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STUDIES IN PEREZONE DERIVATIVES

STRUCTURES OF THE PIPITZOLS AND PEREZINONE

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Abstract—α and β-pipitzols isolated from the roots of *Perezia cuernavacana* and obtained by thermal rearrangement of perezone, (II), have been shown to be sesquiterpenes with structures IIIa and IVa related to cedrene (XXIII). The structure of perezinone has been revised and established as shown in formula XXVI.

THE reputed medicinal properties of certain mexican plants, prompted an investigation of the root extracts of several species of *Perezias*. Recently, hydroxyperezone monoisovalerianate was found as a constituent of *Perezia alamani var. adnata*,[3] and now the results of an investigation of *Perezia cuernavacana*, a compositae distributed in the neighbourhood of Cuernavaca (Estado de Morelos) is reported.

From the hexane extract of the roots two products were isolated and identified as perezone and pipitzol.[4]

Recently, the structure of perezone (I), postulated by Kögl and Boer,[5] was revised,[6,7] the position of the hydroxyl group established as shown in II and this new structure confirmed by synthesis.[8] Perezone and both pipitzols have been synthesized and shown to be identical with the corresponding natural products.

Pipitzol has been described[5,9] as a transformation product of perezone (II), obtained in good yield by its thermal rearrangement. This reaction is inadequate for preparative purposes, but the transformation of perezone (II) into pipitzol proceeds smoothly in tetralin solution. The identity of pipitzol, isolated from the extract of the roots and that obtained by thermolysis of perezone (II), was established by mixed m.p., identical R_f values (TLC) and comparison of spectra.

[1] Facultad de Química (UNAM).

[2] Contribution No. 207 from the Instituto de Química (UNAM).

[3] T. García, E. Domínguez and J. Romo, *Bol. inst. quím. univ. nal. autón. Méx.* XVII, 16 (1965).

[4] A brief report on this subject appeared in *Tetrahedron Letters* 1577 (1965).

[5] F. Kögl and A. G. Boer, *Rec. Trav.Chim.* **54**, 779 (1935).

[6] F. Walls, J. Padilla, P. Joseph-Nathan, M. Salmón and J. Romo. *Bol. inst. quím. univ. nal. autón. Méx.* XVII, 3 (1965). After this report, two additional communications have appeared that confirmed our findings: D. A. Archer and R. H. Thomson, *Chem. Comm.* 354 (1965); R. B. Bates and S. K. Paknikar and V. P. Thalacker, *Chem. & Ind.* 1793 (1965).

[7] K. Yamaguchi synthesized DL-dihydroperezone corresponding to the Kögl and Boer structure of perezone (I). Comparison by the standard methods of a sample kindly sent us by Dr. Yamaguchi with dihydroperezone obtained by hydrogenation of perezone, showed them to be different products. We are indebted also to Dr. Yamaguchi for an english copy of his paper dealing with his synthesis of DL-dihydroperezone [K. Yamaguchi, *J. Pharm. Soc. Japan* **62**, 491 (1942)].

[8] E. Cortés, M. Salmón and F. Walls, *Bol. inst. quím. univ. nal. autón. Méx.* XVII, 19 (1965).

[9] J. McConnel Sanders, *Proc. Chem. Soc.* **22**, 134 (1906).

Although pipitzol appeared to be homogeneous, its NMR spectrum[10] suggested a mixture of two related components, since various characteristic signals showed duplicity. Eventually, from the mother liquors of pipitzol, obtained from both sources, pure samples of a component ($C_{15}H_{20}O_3$), m.p. 146–147°, $[\alpha]_D$ +192° were isolated which do not show duplicity of signals in the NMR spectrum. This component was named α-pipitzol. The acetate, m.p. 103–105°, $[\alpha]_D$ +98°; and the benzoate, m.p. 116–117°, $[\alpha]_D$ +89° were prepared. Since the m.p. of a pipitzol benzoate previously described (m.p. 155°)[11] does not correspond with that found for α-pipitzol benzoate, the mixture of pipitzols was benzoylated. Fractional crystallization of the resulting benzoates gave a derivative with m.p. corresponding to the reported value.[11] It also showed an $[\alpha]_D$ −88°. Careful alkaline hydrolysis yielded an isomer of α-pipitzol, m.p. 132°, $[\alpha]_D$ −172°, for which the name β-pipitzol is proposed. Its acetate has m.p. 105–106°, $[\alpha]_D$ −88°. The chemical and spectral features cited below show that both sesquiterpenes are estereoisomers, α-pipitzol having structure IIIa, and β-pipitzol structure IVa.

Comparison of the NMR spectrum of perezone (II) with those of the pipitzols (IIIa and IVa), afforded preliminary information concerning their structures. Perezone (II) exhibits a doublet (J = 7 c/s), centered at 1·19, corresponding to the secondary methyl group which in α-pipitzol (IIIa) is at 1·37 and in β-pipitzol (IVa) at 1·30. The side chain and quinonoid substituted vinyl methyl groups of perezone (II) are responsible for two singlets at 1·51, 1·62 and a doublet (J = 1·8 c/s) at 2·06 respectively. The pipitzols possess only one vinyl methyl group with the same chemical shift shown by the quinonoid substituted methyl group of perezone (II). α-Pipitzol (IIIa), exhibits two singlets at 1·04 and 1·07, ascribed to a *gem*-dimethyl group, which in β-pipitzol (IVa) is observed as a singlet at 1·07. The side chain and quinonoid vinyl protons of perezone (II) indicate a broad signal at 5·03 and a multiplet (J = 1·8 c/s) at 6·47, not present in the spectra of the pipitzols (IIIa and IVa). A broad signal at 7·19 of the enolic hydroxyl proton of perezone (II) is shifted to higher field in α-pipitzol (6·3) and in β-pipitzol (6·4). These signals disappear on equilibration with deuterium oxide. An allylic proton is responsible in α-pipitzol (IIIa), for a singlet at 2·83. In β-pipitzol (IVa) the singlet is observed at 2·77. Two of the three oxygen atoms of both pipitzols are found as an enolized α-diketone in a six-membered ring, and the remaining oxygen atom is incorporated in a five-membered ring as ketone as shown by the following evidence: The pipitzols (IIIa and IVa) are weak acids, insoluble in sodium carbonate,[11] giving positive ferric chloride (green colour) and Tollens tests. The IR spectra of both pipitzols (IIIa and IVa) exhibit a hydroxyl band at 3400 cm^{-1} which disappears on acetylation. Though it has been reported that "pipitzol" does not form carbonyl derivatives,[11] under drastic conditions, both stereoisomers (IIIa and IVa) yield mono-oximes (IIId and IVd). The cyclopentanone is responsible for the formation of such oximes, since an IR band at 1760 cm^{-1} present in the pipitzols disappears in the oximes. The IR bands at 1635 and at 1670 cm^{-1}, exhibited by the pipitzols (IIIa and IVa) and at 1668 and 1638 in the mono-oximes (IIId and IVd), are attributed to the six-membered enolized α-diketone chromophore. The UV maximum of the mono-oximes

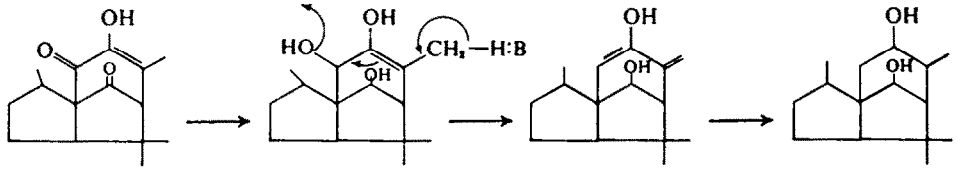
[10] The NMR spectra were measured by Mr. Eduardo Díaz in a Varian A-60 spectrometer, in $CDCl_3$ solution, with tetramethylsilane as internal reference. All chemical shifts are reported in ppm as δ values (c/s, 60).

