dium sulfate and distilled. Crystallization of the product from ether yielded 4.6 g. (95%) of XVIII, m.p. 158–160°. An analytical sample, recrystallized from ether, melted with decomposition at 160–162°.

Anal. Calcd. for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.18; H, 9.23.

1,1,4,7-Tetramethylphenalan (IV).—A solution of 4.2 g. of XVIII in 110 ml. of benzene was added to 10 g. of powdered phosphorus pentoxide and the suspension was heated under gentle reflux for 3 hours. After cooling the mixture, the phosphorus pentoxide was neutralized with an excess of sodium hydroxide and the mixture was diluted with 200 ml. of water. The water layer was separated and extracted with two 100-ml. portions of ether. The benzene and ether layers were combined, extracted once more with sodium hydroxide and washed four times with water. After drying over sodium sulfate, the ether and benzene were distilled, leaving a tarry-looking residue of 3.6 g. This product was dissolved in petroleum ether and passed twice through a chromatographic column packed with 50 g. of alumina. Upon distillation of the petroleum ether 1.2 g. (33%) of a very light-colored semi-liquid, which solidified only upon standing in an ice-box for a week, was obtained. An analytical sample was obtained by distilling a portion of the product in high vacuum.

Anal. Calcd. for $C_{17}H_{20}$: C, 91.01; H, 8.99. Found: C, 90.97; H, 9.13.

The picrate of IV was prepared from stoichiometric amounts of IV and picric acid. When purified by recrystallization from 95% ethanol, this compound melted at 135.5–136.0° (lit.[1a] 138–139°). A mixed melting point with an authentic sample showed no melting point depression.

Anal. Calcd. for $C_{23}H_{23}N_3O_7$: C, 60.89; H, 5.12. Found: C, 60.83; H, 5.34.

The styphnate of IV was prepared from stoichiometric amounts of IV and styphnic acid. When purified by recrystallization from 95% ethanol, this compound melted at 151.6–152.4° (lit.[1a] 153–154°).

CAMBRIDGE, MASSACHUSETTS

[JOINT CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY AND THE INSTITUTO DE QUIMICA DE LA UNIVERSIDAD NACIONAL AUTONOMA DE MEXICO]

Terpenoids. V.[1] The Isolation of Iresin, a New Sesquiterpene Lactone[2]

BY CARL DJERASSI, PASUPATI SENGUPTA,[3] J. HERRAN AND F. WALLS

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From the Mexican plant *Iresine celosioides* there was isolated a new tricyclic sesquiterpene $C_{15}H_{22}O_4$, now named iresin. Two of the oxygen atoms are present as easily acylable hydroxyl groups while the other oxygen atoms are involved in an α,β-unsaturated five-membered lactone ring.

Iresine celosioides, a shrub occurring commonly in the Federal District of Mexico, belongs to the *Amarantacea* plant family, which from a chemical standpoint has hardly been investigated. It is known popularly as "tlatlancuaya"[4] and extracts of this plant and related *Iresine* species have been used by the natives for the treatment of various diseases including malaria and typhoid.[5] During the present chemical study, which confirmed the earlier reported[6] absence of alkaloids, there was isolated a new sesquiterpene, the preliminary characterization of which forms the subject of the present communication.

The alcoholic extract of *Iresine celosioides* upon dilution with water and addition of lead acetate produced a voluminous precipitate which was discarded. Repeated extraction of the filtrate with chloroform and subsequent evaporation of the solvent yielded a semi-crystalline residue which could be purified readily by chromatography. The pure, crystalline substance thus obtained exhibited m.p. 140–142°, $[\alpha]^{25}\mathrm{D}$ +21°, $\lambda_{\max}^{\mathrm{EtOH}}$ 224 mμ (log ϵ 4.16) and pronounced infrared bands (*cf.* Fig. 1) at 2.95, 5.71 and 5.92 μ. The empirical formula $C_{15}H_{22}O_4$ indicates a sesquiterpenoid structure and we have named this new substance "iresin," the ending "-in" following that of the sesquiterpene lactones santonin and artemisin. With acetic anhydride at room temperature, iresin forms a diacetate, the infrared spectrum of which shows the absence of hydroxyl groups; in addition to the bands at 5.70 and 5.92 μ originally present in iresin, there were now also observed the characteristic acetate bands at 5.80 and 8.10 μ. Mild alkaline saponification at room temperature regenerated iresin, thus demonstrating that two of the oxygen atoms are present as hydroxyl groups. Since iresin is unaffected by lead tetraacetate, the hydroxyl functions cannot be vicinal.

