Constituents of *Iva* Species. VIII. Structure of Ivalbin, a Modified Guaianolide from *Iva Dealbata* Gray[1,2]

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Ivalbin, a new monocyclic sesquiterpene lactone, has been isolated from *Iva dealbata* Gray and its structure has been established as **1a**. *Iva cheiranthifolia* H. B. K. furnished ivalin and chrysoeriol.

We have extended our systematic study of the genus *Iva* (*Compositae, Heliantheae*, subtribe *Ambrosiinae*) to *Iva dealbata* Gray, whose distribution is limited to west Texas, New Mexico, and the altiplano region of northern Mexico.[3] In the present paper we discuss the structure of ivalbin, a new sesquiterpene lactone from this species.[4]

produce formaldehyde, the presence of partial structure A, common to sesquiterpene lactones of *Iva* species, was indicated. This was confirmed by the nmr spectra; **1a** and **1b** exhibited the typical doublets of the exocyclic methylene group (see Table I) whereas **2a** and **2b** displayed a new methyl doublet. In conjunction with the empirical formula, the presence of two hydroxyl groups and a lactone of type A required that ivalbin be monocyclic.

TABLE I

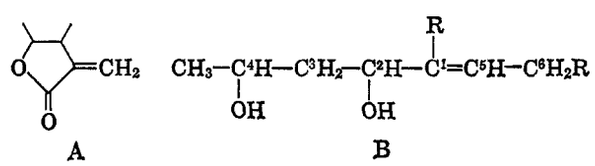
NUCLEAR MAGNETIC RESONANCE SPECTRA OF IVALBIN AND ITS DERIVATIVES[a]

Compd	H_2	H_3	H_4	H_6	H_8[b]	H_{13}	C_4–Me	C_{10}–Me	Misc
1a	4.2 c		4.2 c	5.85 m	4.3 c	6.17 d (3) 5.45 d (3)	1.21 d (6.5)	1.18 d (7.5)	3.3,[c] 3.6[c]
1b	5.22 t (8)		4.85 qd (5)	5.86 dd (10, 4)	4.3 m	6.16 d (3) 5.45 d (3)	1.22 d (6.5)	1.17 d (7.5)	2.05,[d] 2.05[d]
2a	4.2 c		4.2 c	5.82 m	4.2 c	1.21 d (7)	1.21 d (7)	1.21 d (7)	3.6,[c] 3.75[c]
2b	5.25 t (8)		4.85 qd (6)	5.82 dd (9, 5)	4.35 m	1.26 d (7)	1.24 d (7)	1.15 d (7)	2.06,[d] 2.04[d]
3b	...		5.25 sx (7)	7.04 dd (9, 4)	4.30 m	6.13 d (3) 5.47 d (3)	1.28 d (6.5)	1.05 d (7.5)	3.53 m,[e] 1.98[d]
4a	...		4.3 c	6.92 dd (9, 4)	4.3 c	1.24 d (7.5)	1.22 d (6.5)	1.10 d (7)	3.3
4b	...		5.25 sx (7)	6.95 dd (9, 4)	4.30 m	1.26 d (7)	1.22 d (7)	1.08 d (7)	3.56,[e] 1.98[d]
5	...	6.48 dbr (16)[f]	6.9 m[g]	6.85 dd (9, 4)	4.28 m	6.12 d (2.5) 5.45 d (2.5)	1.90 dbr (6)	1.10 d (7.5)	3.48 m[e]
6	...	6.50 dbr (16)[f]	6.9 m[g]	6.85 dd (9, 4)	4.22 m	1.25 d (7)	1.90 dbr (6)	1.12 d (7.5)	3.43 m[e]
8	...	6.10 dd (17, 1)[f]	6.85 m (17, 7)[g,h]		4.06 m	1.18 d (7)	1.98 dd (6.5, 1)	0.97 dd (7.5, 1)	