[11] F. G. P. Remfry, *J. Chem. Soc.* **103**, 1076 (1913).

(IIId and IVd) (λ_{max} 278 mμ) is observed at 248 mμ in the oxime diacetates (IIIe and IVe), in accord with similar shifts of the UV maximum of enolized α-diketones upon acetylation. Brief alkaline treatment of the oxime diacetate (IIIe) of the α-pipitzol series, affords the monoacetate (IIIf). The enolic acetate being preserved, as shown by the UV maximum at 247 mμ. The NMR spectrum shows a sharp singlet at 8·6 ascribed to the proton of the oxime grouping.

The relative position the of oxygen functions was elucidated by lithium in liquid ammonia reduction of the pipitzols (IIIa and IVa) to the respective triols (Va and VIa). Acetylation of Va, yields a triacetate (Vb). The vicinal position of the two hydroxyl groups in the triols (Va and VIa) was demonstrated by periodic acid oxidation, lactols (VIII), with a free aldehyde group being obtained with IR bands at 3400 cm^{-1} (hydroxyl group), at 2880 (weak) and at 1720 cm^{-1} (aldehyde group). Without further purification both lactols may be oxidized with chromium trioxide to the lactone-acids (IX and Xa) with IR bands at 1725 cm^{-1} (carboxyl group) and at 1765 cm^{-1} (five-membered lactone). Treatment with ethereal diazomethane of the lactone-acid (Xa), of the β-pipitzol series, yields the lactone-ester (Xb).

Lithium in liquid ammonia reduction of the pipitzols (IIIa and IVa) affords also two diols to which the structures Vc and VIb, were ascribed in accordance with the following mechanism for their formation:



Chromium trioxide oxidation of Vc, of the α-pipitzol series, furnishes a diketone (VIIa) exhibiting in the IR spectrum two carbonyl bands at 1738 and 1710 cm^{-1} of a cyclopentanone and a cyclohexanone, respectively. The less hindered six-membered ketone is responsible for the formation of the oxime, since only the IR band at 1740 cm^{-1} of the five-membered ketone is observed in VIIb.

Alkaline hydrogen peroxide treatment of both pipitzols gave further proof of their structures. In these oxidations, the enolized α-diketone chromophores are eliminated and liquid cyclopentanones ($C_{11}H_{18}O$) (XI and XII) with camphorlike odour obtained. These ketones were purified by VPC chromatography. The IR bands at 1740 cm^{-1} are assigned to five-membered ketones. The NMR spectra of both ketones indicated the presence of three methyl groups. The cyclopentanone (XI) exhibits a doublet (J = 7 c/s), centered at 1·11 of the secondary methyl group, partially superimposed on two singlets at 1·03 and 1·17, corresponding to the *gem*-dimethyl grouping. In the cyclopentanone (XII), the doublet is centered at 1·0 and the two singlets at 0·98 and 1·12. Deuterium exchange substitutes three protons in the cyclopentanones (XI and XII), as shown by comparison of the NMR spectra of the products prior and after equilibration with MeOD, catalysed by sodium methoxide.

The mass spectrum[12] of the cyclopentanone gives a mol.wt. of 166 in accord with its structure. The peaks *m/e* 110, 109 and *m/e* 56 result by fragmentation of XI in a

[12] Mass spectra were determined through the courtesy of Dr. Herbert Budzikiewicz of Standford University, Palo Alto, Cal.

gem-dimethylcyclopentenone species and a CH_3—CH=CH—CH_3 fragment. Peaks *m/e* 83, 82 and 81 correspond to a methylcyclopentene species. A peak *m/e* 151 results by loss of methyl. An acetylmethylcyclopentene fragment is responsible for a peak *m/e* 124. Mass spectra of the deuterated ketones (XI and XII) indicate substitution of three hydrogen atoms by deuterium. The fragmentation patterns of the ketones (XI and XII) are confirmed by the mass spectra of the deuterated species.

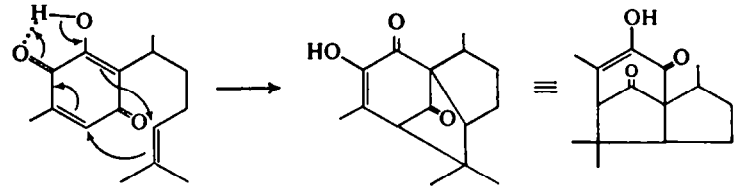
Alkaline cleavage of the β-diketone system in the α-pipitzol series, furnishes the acid (XIIIa) by rupture of the carbonyl bridge. The enolized α-diketone chromophore is preserved, as shown by positive ferric chloride (green colour) and Tollens tests. The acid (XIIIa) exhibits a UV maximum at 277 mμ, which in the acetate (XIIIb) is shifted to 246 mμ. The IR spectrum of the acid (XIIIa) has bands at 3500 cm^{-1} (hydroxyl group), at 1700 cm^{-1} (shoulder at 2650 cm^{-1}) (carboxyl group). The bands at 1670 and 1640 cm^{-1} are assigned to the seven-membered enolized α-diketone chromophore. The NMR spectrum shows two broad singlets centered at 8·7 and 6·5, which disappear on equilibration with deuterium oxide, ascribed to the protons of the carboxyl and enolic hydroxyl groups respectively. The *gem*-dimethyl groups are responsible for two singlets at 0·73 and 1·22. Two superimposed doublets (J = 7 c/s) (intensity six protons), centered at 1·22 and partially superimposed on one of the singlets, are assigned to two secondary methyl groups which indicates that the enolic double bond is exocyclic to the five-membered ring.

Brief treatment of the acid (XIIIa) with ethereal diazomethane yields the methyl ester (XIIIc) which on acetylation affords the acetate (XIIId).

The structure assigned to the acid (XIIIa) was confirmed in the following way: Ozonolysis of the acid (XIIIa), followed by oxidation with hydrogen peroxide, yields the nordicarboxylic acid ($C_{14}H_{22}O_5$) (XIV). The IR spectrum of the anhydride (XV), obtained by thermal dehydration of XIV, shows bands at 1855 and 1780 cm^{-1} (five-membered anhydride) and at 1730 cm^{-1} (cyclopentanone). Sodium borohydride reduction of the acid (XIIIa), yields the hydroxylactone (XVI) with IR bands at 3510 cm^{-1} (hydroxyl group) and at 1760 cm^{-1} (γ-lactone). Chromium trioxide oxidation of XVI affords the keto-lactone (XVII), this keto group being responsible for an IR band at 1720 cm^{-1}.

Further alkaline treatment of XIIIa produces a benzilic rearrangement, yielding the dicarboxylic acid (XVIIIa). The dimethyl ester (XVIIIb), prepared by treatment of XVIIIa with ethereal diazomethane, shows in the NMR spectrum two singlets at 3·82 and 3·64 corresponding to the two methyl esters. A singlet at 3·05, which disappears on equilibration with deuterium oxide, is assigned to the hydroxyl proton. Lead tetra-acetate cleavage of the acid (XVIIIa), affords a ketoacid, characterized as its methyl ester (XIX) with an IR band at 1710 cm^{-1}, corresponding to a cyclohexanone. Treatment of the methyl ester (XIX) with selenium dioxide yields an α,β-unsaturated ketone (XX) λ_{max} 250 mμ), the structure of which is deduced from its spectroscopic features. Its IR spectrum has bands at 1732 cm^{-1} (ester group), at 1660 with a shoulder at 1630 cm^{-1} (α,β-unsaturated six-membered ketone). The NMR spectrum shows a singlet at 3·73 ascribed to the protons of the methyl ester. The *gem*-dimethyl and the two secondary methyl groups are responsible for two superimposed singlets at 1·17 (intensity six protons) and two superimposed doublets (J = 7 c/s), centered at 1·08 (intensity six protons). Alkaline treatment of β-pipitzol (IVa) did not afford crystalline material.