A number of observations lead to the conclusion that the remaining two oxygen atoms form part of a lactone ring. Iresin is soluble in dilute sodium hydroxide solution and cannot be extracted from it with chloroform unless the solution is first acidified. The infrared absorption band at 5.71 μ is typical of an α,β-unsaturated five-membered lactone[7]; this was confirmed by several color reactions[8] given in the experimental portion of this paper and especially by the high intensity ultraviolet absorption maximum at 224 mμ. This is precisely the region in which ultraviolet absorption maxima[9] are exhib-

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(1) Paper IV, C. Djerassi, L. E. Geller and A. J. Lemin, *Chemistry and Industry*, 161 (1954).

(2) We are indebted to the Rockefeller Foundation for funds in support of the plant collections.

(3) Schenley Postdoctorate Research Fellow at Wayne University, 1952–1953.

(4) According to M. Martinez ("Catalogo de Nombres Vulgares y Cientificos de Plantas Mexicanas," Ediciones Botas, Mexico, D.F. 1937) the name "tlatlancuaya" refers to different *Iresine* species depending upon the locality. In the Federal District, it is the presently studied *I. celosioides*, in Puebla, *I. calea*, while in Morelos it applies to *I. interrupta*. We are indebted to Srta. Elizabeth Berlin and Prof. M. Martinez for the botanical identification of our material which was collected in the Federal District.

(5) *Cf.* M. Martinez, "Las Plantas Medicinales de Mexico," 3rd Edition, Ediciones Botas, Mexico, D.F., 1944, p. 285.

(6) F. Villasenor, *Anal. Inst. Medico Nacional* (*Mexico*), **6**, 193 (1903).

(7) *Cf.* J. F. Grove and H. A. Willis, *J. Chem. Soc.*, 877 (1951).

(8) *Cf.* F. A. Kuehl, R. P. Linstead and B. A. Orkin, *ibid.*, 2213 (1950).

(9) *Inter al*, L. J. Haynes and E. R. H. Jones, *ibid.*, 954 (1946); D. D. E. Newman and L. N. Owen, *ibid.*, 4721 (1952); W. G. Dauben and P. D. Hance, THIS JOURNAL, **75**, 3352 (1953).

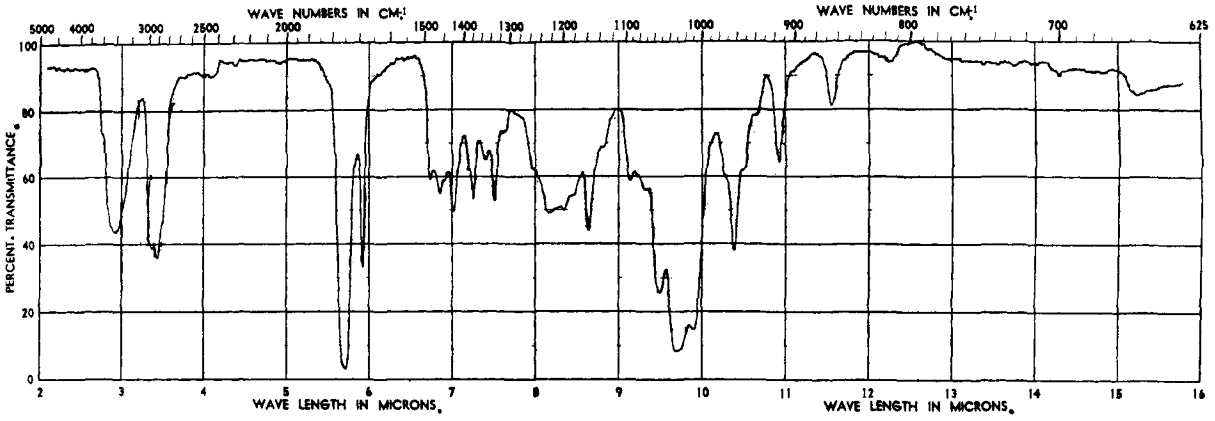
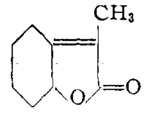


Fig. 1.—Infrared absorption spectrum of iresin in chloroform solution (0.1 cm. cell thickness).

