) and IR bands at 3450 (hydroxyl) 1775 (bridged cyclopentanone), 1725 (ester carbonyl group) and 1675 and 1645 cm^{-1} (enolized α-diketone).

The 220 MHz PMR spectrum of 'perezol' clearly suggests an elemental composition of $C_{20}H_{26}O_5$ and that it must be a mixture of two very closely related compounds. It showed singlets at 0·945, 1·041, 1·073, 1·086, 1·923, 1·927 and 1·991 ppm (the last singlet having twice the area of the remaining signals) and two doublets ($J = 7$ Hz) centered at 1·361 and 1·418 ppm. In addition a double quartet ($J_d = 6$; $J_q = 1{\cdot}4$ Hz) centered at 2·009 ppm corresponds to a methyl group of the esterifing moiety (*vide infra*).

A comparison of the 100 MHz PMR spectra of 'perezol' and 'pipitzol' is shown on

---

[11] G. Snatzke (editor), *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, pp. 13, 135–137, Heyden, London (1967); P. Crabbé, *Applications de la Dispersion Rotatoire Optique et du Dichroisme Circulaire Optique en Chemie Organique*, pp. 339–341, Gauthier-Villars, Paris (1968).

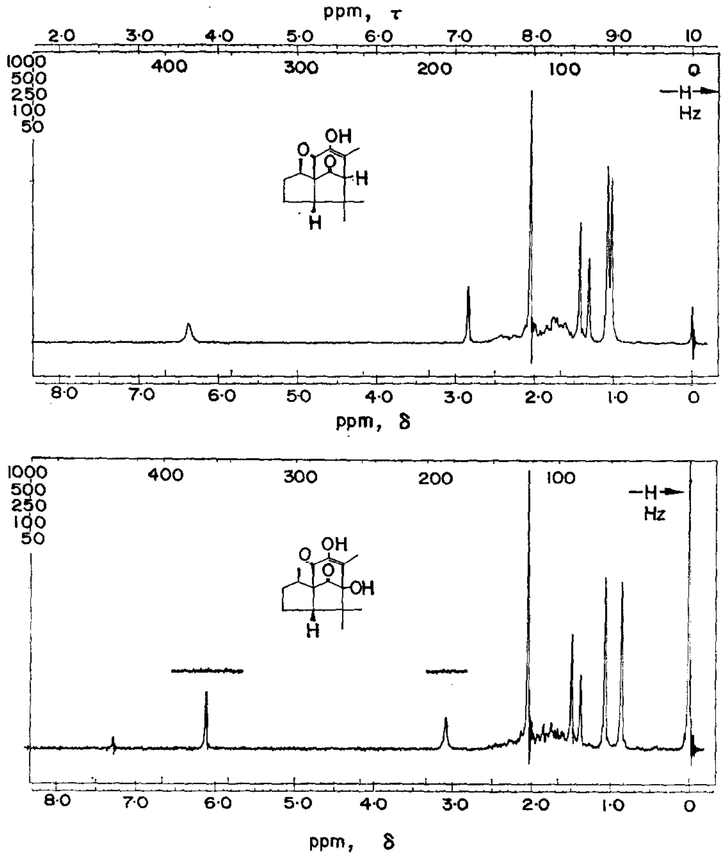


FIG. 1. THE 60 MHz PMR SPECTRA OF α-PIPITZOL (IIIa) AND OF γ-PEREZOL (Ve).

Fig. 2. A close analogy is again observed, although, the 2 ppm region of the lower spectrum is now much more complex due to the signals of the esterifying moiety, which is also responsible for the signal near 6·15 ppm. Hydrogenation of 'perezol' clarified the 6 ppm and 2 ppm regions of the PMR spectrum and complexed the 1 ppm region.

The elemental composition differences between 'pipitzol' and 'perezol' leave tiglic, angelic or senecioic acids as the esterifying moiety in the latter. It is well established[12] that these three unsaturated five carbon esters can be distinguished by PMR. The vinylic proton[13] of senecioic esters shows a different multiplicity than that of the remaining two esters and appears usually around 5·4 ppm. The signals of tigloyl vinyllic protons, have been described around 6·7 ppm, while values between 6·13 and 5·97 ppm are known for angeloyl groups. Since the PMR spectrum of 'perezol' shows (Fig. 2) a characteristic signal at 6·15, the esterifying moieties appear to be angeloyl groups.