Perezone (II) possesses one asymmetric center, the absolute configuration of which has been established.[13] Since this center is not involved in the thermal rearrangement of perezone, its configuration is preserved in the pipitzols (IIIa and IVa). The rearrangement of perezone to the pipitzols has been rationalized through the following mechanism.[6]



I II III

Its transition state appears more favorable for the formation of the *cis* rather than the *trans* stereoisomers. The ORD curve of the norsteroid acid (XXI) has a positive Cotton effect[14] as shown by those of α-pipitzol (IIIa)[15] ($[\alpha]_{335}$ +5020°) and its derived ketone (XI) ($[\alpha]_{332\cdot5}$ +3930°). The sapogenin derivative (XXII)[16] exhibits a negative Cotton effect which is in accord with β-pipitzol (IVa). ($[\alpha]_{335}$ −4053°) and the ketone (XII), ($[\alpha]_{317\cdot5}$ −5305°). Dissymmetric β,γ-unsaturated chromophores[16] as those shown by the pipitzols (IIIa and IVa) are associated with a strengthened $n \rightarrow \pi^*$ transition, which in the pipitzols must overlap the UV maximum of the enolized α-diketone chromophore (λ_{max} 280 mμ; log ε, 3·89). The other maximum (λ_{max} 240 mμ; log ε, 3·60)[17] shown by the pipitzols, can be assigned to the $\pi \rightarrow \pi^*$ transition, described previously[18] for related unsaturated ketones.

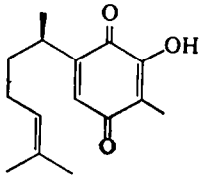
The signs of the Cotton effects exhibited by the ORD curves of the pipitzols are in accord with the chirality of their dissymmetric β,γ-unsaturated ketone chromophores.[1] Therefore, we tentatively assign to the asymmetric centers of α-pipitzol the configuration represented in IIIa [identical to those of cedrene (XXIII)[19]]. The stereochemistry of β-pipitzol should be as shown in IVa.

Perezinone has been obtained by cyclization of hydroxyperezone (XXIV).[20] Kögl and Boer[5] assigned structure XXV to this product but evidence indicates that structure XXVI is correct. Perezinone (λ_{max} 204, 324 mμ) exhibits in the IR spectrum a hydroxyl band at 3330 cm^{-1}. In the carbonyl region it shows two bands, at 1674 cm^{-1} (weak) and at 1635 cm^{-1} (strong). The extinction of both bands correspond to one carbonyl group. A dilute solution of perezinone (XXVI) shows only one band at 1635 cm^{-1}. This indicates an equilibrium between the intramolecular hydrogen bonded carbonyl and the non-chelated one. Its NMR spectrum shows a doublet (J = 7 c/s), centered at 1·22 ascribed to a secondary methyl group. The chemical shift of a singlet (intensity six protons) at 1·52 corresponds to a *gem*-dimethyl group attached to a carbon atom bearing an oxygen function. The vinylic methyl group of perezinone (XXVI)

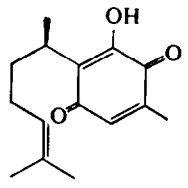
[13] D. Arigoni and O. Jeger, *Helv. Chim. Acta* **37**, 881 (1954).
[14] C. Djerassi, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **78**, 6362 (1956).
[15] The previously reported (Ref. 4) rotatory dispersion data, correspond to Φ values.
[16] A. Moscowitz, K. Mislow, M. A. W. Glass and C. Djerassi, *J. Amer. Chem. Soc.* **84**, 1945 (1962).
[17] The UV maxima corresponds to IIIa. β-pipitzol (IVa) maxima has a small shift to higher wavelengths, see Experimental part.
[18] S. Winstein, L. de Vries and R. Orloski, *J. Amer. Chem. Soc.* **83**, 2020 (1961).
[19] G. Stork and F. H. Clarke, *J. Amer. Chem. Soc.* **77**, 1072 (1955).
[20] F. Mylius, *Chem. Ber.* **18**, 936 (1885).

is responsible for a singlet at 1·93. A singlet at 7·38, which disappears on equilibration with deuterium oxide, is assigned to the enolic hydroxyl proton. Hydrogenation of perezinone (XXVI) with Adams catalyst in acetic anhydride solution, affords a diacetate ($C_{19}H_{24}O_5$) (carbonyl ester IR band at 1760 cm^{-1}). Its NMR spectrum is in accord with structure XXVII. Two singlets, with different chemical shifts at 1·15 and at 1·59, are assigned to the *gem*-dimethyl group. A doublet (J = 7 c/s), centered at 1·12 (partially superimposed on one of the singlets of the gem dimethyl group), corresponds to the secondary methyl group. The aromatic methyl group is responsible for a singlet at 1·95. A singlet at 2·25 (intensity six protons) is ascribed to the hydrogens of the two acetyl groups. Two allylic protons are responsible for a multiplet centered at 2·96. Basic hydrolysis of the diacetate (XXVII) followed by air oxidation, regenerates perezinone (XXVI).

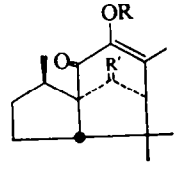
2,3-Dichloro-5,6-dicyanobenzoquinone aromatization of the diacetate (XXVII), yields the furonaphthalene derivative (XXVIII) as showed by its NMR spectrum: singlets at 1·63 (intensity six protons) (*gem*-dimethyl group), at 2·33 (intensity six protons) (two acetyl groups), at 2·18 and at 2·6 (two aromatic methyl groups), two doublets (J = 7 c/s) (intensity one proton each), centered at 7·16 and at 6·88 (AB system) and corresponding to two aromatic protons. Treatment of an ethereal solution of perezinone (XXVI) with silver oxide yields the red *o*-quinone (XXIX) with IR bands at 1685 (weak) at 1615 cm^{-1} (carbonyl bands), and at 1558 cm^{-1} (weak) (C=C double bonds). Similar bands are exhibited by the IR spectrum of the *o*-quinone biflorin (XXXI).[21] The *o*-quinone (XXIX) shows a maximum at the same wavelength (λ_{max} 261 mμ) as that observed in the UV spectrum of tetrahydrobiflorin (XXXII),[22] which indicates a close relationship in their chromophores. The *o*-quinone (XXIX) yields the quinoxaline (XXX).



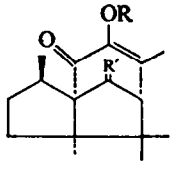
I



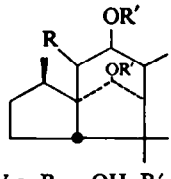
II



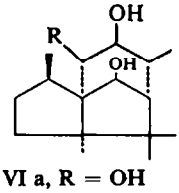
III a, R = H, R′ = O
b, R = Ac, R′ = O
c, R = Bz, R′ = O
d, R = H, R′ = NOH
e, R = Ac, R′ = NOAc
f, R = Ac, R′ = NOH



IV a, R = H, R′ = O
b, R = Ac, R′ = O
c, R = Bz, R′ = O
d, R = H, R′ = NOH
e, R = Ac, R′ = NOAc

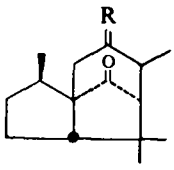


V a, R = OH, R′ = H
b, R = OAc, R′ = Ac
c, R = H, R′ = H

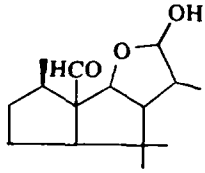


VI a, R = OH
b, R = H

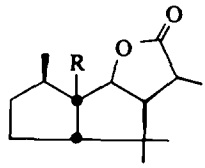
[21] O. Gonçalves de Lima, W. Keller-Schierlein and V. Prelog. *Helv. Chim. Acta* **41**, 1386 (1958).
[22] J. Comin, O. Gonçalves de Lima, H. N. Grant, L. M. Jackman, W. Keller-Schierlein and V. Prelog, *Helv. Chim. Acta* **46**, 409 (1963).