ited by α,β-unsaturated butenolides and the ultraviolet and infrared spectral properties of iresin are thus fully consistent. Of interest is the position of the rather strong infrared band (chloroform solution) at 5.92 μ, to be ascribed to the double bond in the unsaturated lactone ring, and which was also observed ($\lambda_{\max}^{\mathrm{CHCl_3}}$ 5.72 and 5.92 μ) in the lactone of 2-(2-hydroxycyclohexylidene)-propionic acid (I).[10]



I

Iresin did not give any color with tetranitromethane but readily consumed one equivalent of hydrogen in presence of palladized charcoal catalyst to furnish a crystalline dihydro derivative and upon acetylation a diacetate. The spectral properties of this compound further support the presence of an α,β-unsaturated butenolide ring in iresin. Thus, dihydroiresin did not show any selective absorption in the ultraviolet and the infrared spectrum exhibited a carbonyl band at 5.65 μ (5-membered lactone) but no band at 5.92 μ (due to the original double bond in iresin). Of interest is the observation that basic hydrolysis of dihydroiresin diacetate did not regenerate dihydroiresin (by analogy to the ready reconversion of iresin diacetate to iresin) but rather furnished an isomer, isodihydroiresin, further characterized by the formation of a diacetate. Isodihydroiresin could also be obtained directly by base treatment of dihydroiresin and the complete interrelations are summarized

$$\begin{tikzcd}
\text{iresin} \arrow[r, "H_2"] \arrow[d, shift right, "Ac_2O"'] & \text{dihydroiresin} \arrow[r, "OH^-"] \arrow[d, "Ac_2O"] & \text{isodihydroiresin} \arrow[d, "Ac_2O"] \\
\text{iresin diacetate} \arrow[u, shift right, "OH^-"'] \arrow[r, "H_2"] & \text{dihydroiresin diacetate} \arrow[ru, "OH^-"] & \text{isodihydroiresin diacetate}
\end{tikzcd}$$

The base-catalyzed conversion[11] of dihydroiresin to isodihydroiresin could be due either to inversion of the carbon atom adjacent to the lactone carbonyl function (*e.g.*, *cis*-hydrindanone → *trans*-hydrindanone) on the assumption that the unstable isomer was produced in the hydrogenation, or due to relactonization with another hydroxyl group, this alternate relactonization having been inhibited in the case of iresin itself by the double bond. The latter possibility (unless also accompanied by inversion) was excluded by the course of the lithium aluminum hydride reduction of the three lactones: iresin and dihydroiresin furnished the same tetrol[12] while isodihydroiresin yielded an isomer.

Since iresin contains only one double bond, it must possess two rings in addition to the butenolide system. The nature of this ring system and the mode of attachment of the lactone moiety should become apparent from dehydrogenation and other degradation experiments which are now in progress.

Experimental[13]

Isolation of Iresin from *Iresine celosioides*.—The fresh plant (30 kg.), collected near Mexico City, was dried in the sun and then reduced to a coarse, dry powder (4.52 kg.). The entire material was extracted exhaustively with 80% methanol by boiling it repeatedly for 3-hour periods with fresh solvent. The combined methanolic extracts were concentrated to a volume of 2 l., diluted with 3 l. of water and then treated with stirring with an aqueous solution of lead acetate until no more precipitate was formed. After 2 hours, the precipitate was centrifuged and discarded and the clear supernatant liquid was extracted several times with chloroform or ethyl acetate, the organic layers were dried with sodium sulfate and evaporated. Pure iresin could be obtained from the semi-crystalline residue on repeated recrystallization, but this entailed losses which could be avoided by chromatography. The residue, dissolved in chloroform, was chromatographed on 1.3 kg. of activated alumina (ALCOA grade F-20) and the product was eluted with chloroform–acetone. Combination of the crystalline fractions and recrystallization from acetone–hexane furnished 14.4 g. of nearly colorless crystals with m.p. 132–135°.

Further recrystallization from the same solvent furnished the analytical sample of iresin as colorless plates with m.p. 140–142°, $[\alpha]^{28}\mathrm{D}$ +21°, $\lambda_{\max}^{\mathrm{EtOH}}$ 224 mμ, log ε 4.16; the infrared spectrum (chloroform) shown in Fig. 1 shows bands at 2.95, 5.71 and 5.92 μ.[14]

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[10] We are indebted to Dr. W. G. Dauben (*cf.* ref. 9), of the University of California for a sample of this lactone.