---

[12] M. D. NAIR and R. ADAMS, *J. Am. Chem. Soc.* **82**, 3786 (1960); R. R. FRASER, *Can. J. Chem.* **38**, 549 (1960); W. HERZ and M. L. LAKSHMIKANTHAM, *Tetrahedron* **21**, 1711 (1965); W. HERZ, S. RAJAPPA, S. K. ROY, J. J. SCHMID and R. N. MIRRINGTON, *Tetrahedron* **22**, 1907 (1966); T. SAITOH, T. A. GEISSMAN, T. G. WADDELL, W. HERZ and S. V. BHAT, *Rev. Latinoamer. Quím.* **2**, 69 (1971); T. A. GEISSMAN and T. S. GRIFFIN, *Rev. Latinoamer. Quím.* **2**, 81 (1971).

[13] P. JOSEPH-NATHAN and E. DÍAZ, *Introducción a la Resonancia Magnética Nuclear*, Chap. 3, Limusa Wiley, Mexico (1970).

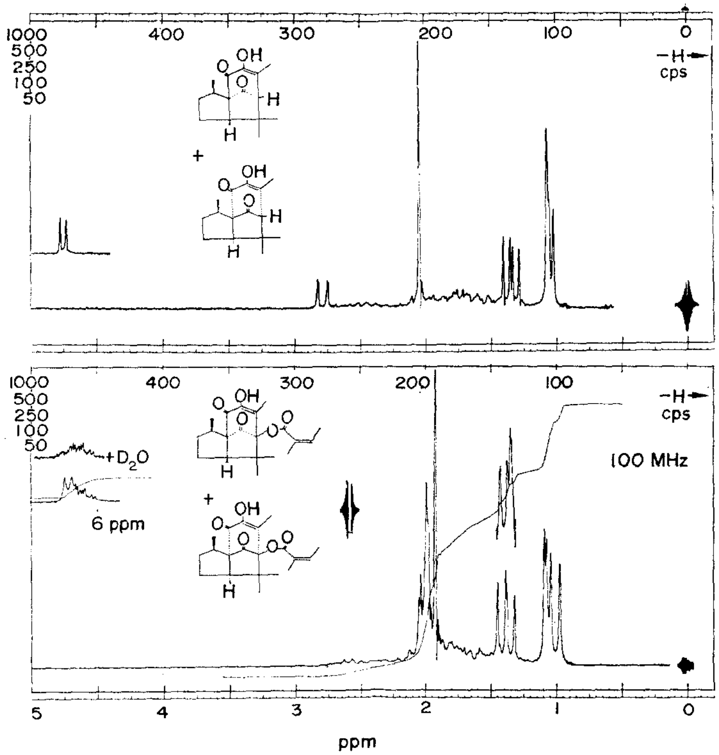


FIG. 2. THE 100 MHz PMR SPECTRA OF A MIXTURE OF α- (IIIa) AND β-PIPITZOLS (IVa) AND OF A MIXTURE OF α- (Va) AND β-PEREZOLS (VIa).

Perezol acetate and perezol benzoate were also compared with 'pipitzol acetate' (IIIb and IVb) and 'pipitzol benzoate' (IIIc and IVc) with similar results. Therefore structures Va and VIa represent α- and β-perezols respectively.

Apart from cedrol,[14] and cedrenes[14] and shellolic acid,[15] only a few other compounds possessing the cedranoic skeleton have been described. We reported[7] α-(IIIa) and β-pipitzols (IVa) and more recently α- and β-biotols[16] and some constituents of *Juniperus* plants[17] having this skeleton have been described. All these compounds except β-pipitzol (IVa) possess the same stereochemistry at their ring junctions as cedrene. Therefore, β-perezol (VIa) is the second known natural product having a different stereochemistry from cedrene. It is also possible that a fourth compound (VIe) having a structure of γ-perezol (Ve) and the stereochemistry of β-perezol (VIa) [the same as β-pipitzol (IVa)] might be present in the plant but we have been unable to isolate it.

[14] G. STORK and R. BRESLOW, *J. Am. Chem. Soc.* **75**, 3291, 3292 (1953); G. STORK and F. H. CLARKE, JR., *J. Am. Chem. Soc.* **77**, 1072 (1955); **83**, 3114 (1961); PL. A. PLATTNER, A. FÜRST, A. ESCHENMOSER, W. KELLER, H. KLÄNE, ST. MEYER and M. ROSNER, *Helv. Chim. Acta* **36**, 1845 (1953); PL. A. PLATTNER, A. FÜRST, ST. MEYER and W. KELLER, *Helv. Chim. Acta* **37**, 266 (1954).

[15] P. YATES and G. F. FIELD, *J. Am. Chem. Soc.* **82**, 5764 (1960); R. C. COOKSON, N. LEWIN and A. MORRISON, *Tetrahedron* **18**, 547 (1962); U. WEISS and H. ZIFFER, *J. Org. Chem.* **28**, 1248 (1963).