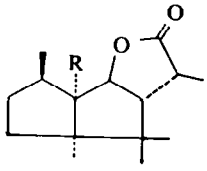
VII a, R = O
b, R = NOH



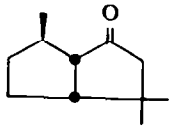
VIII



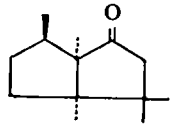
IX, R = COOH



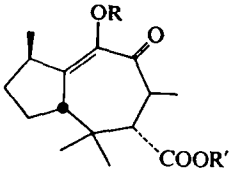
X a, R = COOH
b, R = COOMe



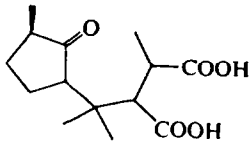
XI



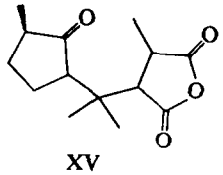
XII



XIII a, R = H, R′ = H
b, R = Ac, R′ = H
c, R = H, R′ = Me
d, R = Ac, R′ = Me



XIV



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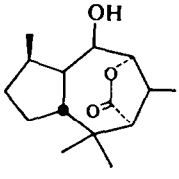

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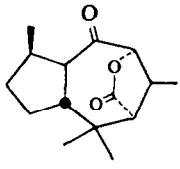

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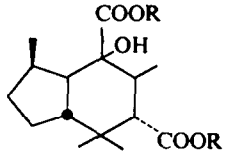

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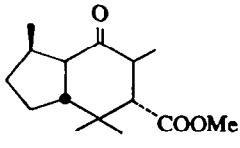
b, R = Me



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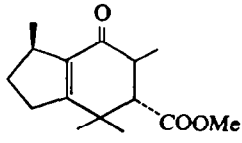

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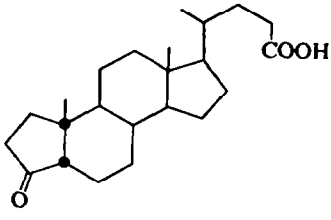

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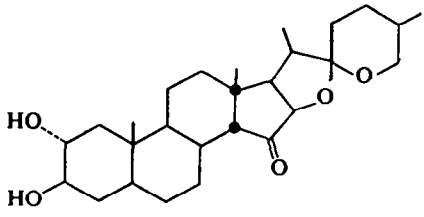

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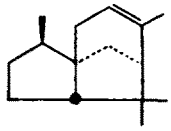

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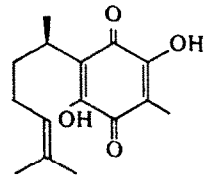

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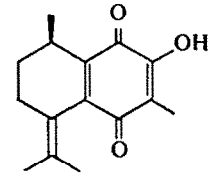

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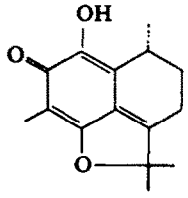

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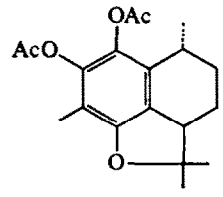

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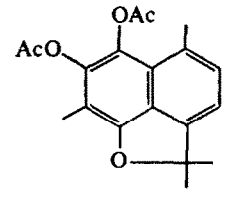

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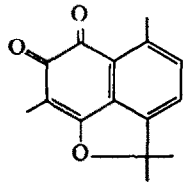

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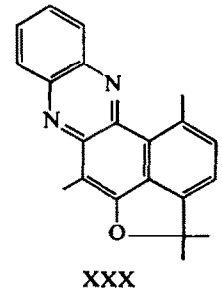

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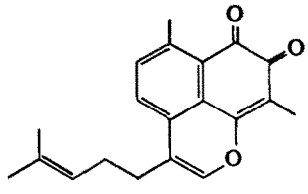
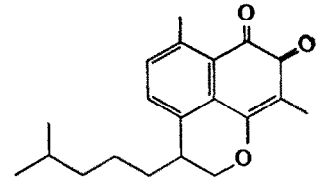


XXXI



XXXII

EXPERIMENTAL[23]

Isolation of pipitzols from Perezia cuernavacana[24,25]

The dried and ground roots of *Perezia cuernavacana* (1 Kg) were extracted under reflux with hexane (5 l.) for 6 hr, the treatment being repeated twice. The mixture of pipitzols crystallized upon concentration of the combined hexane extracts, m.p. 135–139°, yield 35 g. Crystallization from acetone–hexane yielded prisms, m.p. 141–143°, $[\alpha]_D$ +14°. (Reported:[9] m.p. 141°, $[\alpha]_D$ +14°.)

[23] M.ps are uncorrected. The chromatograms were carried out on alumina Alcoa F-20, VPC determinations on an Aereograph, Autoprep Mod. A-700 with Leeds and Northrup Mod. H recorder. UV spectra were determined on a Beckman DK2 spectrophotometer in 95% EtOH solution; IR were run in KBr disk (unless noted otherwise) on a Perkin–Elmer double beam spectrophotometer. Rotations were determined in $CHCl_3$ solution at 20°. The microanalyses were performed by Dr. Franz Pascher, Bonn, Germany. We are indebted to Syntex, S.A. for the determinations of the rotations, ORD curves and UV spectra.

[24] The mixture of pipitzols were isolated from the roots of the plant collected in June. From the extract of the roots collected in November only perezone was obtained.

[25] The late Dr. Faustino Miranda classified the plant. We wish to acknowledge our gratitude to Prof. Miranda, an illustrious botanist, who kindly collaborated with our Institute. Deceased December, 1964.

Transformation of perezone (II) *into the mixture of α and β-pipitzols*

A solution of II (30 g) in tetralin (150 ml) was heated under reflux for 5 hr. The cold solution was diluted with hexane (300 ml) and extracted twice with cold 15% NaOHaq. The combined alkaline solutions were acidified with dil HCl and the solid precipitate extracted with AcOEt. The organic layer was washed with water, dried with Na_2SO_4, evaporated to dryness and the residue dissolved in benzene was passed through alumina (120 g). The solid residue left after evaporation of the solvent was crystallized from acetone–hexane yielding prisms (17 g), m.p. 135–138° identical with the product obtained from the plant.

α-Pipitzol (IIIa). The first mother liquors left after the isolation of the mixture of pipitzols, from the extract of the plant, were further concentrated, furnishing a second crop of crystalline material. After several crystallizations from acetone–hexane, α-pipitzol (700 mg) was obtained, uncontaminated with β-pipitzol. It showed m.p. 146–147°, positive $FeCl_3$ (green colour) and Tollens tests: $[\alpha]_D$ +192°. Rotatory dispersion (in dioxan);[26] $[\alpha]_{589}$ +234°; $[\alpha]_{350}$ +3414°; $[\alpha]_{335}$ +5020°; $[\alpha]_{300}$ −4828° λ_{max}; 240, 280 mμ; ε, 4000, 7800; IR bands at 3450 cm^{-1} (hydroxyl group), at 1760 cm^{-1} (cyclopentanone); at 1670 and 1635 cm^{-1} (enolized six-membered α-diketone). (Found: C, 72·64; H, 8·35; O, 19·33. Calc. for $C_{15}H_{20}O_2$: C, 72·55; H, 8·12; O, 19·33%.)