[11] The reaction mixture always had to be acidified before the product could be extracted with an organic solvent.

[12] The reduction of the double bond of iresin in the lithium aluminum hydride reduction is not unexceptional (*cf.* W. G. Brown, *Org. Reactions*, **6**, 481 (1951)).

[13] Melting points are uncorrected. Rotations were determined in chloroform and ultraviolet absorption spectra in absolute ethanol solution. The infrared absorption spectra were measured with a Baird Associates double beam recording spectrophotometer. The microanalyses were carried out in part by Mr. Joseph F. Alicino, Metuchen, N. J., and partly by Messrs. R. Mullins and M. Papo (Wayne University).

[14] When measured on a Perkin-Elmer double beam instrument, these bands were found at 1756 and 1691 cm.$^{-1}$. We are indebted to Dr. R. N. Jones of the National Research Council (Ottawa) for this information.

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33; 2-(C)-CH_3, 11.20; mol. wt., 266. Found: C, 67.54; H, 8.36; (C)CH_3 (Kuhn–Roth), 11.44; mol. wt. (Rast), 287.

Miscellaneous Reactions of Iresin.—Iresin did not give any color with tetranitromethane and did not react with semicarbazide or 2,4-dinitrophenylhydrazine. It gave a reddish color in the Legal reaction,[15] with strophanthidin as comparison, while dihydroiresin produced no color. When the sodium nitroprusside and 2,6-dichlorophenolindophenol tests were carried out on iresin according to Linstead's directions,[8] color changes (to yellow) were not observed until *p*H 13 in agreement with the behavior of α,β-unsaturated butenolides. Further evidence for the presence of a lactone ring was presented when 25 mg. of iresin was dissolved in 1 cc. of 0.1 *N* sodium hydroxide solution. Extraction with chloroform removed no material, but acidification, followed by extraction with chloroform, evaporation to dryness and crystallization afforded 20 mg. of iresin with m.p. 138–140° and showing the same infrared spectrum as the original sample.

Iresin Diacetate.—A mixture of 0.5 g. of iresin, 5 cc. of pyridine and 5 cc. of acetic anhydride was kept at room temperature for 24 hours and then was poured into a large volume of ice-water. The precipitate was collected (0.52 g., m.p. 124–125°) and recrystallized from dilute methanol; m.p. 126–127°, unchanged after sublimation at 190° and 0.4 mm., $[\alpha]^{28}D$ +16°, λ_{max}^{EtOH} 224 mμ, log ϵ 4.06, $\lambda_{max}^{CHCl_3}$ 5.70 (lactone), 5.80 (acetate), 5.92 (double bond) and 8.1 μ (acetate).

Anal. Calcd. for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48; 2-CH_3-CO, 25.14. Found: C, 65.59; H, 7.66; CH_3CO, 24.65.

Saponification with 5% methanolic potassium hydroxide solution at room temperature for 20 hours followed by acidification and extraction with chloroform furnished iresin, identified by mixture melting point and infrared spectrum.

Dihydroiresin.—A solution of 0.5 g. of iresin in 50 cc. of ethyl acetate was shaken in an atmosphere of hydrogen at room temperature and atmospheric pressure with 100 mg. of 5% palladized charcoal catalyst. One mole of hydrogen was absorbed within 15 minutes whereupon the catalyst was filtered, the solvent evaporated to dryness and the residue was crystallized from hexane–acetone furnishing 0.41 g. with m.p. 136–140°. Two recrystallizations from the same solvent pair raised the m.p. to 147–148°, $[\alpha]^{28}D$ +5°, no selective absorption in the ultraviolet. The infrared spectrum showed bands at 2.85 and 5.65 μ, but the band at 5.92 μ found in iresin and ascribed to the double bond, was now absent. After drying at 100° and 0.01 mm. for 30 hours, the m.p. was 173–175° (Kofler).

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.01. Found: C, 67.51; H, 9.28.

Dihydroiresin diacetate was obtained in nearly 90% yield by acetylation of dihydroiresin with acetic anhydride–pyridine or by catalytic hydrogenation of iresin acetate, m.p. 210–212° (from methanol), $[\alpha]^{25}D$ +8°, $\lambda_{max}^{CHCl_3}$ 5.64, 5.79 and 8.1 μ.