[16] B. TOMITA, Y. HIROSE and T. NAKATZAKA, *Tetrahedron Letters* 843 (1968).

[17] K. H. BAGGALEY, H. ERDTMAN and T. NORIN, *Tetrahedron*, **24**, 3399 (1968); J. RUNEBERG, *Arkiv Kemi* **15**, 945 (1961).

The biogenesis of cedrene from β-curcumene has been postulated[18] and perezone (I) is transformed into the mixture of the pipitzols either by a sigmatropic change[6c] of order (1,9) or by a class B cycloaddition.[19] Therefore, biogenetic considerations render it very probable that hydroxyperezone moniosovalerate, in which the position of the ester is not precisely known, has structure IIb and that it undergoes a similar transformation to yield the perezols. However, after heating either hydroxyperezone (IIa) or its monoisovalerate (IIb) under the same conditions in which the perezone–pipitzol transformation occurs,[7] we could not detect any trace of a perezol.

EXPERIMENTAL

M.ps are uncorrected. IR spectra were determined in $CHCl_3$, UV spectra in 95% EtOH. NMR spectra was obtained from $CDCl_3$ solutions; chemical shifts are related to internal TMS as standard and reported in ppm as δ values. The microanalytical determinations were performed in Alfred Bernhard's laboratories, West Germany.

Extraction of Perezia *sp.* The dried and ground roots (2·5 kg) of a *Perezia* purchased in May 1966 were extracted twice with 12 l. of hexane under reflux during 6 hr. The compined extracts were evaporated to a small volume and left overnight at 4°. The crystalline product was decanted and recrystallized from hexane yielding 12 g of perezone (I), m.p. 102–103° identical with an authentic sample.[5]

The original extract was evaporated to dryness, diluted with pentane, cooled at −5°, chilled and left for 5 hr. The crystalline material was decanted and recrystallized from acetone-hexane yielding 6·5 g of the mixture of α- (Va), β- (VIa) and γ-perezols (Ve), m.p. 128–132°.

Fractions crystallization of the above from acetone–hexane gave as the less soluble fraction, pure γ-perezol (Ve) m.p. 182–184°, positive chloride test, λ_{max} 242, 280 nm; ε 3400, 7400, IR bands at 3525 and 3450 (hydroxyl groups), 1760 (cyclopentanone) and at 1670 and 1635 cm^{-1} (enolized six-membered α-diketone) Found: C, 68·20; H, 7·54; O, 24·29%. $C_{15}H_{20}O_4$ required: C, 68·16; H, 7·63; O, 24·21%.

The more soluble fraction consisted of a mixture of α- (Va) and β-perezols (VIa) m.p. 154–156°, positive $FeCl_3$, λ_{max} 218, 281 nm; ε 10 800, 8500. IR bands at 3450 (hydroxyl), 1775 (cyclopentanone), 1725 (α,β-unsaturated ester) and 1675 and 1645 cm^{-1} (enolized six-membered α-diketone) Found: C, 69·35; H, 7·33; O, 23·29%; MW (Rast) 332. $C_{20}H_{26}O_5$ required: C, 69·34; H, 7·57; O, 23·09%; MW 346.

The mother liquors of the original extract were evaporated to dryness (132 g), dissolved in MeOH (500 ml) and heated during 5 min in the presence of 20 g of KOH in 25 ml H_2O. After acidification with HCl, the characteristic odour of isovaleric acid became immediately apparent.[10] The organic layer was concentrated, yielding 4·5 g of hydroxyperezone (IIa) m.p. 136–138°. Recrystallization from acetone–hexane raised the m.p. to 142–143°. The compound was identified with an authentic sample by standard methods.[10]

Extraction of Perezia hebeclada *(Gray).* Material was collected some 20 miles from Mexico City at El Cantil near Mexican Federal Road 95 in April 1968. Extraction of the dried and ground roots (4·5 kg) of *P. hebeclada* with hexane in a similar way as described previously, provided 92 g of pure perezone (1), m.p. 102–103°, identified with an authentic sample.[5]

The original extract was then evaporated to dryness (297 g) and an aliquot of the dark red oil (20 g) was dissolved in MeOH (150 ml) and treated with 5 g of KOH in 10 ml H_2O under relux for 5 min. After acidification with HCl and concentration of the solution, hydroxyperezone (IIa) crystallized. It was recrystallized yielding 3·3 g of material, m.p. 139–141° which was identified as usual.[10]

The organic layer was evaporated to dryness and the residue distilled at 0·05 torr. A fraction collected between 150 and 170° contained semisolid material. It was dissolved in acetone, decolorised with Norite, filtered and concentrated. After addition of hexane, then crystallized 175 mg of the mixture of α- (Va), β- (VIa) and γ-perezols (Ve) m.p. the 126–131°. Fractional crystallization of this material afforded 25 mg of γ-perezol (Ve) m.p. 181–183° and a mixture of 95 mg of α- (Va) and β-perezols (VIa), m.p. 154–156°. These compounds were identified with the samples obtained previously (*vide supra*) by standard procedures.