In addition, a small amount of α-pipitzol could be isolated from the mother liquors of the mixture of pipitzols obtained in the thermolysis of perezone (II).

α-Pipitzol acetate (IIIb). Acetylation of IIIa with pyridine and Ac_2O (1 hr on the steam bath) afforded the acetate m.p. 103–105° (prisms from acetone–hexane), $[\alpha]_D$ +98°; λ_{max}; 232, 263 mμ; ε, 6800, 4500; IR bands at 1758 cm^{-1} (broad, enolic acetate and cyclopentanone), at 1680 and 1640 cm^{-1} (enolized *a*-diketone), (Found: C, 70·65; H, 7·69; O, 22·09. Calc. for $C_{17}H_{22}O_4$: C, 70·32; H, 7·64; O, 22·04%.)

α-Pipitzol benzoate (IIIc). Benzoylation of IIIa with pyridine–benzoyl chloride (2 hr on the steam bath) yielded IIIc, m.p. 116–117° (brilliant plates from MeOH); $[\alpha]_D$ +89°; λ_{max}, 232, 260 mμ; ε, 15600, 4400; IR bands at 1740 with a shoulder at 1755 cm^{-1} (enolic benzoate and cyclopentanone), at 1690 and 1640 cm^{-1} (enolized α-diketone), at 1600 cm^{-1} (aromatic double bonds). (Found: C, 74·95; H, 6·69; O, 18·25. Calc. for $C_{22}H_{24}O_4$: C, 74·98; H, 6·86; O, 18·16%.)

β-Pipitzol benzoate (IVc). A solution of the mixture of pipitzols (15 g) in pyridine (70 ml) was treated with benzoyl chloride (30 ml), heated on the steam bath for 3 hr, poured into cold water with mechanical stirring and the oily precipitate, extracted with AcOEt. The organic layer was washed with dil HCl, $NaHCO_3$aq and evaporated to dryness. Crystallization of the oily residue from benzene–hexane afforded IVc, m.p. 151–153°, yield 4·4 g. From the mother liquors a second crop of crystals was obtained (2·8 g), m.p. 148–151°. The analytical sample showed m.p. 155–156° (needles from acetone–hexane), $[\alpha]_D$ −87·6°; λ_{max} 233, 266 mμ; ε, 21000, 5800; IR bands at 1760 and 1600 cm^{-1} (enolic benzoate), at 1735 cm^{-1} (cyclopentanone), at 1685 and 1635 cm^{-1} (enolized α-diketone). (Found: C, 74·82; H, 6·76; O, 18·51. Calc. for $C_{22}H_{24}O_4$: C, 74·98; H, 6·86; O, 18·16%.)

From the mother liquors were obtained 5 g of impure Vc, m.p. 110°.

β-Pipitzol (IVa). β-Pipitzol benzoate (IVc; 6 g) in MeOH (80 ml) was treated with KOH (6 g) in water (12 ml) and refluxed for 10 min. The clear solution was diluted with water (200 ml), acidified with 20% HCl and the precipitate extracted with AcOEt. The organic layer was washed with $NaHCO_3$aq, water, dried (Na_2SO_4) and evaporated. Crystallization from AcOEt–hexane yielded brilliant plates (3·41 g) m.p. 131–132°, $[\alpha]_D$ −172° positive $FeCl_3$ and Tollens tests; λ_{max}; 244, 282 mμ; ε, 3800, 7100; IR bands at 3450 cm^{-1} (hydroxyl group), at 1760 cm^{-1} (cyclopentanone), at 1670 and 1635 cm^{-1} (enolized, six membered α-diketone). Rotatory dispersion (in dioxan); $[\alpha]_{589}$ −241°; $[\alpha]_{350}$ −2798°; $[\alpha]_{335}$ −4053°; $[\alpha]_{304}$ +4472°. (Found: C, 72·65; H, 8·05; O,19·47. Calc. for $C_{15}H_{20}O_2$: C, 72·55; H, 8·12; O, 19·33%.)

β-Pipitzol acetate (IVb). Acetylation of IVa with Ac_2O and AcONa at room temp for 36 hr, yielded IVb, m.p. 105–106° (prisms from AcOEt) $[\alpha]_D$ −88°; λ_{max} 232, 266 mμ; ε, 6600, 4200; IR bands at 1765 cm^{-1} (broad, enolic acetate and cyclopentanone), at 1680 and 1640 cm^{-1} (enolized α-diketone). (Found: C, 70·47; H, 7·74; O, 22·02. Calc. for $C_{17}H_{22}O_4$: C, 70·33; H, 7·64; O, 22·04%.) A mixture of α and β-pipitzol diacetates showed m.p. 116–117°.

α-Pipitzol oxime (IIId). A solution of IIIa (500 mg) and hydroxylamine hydrochloride (500 mg) in pyridine (8 ml) was heated under reflux for 3 hr, diluted with water and extracted with AcOEt.

[26] See ref. 14.

The organic layer was washed with dil HCl, water and evaporated. Crystallization from MeOH afforded small prisms (170 mg), m.p. 270° (with partial sublimation), $[\alpha]_D$ +163°; λ_{max}; 278 mμ; ε, 7400; IR bands at 3420 cm^{-1} (hydroxyl groups), at 1698 cm^{-1} (C=N double bond), at 1668 and 1638 cm^{-1} (enolized α-diketone). (Found: C, 68·23; H, 7·98; O, 18·63; N, 5·26. Calc. for $C_{18}H_{31}O_3N$: C, 68·41; H, 8·04; N, 5·32%.)

α-Pipitzol oxime diacetate (IIIe). Acetylation of IIId with Ac_2O and pyridine for 1 hr on the steam bath yielded an oily IIIe (this derivative was purified by chromatography on alumina prior to analysis). $[\alpha]_D$ +125·6°; λ_{max}; 248 mμ; ε, 7400. IR bands at 1765 cm^{-1} (broad, acetyl groups), at 1700 and 1668 cm^{-1} (enolized α-diketone), shoulder at 1668 cm^{-1} (C=N double bond). (Found: C, 65·78; H, 7·12; O, 23·26; N, 3·93. Calc. for $C_{19}H_{33}O_5N$: C, 65·69; H, 7·25; O, 23·03; N, 4·03%.)

α-Pipitzol oxime monoacetate IIIf. A solution of Ve (300 mg) in MeOH (7 ml) was treated with $KHCO_3$ (300 mg) in water (3 ml) and heated under reflux for 10 min. The solution crystallized by addition of water. The precipitate was collected and recrystallized from acetone–hexane. This yielded Vf (190 mg), m.p. 181–183°, $[\alpha]_D$ +88°; λ_{max} 247 mμ; ε, 6300; IR bands at 3420 cm^{-1} (hydroxyl group), at 1737 cm^{-1} (acetyl oxime grouping), at 1695 and 1673 cm^{-1} (enolized α-diketone), at 1652 cm^{-1} (C=N double bond). (Found: C, 66·70; H, 7·58; O, 20·79; N, 4·52. Calc. for $C_{17}H_{33}O_4N$: C, 66·86; H, 7·59; O, 20·96; N, 4·59%.)

β-Pipitzol oxime (IVd). Following the procedure described above, IVa (300 mg) yielded IVd (90 mg), m.p. 216–222°. The analytical sample showed m.p. 228° (partial sublimation) (prisms from MeOH), $[\alpha]_D$ −143°; λ_{max} 278 mμ; 7400; IR bands at 3420 cm^{-1} (hydroxyl group), at 1668 and 1638 cm^{-1} (enolized *a*-diketone). (Found: C, 68·33; H, 7·98; O, 18·43; N, 5·30. Calc. for $C_{18}H_{31}O_3N$: C, 68·41; H, 8·04; O, 18·23; N, 5·32%.)