[a] Spectra were determined in deuteriochloroform solution on a Varian A-60 spectrometer using tetramethylsilane as internal standard. Chemical shifts were in parts per million (ppm), signals denoted in the usual way: d, doublet; t, triplet; q, quartet; sx, sextet; m, multiplet; c, complex band whose center is given; br, slightly broadened singlet; unmarked signals are singlets. Figures in parentheses are line separations in cps. Signals in first five columns correspond to one proton, in sixth column to three protons except for **1a, 1b, 3b,** and **5,** in seventh and eighth column to three protons. [b] Appears generally as a triplet (line separation 11 cps) whose outside components are split into doublets and whose center component is split into a triplet. [c] O*H*, disappears on adding D_2O. [d] Acetate. [e] H-7. [f] Center of A part of ABX_3 spectrum. [g] Center of B part of ABX_3 spectrum. [h] Bands complicated by presence of second conformer.

Ivalbin, $C_{15}H_{22}O_4$, mp 160–162°, $[\alpha]D$ −44.7°, had two hydroxyls (infrared bands at 3750 cm^{-1}, formation of a diacetate **1b**) and a conjugated γ-lactone group (infrared bands at 1760 and 1660 cm^{-1}, very strong end absorption at 205 mμ). Consumption of 3 molar equiv of hydrogen during microhydrogenation suggested that the saturation of two double bonds (disappearance of infrared bands at 1660 and 1630 cm^{-1}) was accompanied by hydrogenolysis of an allylic hydroxyl group. The product appeared to be a mixture of epimers which could be oxidized to a methyl ketone (iodoform test, nmr signal at 2.18 ppm).

Ozonolysis of **1b** indicated the presence of a methylene group (formation of formaldehyde). Treatment of ivalbin or **1b** with sodium amalgam–acetic acid–ethanol or sodium borohydride resulted in reduction of the conjugated lactone and formation of crystalline dihydro derivatives **2a** and **2b** which retained one isolated double bond (nmr spectrum). Since ozonolysis of **2b** did not



The suspected allylic nature of one of the hydroxyl groups was made evident by manganese dioxide oxidation of **1a** and **2a**. The products (**3a** and **4a**) were α,β-unsaturated ketones (infrared bands near 1660 and 1620 cm^{-1}) and were characterized as crystalline acetates **3b** and **4b**. The ultraviolet spectrum of **4b** exhibited a characteristic maximum at 232 mμ (ϵ 11,300); in **3b**, superposition of the π–π^* transitions of the α,β-unsaturated lactone and the α,β-unsaturated ketone resulted in a broad band which obscured the expected peak near 235 mμ.