Acetylation of 'perezol'. [*α- (Vb) and β-perezol acetates* (VIb). 300 mg of 'perezol' was acetylated with Ac_2O-pyridine in the usual way. Crystallization from Et_2O–hexane gave 280 mg of 'perezol acetate', m.p. 113–114°, λ_{max} 218, 262 nm; ε 15 900, 5400; IR bands at 1775 (cyclopentanone), 1760 (enol acetate), 1725 (α,β-unsaturated ester) and 1690 and 1645 cm^{-1} (enolized six-membered α-diketone) Found: C, 67·88; H, 7·13; O, 24·87%. $C_{22}H_{28}O_5$ required: C, 68·02; H, 7·27; O, 24·71%. The NMR spectrum of the mixture showed signals at 6·13 broad (angeloyl vinyl protons) 2·27 singlet (acetyl methyl groups), 1·82 singlet (vinylic methyl groups). In addition, partial superimposed doublets ($J = 7$ Hz each) at 1·40 and 1·35 ppm correspond

---

[18] P. YATES, *Structure Determination*, p. 19, Benjamin, New York (1967).

[19] R. B. WOODWARD and R. HOFFMAN, *The Conservation of Orbital Symmetry*, p. 87, Verlag Chemie GmbH–Academic Press, New York (1970).

to the methyl groups in the five membered ring and singlets at 1·55, 1·12, 1·03 and 0·97 ppm are attributed to the *gem*-dimethyl groups.

Benzoylation of 'perezol' [*α*- (Vc) and *β-perezol benzoates* (VIc). The reaction was carried out as for acetylation. Crystallization from EtoAc–hexane gave 300 mg of material m.p. 165–166°, λ_{max} 230, 262 nm; ϵ 28 000, 8800, IR bands at 1780 (cyclopentanone), 1745 (benzoate), 1730 (α,β-unsaturated ester) and 1695 and 1645 cm^{-1} (enolized six-membered α-diketone) Found: C, 71·91; H, 6·65; O, 21·50, $C_{27}H_{30}O_6$ required: C, 71·98; H, 6·71; O, 21·31%. The NMR spectrum showed the benzoate protons as a double doublet ($J = 2$; $J = 8$ Hz) at 8·17 (4H) and a broad signal (6H) at 7·58 ppm. The angeloyl vinylic protons appeared as a broad signal at 6·16 and the methyl groups of the ring as a singlet at 1·95 ppm. The remaining methyl groups of the mixture appeared as doublets ($J = 7$ Hz) at 1·40 and 1·35 ppm and singlets at 1·23, 1·18 and 1·02 ppm.

Hydrogenation of perezol. Compounds Vd *and* VId. A solution of 300 mg of 'perezol' in 70 ml EtOAc was hydrogenated with 30 mg of 10% Pd–C. The uptake of H_2 ceased after one equivalent was absorbed. The product crystallized from Et_2O–hexane yielding 215 mg of a material showing erratic m.p. behavior, either 92–95°, on 107–110°, λ_{max} 208, 235, 278 mn; ϵ 5900, 5200, 8300; IR bands at 3480 (hydroxyl), 1780 (cyclopentanone), 1750 (ester) and 1675 and 1645 cm^{-1} (enolized six-membered α-diketone). The NMR spectrum showed singlets at 6·13 and 6·05 (hydroxyl protons) which disappears after equilibration with D_2O. The vinylic methyl groups appear as a singlet at 1·88 ppm. Four doublets ($J = 7$ Hz) at 1·42, 1·35, 1·27 and 1·23 ppm a triplet ($J = 7$ Hz) at 1·02 ppm and singlets at 1·08, 1·06, 1·02 and 0·95 ppm could be recognized.

Acknowledgements—We are grateful to Dr. Jirzy Rzedowsky (Departamento Botánico de la Escuela Nacional de Ciencias Biológicas, IPN, México) for the classification of the plant material and to Dr. LeRoy F. Johnson (Varian Associates, Palo Alto, Calif., U.S.A.) for some NMR measurements.

Key Word Index—Perezia hebeclada; Compositae; α-, β- and γ-perezols; cyclic sesquiterpenes.