β-Pipitzol oxime diacetate (IVe). Acetylation of IVd with Ac_2O and pyridine for 1 hr on the steam bath, afforded an oily IVe which was purified by chromatography; $[\alpha]_D$ −122°; λ_{max} 248 308–310 mμ; ε, 7400, 130; IR bands at 1765 cm^{-1} (acetyl groups), at 1700 and 1660 cm^{-1} (enolized α-diketone). (Found: C, 65·73; H, 7·27; O, 22·88; N, 3·90. Calc. for $C_{19}H_{35}O_5N$: C, 65·69; H, 7·25; O, 23·03; N, 4·03%.)

Lithium in liquid ammonia reduction of α-pipitzol (IIIa)

A solution of IIIa (1 g) in THF (8 ml), MeOH (8 ml) and liquid NH_3 (100 ml) with mechanical stirring, was treated with Li (2·5 g) until persistence of a blue color (45 min), solid NH_4Cl (8 g) was then added. After evaporation of the NH_3, the residue was acidified with dil HCl and extracted with AcOEt. The organic layer was washed with water, dried (Na_2SO_4), evaporated and the residue (800 mg) chromatographed on alumina (800 g). In the less polar fractions eluted with AcOEt–5% MeOH a small amount (60 mg) of Vc was obtained, m.p. 187–188° (small needles from MeOH–ether, $[\alpha]_D$ +0° (in MeOH); IR band at 3340 cm^{-1} (hydroxyl groups). (Found: C, 75·32; H, 10·56; O, 14·00. Calc. for $C_{15}H_{26}O_2$: C, 75.58; H, 11·00; O, 13·42%.)

From the more polar fractions eluted with AcOEt–10% MeOH, Va (430 mg) was isolated. Crystallization from MeOH–ether yielded needles, m.p. 205–206°, $[\alpha]_D$ +22·6° (in MeOH); IR band at 3340 cm^{-1} (hydroxyl groups). (Found C, 71·06; H, 10·25; O, 18·93. Calc for $C_{15}H_{28}O_2$: C, 70·83; H, 10·30; O, 18·87%.)

Triacetate (Vb). Acetylation of Va with Ac_2O and AcONa (2 hr under reflux) afforded Vb, m.p. 123–124° (prisms from pentane), $[\alpha]_D$ +7°; IR bands at 1740 cm^{-1} (acetyl groups). (Found: C, 6·21; H, 8·65; O, 25·12. Calc. for $C_{21}H_{32}O_6$: C, 66·24; H, 8·48; O, 25·28%.) (Acetyl index 31·41; Calc. for 3 acetyl groups 33·93%.)

Alkaline hydrolysis of Vb regenerated Va.

Lithium in liquid ammonia reduction of β-pipitzol (IVa)

The reduction of IVa was carried out as described for IIIa. The diol (VIb; 70 mg) showed m.p. 230–231°, (needles from acetone–hexane); IR band at 3340 cm^{-1} (hydroxyl groups). (Found: C, 76·03; H, 11·08; O, 13·31. Calc. for $C_{15}H_{28}O_2$: C, 75·58; H, 11·00; O, 13·42%.) The triol (VIa) showed m.p. 156–157° (needles from acetone–hexane): $[\alpha]_D$ −16·3°; IR band at 3340 cm^{-1} (hydroxyl groups). (Found: C, 70·45; H, 10·26; O. 18·94. Calc. for $C_{15}H_{28}O_3$: C, 70·83; H, 10·30; O, 18·87%.)

Oxidation of the diol (Vc). A solution of Vc (50 mg) in AcOH (4 ml) was treated with CrO_3 (60 mg) dissolved in water (0·5 ml). The mixture was left at room temp for 1 hr, diluted with water

and extracted with ether. The organic layer was washed with water and evaporated. Crystallization of the oily residue from aq MeOH yielded VIIa (20 mg), as needles, m.p. 76°, $[\alpha]_D$ +6°; λ_{max} 294 mμ; ε, 50. IR bands at 1738 cm^{-1} (cyclopentanone) and at 1710 cm^{-1} (cyclohexanone). (Found: C, 76·97; H, 9·30; O, 13·92. Calc. for $C_{15}H_{22}O_2$: C, 76·88; H, 9·47; O, 13·65%.)

Mono-oxime (VIIb). It was prepared, following the procedure described for α-pipitzol oxime. It showed m.p. 178° (prisms from MeOH–ether); IR bands at 1740 cm^{-1} (cyclopentanone) and at 1675 cm^{-1} (weak, C=N double bond). (Found: C, 72·27; H, 8·84; O, 13·30; N, 5·75. Calc. for $C_{15}H_{23}O_2N$: C, 72·25; H, 9·30; O, 12·83; N, 5·62%.)

Lactone acid (IX) *of the α-pipitzol series.* The triol (Va; 370 mg) was dissolved in 20 ml MeOH and treated with a solution of HIO_4 (400 mg) in water (5 ml). The mixture was left overnight at room temp, diluted with water and extracted with AcOEt. The organic layer was washed with water, dried over Na_2SO_4 and evaporated to dryness. The crude VIII (360 mg) had an IR band ($CHCl_3$) at 1720 cm^{-1} (aldehyde group). It was dissolved in AcOH (6 ml) and oxidized for 1 hr at room temp with 2 ml of an 20% aq solution of CrO_3, poured in water and extracted with $CHCl_3$. The organic layer was washed with water and extracted with 10% $NaHCO_3$aq. The alkaline solution was acidified with dil H_2SO_4 and extracted with $CHCl_3$. The organic layer was washed with water, dried, evaporated to dryness and the residue (150 mg) sublimed under high vacuum. Crystallization of the sublimate from acetone–hexane yielded IX, m.p. 185–187°; $[\alpha]_D$ +42°; IR bands at 3450 and 1725 cm^{-1} (carboxyl group), at 1765 cm^{-1} (five-membered lactone). (Found: C, 67·59; H, 8·84; O, 24·15. Calc. for $C_{15}H_{22}O_4$: C, 67·64; H, 8·83; O, 24·03%.)

Lactone acid (Xa) *of the β-pipitzol series.* A similar procedure was followed with VIa (500 mg). The oily VIII obtained after the HIO_4 oxidation had an IR band ($CHCl_3$) at 1720 cm^{-1} (aldehyde group). Treatment with CrO_3 afforded Xa (140 mg), m.p. 225–226° (needles from MeOH–ether); $[\alpha]_D$ −6·6°; IR bands at 3450 and 1725 cm^{-1} (carboxyl group), at 1765 cm^{-1} (five-membered lactone). (Found: C, 67·37; H, 8·58; O, 23·84. Calc for $C_{15}H_{22}O_4$: C, 67·64; H, 8·33; O, 24·03%.)

Methyl ester (XIb). Esterification of Xa with an ethereal solution of diazomethane yielded Xb, m.p. 146–147°; (needles form hexane); $[\alpha]_D$ −52·5°. (Found: C, 68·82; H, 9·09; O, 22·42. Calc. for $C_{16}H_{24}O_4$: C, 68·54; H, 8·63; O, 22·83%.)