Anal. Calcd. for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01; 2-CH_3-CO, 25.00. Found: C, 64.53; H, 8.18; CH_3CO, 25.13.

Isodihydroiresin. (a) **From Dihydroiresin.**—A solution of 100 mg. of dihydroiresin (m.p. 138–140°) in 2 cc. of methanol containing 100 mg. of potassium hydroxide was allowed to stand at room temperature for 24 hours. After acidification with cold, dilute hydrochloric acid, the product was extracted with chloroform, the latter was washed with water, dried and evaporated; yield 80 mg., m.p. 204–206°. Recrystallization from hexane–chloroform raised the m.p. to 207–208°, no perceptible optical rotation, $\lambda_{max}^{CHCl_3}$ 2.85 and 5.65 μ, with marked differences in the fingerprint region as compared to dihydroiresin.

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.01. Found: C, 67.07; H, 9.01.

(b) **From Dihydroiresin Diacetate.**—Dihydroiresin diacetate (50 mg.) was treated with methanolic potassium hydroxide exactly as described under (a) except that the time was increased to 48 hours. The usual work-up produced 30 mg. of crystals with m.p. 204–206°, raised to 207–208° on recrystallization. Identity with a specimen prepared according to (a) was established by infrared comparison and mixture melting point.

Isodihydroiresin Diacetate.—Acetylation of 90 mg. of isodihydroiresin with acetic anhydride–pyridine followed by recrystallization from methanol yielded 85 mg. of the acetate with m.p. 170–172°, no perceptible rotation, $\lambda_{max}^{CHCl_3}$ 5.65, 5.80 and 8.1 μ.

Anal. Calcd. for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01; 2-CH_3-CO, 25.00. Found: C, 64.88; H, 8.03; CH_3CO, 24.66.

Lithium Aluminum Hydride Reduction of Iresin.—A solution of 0.52 g. of iresin in 20 cc. of tetrahydrofuran was added dropwise with cooling to a suspension of 1 g. of lithium aluminum hydride in 25 cc. of tetrahydrofuran. After standing for one hour at room temperature, the mixture was refluxed for 5 hours and water was added dropwise to decompose the reagent and any complex formed. The mixture was now dried by the addition of anhydrous sodium sulfate, the precipitated solids and sodium sulfate were removed by centrifugation and the solvent was evaporated *in vacuo*. Trituration of the residue with acetone furnished 0.16 g. of crystals (m.p. 195–205°), while the remainder (0.25 g.) represented an oil (no carbonyl absorption in the infrared) which resisted all attempts at crystallization. Several recrystallizations of the solid from methanol-acetone raised the m.p. to 212–216°, undepressed upon admixture with a sample of the tetrol prepared by reduction of dihydroiresin, λ_{max}^{Nujol} 3.05 μ.

Lithium Aluminum Hydride Reduction of Dihydroiresin.—Dihydroiresin (0.5 g.) was reduced exactly as described above for iresin and yielded 0.15 g. of crystals with m.p. 206–212°. Recrystallization from methanol–acetone furnished the analytical sample of the *tetrol* with m.p. 212–216°, λ_{max}^{Nujol} 3.05 μ. The melting point range could not be narrowed further in spite of additional recrystallizations.

Anal. Calcd. for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36. Found: C, 66.45; H, 10.13.

Acetylation with acetic anhydride–pyridine in the standard manner gave the tetraacetate as a colorless oil which could not be crystallized. A sample for analysis was distilled at 150° (bath temperature) and 0.5 mm.: $\lambda_{max}^{CHCl_3}$ 5.78 and 8.1 μ.

Anal. Calcd. for $C_{23}H_{36}O_8$: C, 62.71; H, 8.24; 4-CH_3CO, 38.74. Found: C, 62.49; H, 8.31; CH_3CO, 37.91.

Lithium Aluminum Hydride Reduction of Isodihydroiresin.—Reduction of 0.5 g. of isodihydroiresin by exactly the same procedure described above for iresin and dihydroiresin furnished 0.24 g. of a crystalline tetrol with m.p. 130–132°, raised to 136–140° upon recrystallization from acetone–hexane: λ_{max}^{Nujol} 2.95 and 3.1 μ.

Anal. Calcd. for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36. Found: C, 65.57; H, 10.08.

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(15) *Cf.* W. D. Paist, E. R. Blout, F. C. Uhle and R. C. Elderfield, *J. Org. Chem.*, **6**, 273 (1941).