Alkaline hydrogen peroxide oxidation of α-pipitzol (IIIa). A solution of IIIa (1 g) in 12% NaOHaq (24 ml) was treated with 30% H_2O_2 (8 ml) and distilled until no more oily material was collected, followed by extraction of the distillate with pentane. The organic layer was dried with Na_2SO_4 and evaporated to dryness. The liquid residue (285 mg), according to high resolution gas chromatography (30% silicon SE-30 on chromosorb W), contained 99% of XI. An analytical sample collected, had $[\alpha]_D$ +186°. Rotatory dispersion (in MeOH); $[\alpha]_{589}$ +150°; $[\alpha]_{330}$ +2720°; $[\alpha]_{325}$ +3930; $[\alpha]_{320}$ +3510°. IR band (film) at 1740 cm^{-1} (cyclopentanone). (Found: C, 79·02; H, 10·79. Calc. for $C_{11}H_{16}$: C, 79·46; H, 10·91%.)

The semicarbazone showed m.p. 197·5–198·5°; (needles from aq EtOH). $[\alpha]_D$ +77°. (Found: C, 64·21; H, 9·52; O, 7·12; N, 18·79. Calc. for $C_{12}H_{21}ON_3$: C, 64·54; H, 9·48; O, 7·16; N, 18·82%.)

Alkaline H_2O_2 *oxidation of β-pipitzol* (IVa). The ketone (XII) was obtained similarly by alkaline H_2O_2 oxidation of IVa, with comparable yield and purity. The analytical sample had $[\alpha]_D$ −289°. Rotatory dispersion (in MeOH); $[\alpha]_{589}$ −216°; $[\alpha]_{330}$ −5234°; $[\alpha]_{317.5}$ −5305°; $[\alpha]_{315}$ −4580°. IR band (film) at 1740 cm^{-1} (cyclopentanone). (Found: C, 79·51; H, 10·48; O, 9·90. Calc. for $C_{11}H_{16}O$: C, 79·46; H, 10·91; O, 9·63%.)

The semicarbazone showed m.p. 187–188° (needles from aq EtOH); $[\alpha]_D$ −164°. (Found: C, 64·04; H, 9·40. Calc. for $C_{12}H_{21}ON_3$: C, 64·54; H, 9·4%.)

Deuterium exchange in ketones (XI) *and* (XII). A solution of Na (50 mg) in MeOD (3·5 ml) and D_2O (1·5 ml) was prepared. The ketone (XI; 50 mg) was dissolved in 2 ml of the above solution and left for 4 days at room temp. MeOD was evaporated and the oily layer withdrawn with a pipette. Mass spectrum and NMR analysis showed that 3H were exchanged by D. Similar treatment of XII indicated the presence of a D_3-ketone accompanied by small amount of a D_2-species.

Alkaline treatment of α-pipitzol (IIIa). To a solution of IIIa (1·5 g) in MeOH (30 ml), KOH (3 g) dissolved in water (6 ml) was added and the mixture heated under reflux for 2 hr, concentrated to a small volume *in vacuo*, diluted with water, acidified with dil HCl and the oily precipitate extracted with ether. The organic layer was washed with water, dried over Na_2SO_4 and evaporated. Crystallization of the gummy residue from ether afforded XIIIa as brilliant plates (600 mg), m.p. 192—197°

dec. The analytical sample showed m.p. 206–207°, positive $FeCl_3$ (green colour) and Tollens tests. $[\alpha]_D$ −238°; λ_{max} 277 mμ; ε, 9000; IR bands at 3500 cm^{-1} (hydroxyl groups); at 1700 cm^{-1} (carboxyl group), at 1670 and 1640 cm^{-1} (enolized seven-membered α-diketone). (Found: C, 67·97; H, 8·12; O, 23·85. Calc. for $C_{15}H_{22}O_4$: C, 67·64; H, 8·33; O, 24·03%.)

Acetate (XIIIb). Acetylation with Ac_2O–pyridine for 1 hr on the steam bath afforded XIIIb, m.p. 230–231° dec., (prisms from acetone–hexane); negative test with $FeCl_3$; $[\alpha]_D$ −176·4°; λ_{max} 246 mμ; ε, 10800; IR bands ($CHCl_3$), at 3500 and 1710 cm^{-1} (carboxyl group), at 1680 and 1640 cm^{-1} (enolized α-diketone), at 1750 cm^{-1} (enolic acetate group). (Found: C, 65·91; H, 7·65; O, 26·26. Calc. for $C_{17}H_{24}O_5$: C, 66·21; H, 7·84; O, 25·95%.)

Methyl ester (XIIIc). Brief treatment of a methanolic solution of XIIIa (250 mg) with ethereal diazomethane yielded XIIIc (180 mg); plates from ether hexane, m.p. 114–115°; positive $FeCl_3$ (green colour); $[\alpha]_D$ −160°; λ_{max} 275 mμ; ε, 5600; IR bands at 3450 cm^{-1} (hydroxyl group), at 1732 cm^{-1} (ester group), at 1680 (weak) and 1655 cm^{-1} (enolized α-diketone). (Found: C, 68·46; H, 8·47; O, 23·02. Calc. for $C_{16}H_{24}O_4$: C, 68·54; H, 8·63; O, 22·83%.)

Acetate (XIIId). Acetylation of XIIIc with Ac_2O and pyridine for 1 hr on the steam bath yielded XIIId, m.p. 141–142° (prisms from acetone–hexane); negative $FeCl_3$ test; $[\alpha]_D$ −138°; λ_{max} 246 mμ; ε, 1800. IR bands at 1765 cm^{-1} (enolic acetate group), at 1730 cm^{-1} (ester group), at 1682 and 1640 (enolized α-diketone). (Found: C, 67·04; H, 8·20; O, 25·02. Calc. for $C_{18}H_{26}O_5$: C, 67·06; H, 8·13; O, 24·81%.)

Ozonolysis of the acid (XIIIa). To a solution of XIIIa (500 mg) in AcOEt (25 ml) at −70° a stream of O_3 was passed for 15 min, H_2O_2 (4 ml) was added and the mixture stirred at room temp for 2 hr, concentrated *in vacuo* to a small volume and extracted with sat. $NaHCO_3$aq. The alkaline solution was acidified with dil HCl and the oily precipitate extracted with AcOEt. The organic layer was washed with water and evaporated. Crystallization of the gummy residue from benzene, yielded XIV, m.p. 162°; IR bands at 3460 cm^{-1} (hydroxyl groups) and at 1722 cm^{-1} (cyclopentanone and carboxyl groups). (Found: C, 62·16; H, 8·06; O, 29·86. Calc. for $C_{14}H_{22}O_5$: C, 62·20; H, 8·20; O, 29·59%.)

A small sample sublimed in high vacuum, yielded XV as a viscous oil. It had IR bands (in $CHCl_3$) at 1855 and 1780 cm^{-1} (five-membered anhydride) and 1730 cm^{-1} (cyclopentanone).

$NaBH_4$ *Reduction of the acid* (XIIIa). The acid (XIIIa; 200 mg) was dissolved in THF (20 ml) and $NaBH_4$ (200 mg) added. The mixture was heated under reflux for 5 hr, concentrated to a small volume, diluted with water, acidified with dil HCl and extracted with ether. The ethereal extract was washed with water dried and evaporated. Crystallization of the residue from ether–pentane yielded XVI (50 mg) as prisms, m.p. 138–141°, $[\alpha]_D$ +5°, IR bands at 3510 cm^{-1} (hydroxyl group) and at 1760 cm^{-1} (five-membered lactone). (Found: C, 71·40; H, 9·73; O, 18·98. Calc. for $C_{15}H_{24}O_3$: C, 71·39; H, 9·59; O, 19·02%.)

CrO_3 *Oxidation of the lactone* (XVI). A solution of XVI (200 mg) in AcOH (6 ml) was treated at room temp for 2 hr with CrO_3 (200 mg) in water (1 ml), diluted with water and extracted with ether. The ethereal extract was washed with water, $NaHCO_3$aq, evaporated to dryness and the residue dissolved in hexane was chromatographed on alumina. The crystalline fractions eluted with hexane were combined and recrystallized from pentane yielding XVII (140 mg), as prisms, m.p. 80°; $[\alpha]_D$ −25°, λ_{max} 304 mμ; ε, 50; IR bands at 1780 cm^{-1} (five-membered lactone) and at 1720 cm^{-1} (cycloheptanone). (Found: C, 72·06; H, 8·91; O, 19·05. Calc. for $C_{15}H_{22}O_3$: C, 71·97; H, 8·86; O, 19·17%.)

Benzilic acid rearrangement of the acid (XIIIa). The acid (XIIIa; 500 mg) was dissolved in 10% KOHaq (15 ml) and heated under reflux for 3·5 hr, acidified with dil HCl and extracted with AcOEt. The organic layer was washed with water and evaporated. Crystallization of the residue from acetone–hexane and acetone–benzene yielded XVIIIa (240 mg), m.p. 270–271°, $[\alpha]_D$ −42·5°; IR bands at 3550 cm^{-1} (hydroxyl group) at 1742 (weak) and 1710 cm^{-1} (carboxyl groups). (Found: C, 63·04; H, 8·34; O, 28·21. Calc. for $C_{15}H_{24}O_5$: C, 63·36; H, 8·51; O, 28·13%.)

Dimethyl ester (XVIIIb). The diacid (XVIIIa) was esterified with ethereal diazomethane. It showed m.p. 103–104°; $[\alpha]_D$ −29°; IR bands at 3600 cm^{-1} (hydroxyl group) and at 1720 cm^{-1} (ester groups). (Found: C, 65·41; H, 8·94; O, 25·87; Calc. for $C_{17}H_{28}O_5$: C, 65·36; H, 9·03; O, 25·61%.)

Lead tetra-acetate oxidation of the acid (XVIIIa). The acid (XVIIIa; 500 mg) was dissolved in AcOH (15 ml), treated with lead tetra-acetate (400 mg) and heated for 15 min on the steam bath. The

excess lead tetra-acetate was destroyed with ethylene glycol (1 ml) and the solution diluted with water and extracted with AcOEt. The organic layer was washed with water; evaporated *in vacuo* and the gummy residue dissolved in ether, was treated with an ethereal solution of diazomethane. After 30 min the excess diazomethane was decomposed with a few drops of AcOH; the solution evaporated to dryness; and the residue (360 mg) dissolved in hexane chromatographed on alumina (10 g). The crystalline fractions were eluted with hexane and combined. Crystallization from pentane afforded XIX (170 mg), as prisms, m.p. 97–98°; $[\alpha]_D$ +5°; IR bands at 1730 cm^{-1} (ester group) and at 1710 cm^{-1} (cyclohexanone). (Found: C, 71·35; H, 9·47; O, 19·14. Calc. for $C_{15}H_{24}O_3$: C, 71·39; H, 9·59; O, 19·02%.)

Oxidation of the ester (XIX). A solution of XIX (200 mg) in AcOH (8 ml) was treated with SeO_2 (400 mg), heated under reflux for 20 min, diluted then with water and extracted with $CHCl_3$. The organic layer was washed with $NaHCO_3$aq, water, evaporated and the residue dissolved in hexane chromatographed on alumina. Crystallization from pentane yielded XX (120 mg), m.p. 76–77°. The analytical sample showed m.p. 84–85° (prisms from pentane); $[\alpha]_D$ −122°; λ_{max} 250 mμ; ε, 9800; IR bands at 1732 cm^{-1} (ester group), at 1660 cm^{-1} with a shoulder at 1630 cm^{-1} (α,β-unsaturated cyclohexanone). (Found: C, 72·22; H, 8·42; O, 19·55. Calc. for $C_{15}H_{22}O_3$: C, 71·97; H, 8·86; O, 19·17%.)

Perezinone (XXVI). To a solution of P_2O_5 (50 g) in polyphosphoric acid (150 g), XXIV (8 g) was added and the mixture heated for 5 hr at 70°. The cold solution was poured with mechanical stirring in ice-water, and the precipitate collected and washed with water. The dried product mixed with Na_2SO_4 (8 g) was extracted in a Soxhlet with pentane. From the pentane solution, XXVI (600 mg) crystallized as yellow plates m.p. 146–147°; λ_{max} 204, 324 mμ; ε, 20072, 26500. IR bands ($CHCl_3$) at 3330 cm^{-1} (hydroxyl group), at 1674 cm^{-1} and at 1635 cm^{-1} (α,β-unsaturated ketone). (Found: C, 73·22; H, 7·13; O, 19·83. Calc. for $C_{15}H_{18}O_3$: C, 73·14; H, 7·37; O, 19·49%.)

Dihydroperezinone diacetate (XXVII). A solution of XXVI (1 g) in Ac_2O (15 ml) was hydrogenated with PtO_2 (100 mg) until the absorption of H_2 ceased, AcONa (1 g) was added and the mixture stirred mechanically was left at room temp for 20 hr in H_2 atmosphere. The solution was then poured in water and the precipitate collected washed with water. Crystallization of the dried product from hexane, yielded 910 mg, m.p. 108–109°; λ_{max} 206, 332, 265; ε, 8406, 8208, 5220; IR band at 1760 cm^{-1} (acetyl groups). (Found: C, 68·78; H, 7·27; O, 23·86. Calc. for $C_{19}H_{24}O_5$: C, 68·65; H, 7·28; O, 24·07%.)

Alkaline hydrolysis of XXVII, followed by air oxidation regenerated XXVI.

DDQ *aromatization of the diacetate* (XXVII). A solution of XXVII (500 mg) and DDQ (1·25 g) in xylene (25 ml) was heated under reflux for 6 hr. cooled, filtered and the precipitate discarded. The solution was evaporated to dryness *in vacuo*. The residue was dissolved in benzene–hexane (3:1) filtered and chromatographed on alumina (10 g). The crystalline fractions eluted with benzene–hexane (3:1) were combined and recrystallized from hexane. This yielded 145 mg of XXVIII, m.p. 156–157°, λ_{max} 214, 227, 236 mμ; 31360, 36540, 39129. IR bands ($CHCl_3$) at 1770 cm^{-1} (acetyl groups), at 1660 and 1615 cm^{-1} (C=C double bonds). (Found: C, 69·56; H, 6·19; O, 24·49. Calc. for $C_{19}H_{20}O_5$: C, 69·50; H, 6·14; O, 24·36%.)

Elution with benzene afforded a small amount of a red product, which proved to be identical with the *o*-quinone (XXIX). It showed m.p. 255–260° (see below).

Quinone (XXIX). A solution of XXVI (100 mg) in anh. ether (10 ml), containing freshly prepared Ag_2O (1 g) and Na_2SO_4 (1 g) was left in a stoppered vessel, with mechanical stirring for 48 hr. The solution was filtered, evaporated to dryness and the residue (90 mg) crystallized from benzene–hexane. This yielded red prisms, m.p. 255–260°, λ_{max} 215, 261, 272, 440; ε, 24500, 26190, 21540, 2971. IR bands ($CHCl_3$) at 1685 (weak), at 1615 cm^{-1} (carbonyl bands) and at 1558 (weak, C=C double bonds).

Quinoxaline (XXX). The crude XXIX (90 mg) was dissolved in AcOH (8 ml), treated with *o*-phenylenediamine (90 mg), heated under reflux for 8 hr, left at room temp overnight, the precipitate collected and recrystallized from acetone. This yielded 65 mg of XXX, as yellow needles, m.p. 234–236°. (Found: C, 79·99; H, 5·94; O, 5·30; N, 8·84. Calc. for $C_{21}H_{18}ON_2$: C, 80·23; H, 5·77; O, 5·09; N, 8·91%.)

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