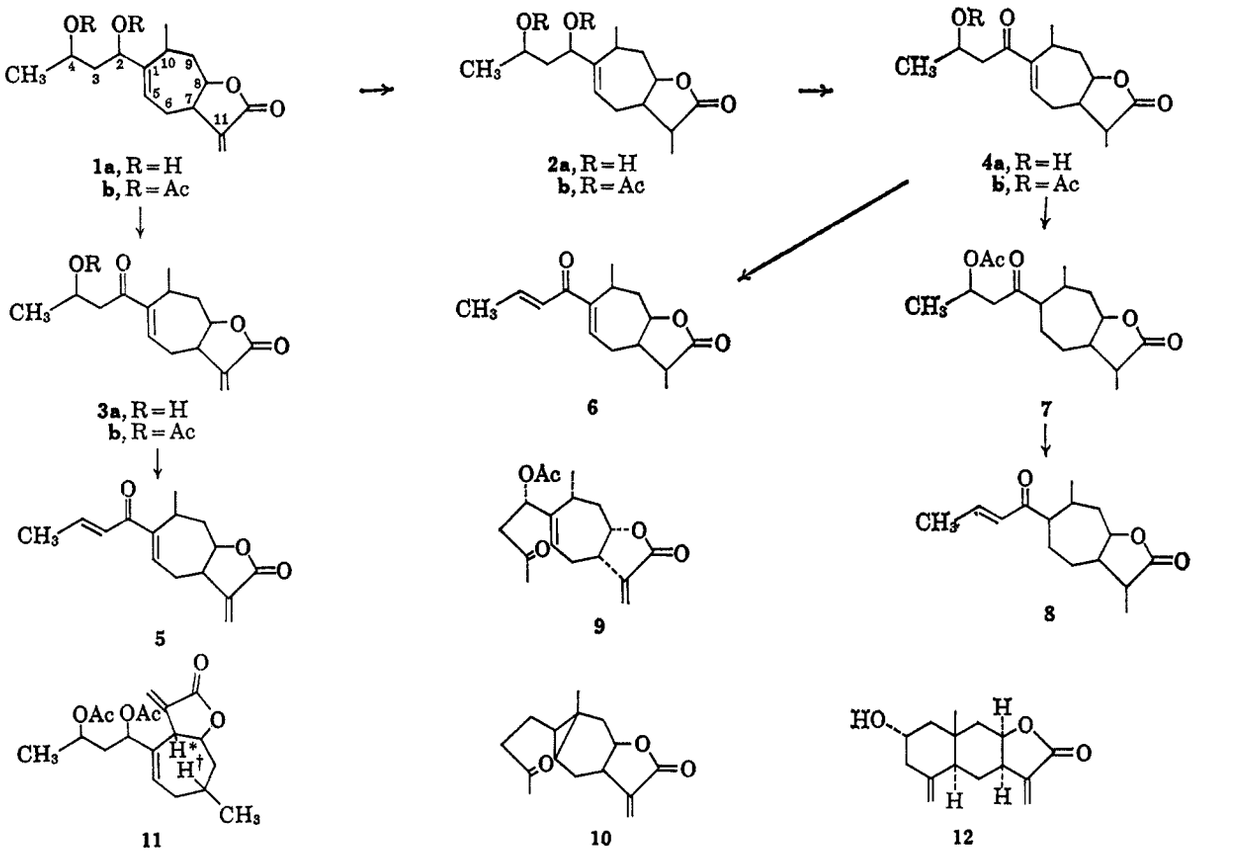
Treatment of **3b** and **4b** with basic alumina resulted in facile elimination of the elements of acetic acid and formation of crystalline, apparently cross-conjugated dienones **5** and **6** [λ_{max} 245 mμ (ϵ 13,000) and 246 mμ

(1) Previous paper: W. Herz, V. Sudarsanam, and J. J. Schmid, *J. Org. Chem.*, **31**, 3232 (1966).

(2) Supported in part by a grant from the U. S. Public Health Service (GM-05814).

(3) R. C. Jackson, *Univ. Kansas Sci. Bull.*, **41**, 793 (1960).

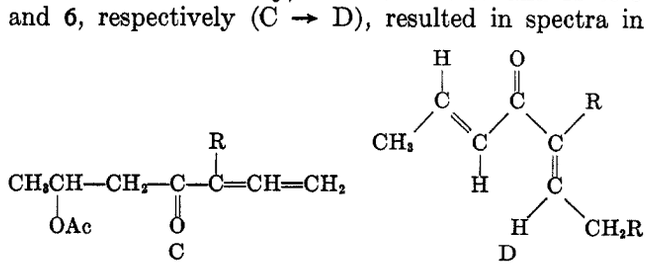
(4) For references to sesquiterpene lactones isolated previously from other *Iva* species, see ref 1.



(ϵ 14,800)].[5] The 1,3 relationship of the two hydroxyl groups indicated in this manner was confirmed by catalytic hydrogenation of **4b** to **7** which on chromatography over alumina was converted to α,β-unsaturated ketone **8**. The ultraviolet maximum of the latter [λ_{max} 227 mμ (ϵ 28,500)] made likely the substitution pattern implied in partial structure B.

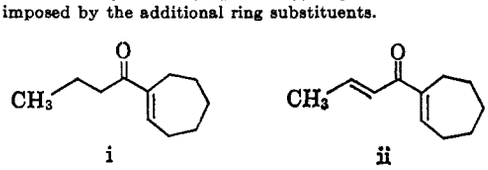
Inspection of the nmr spectra of ivalbin and its derivatives provided proof for B and further delineated structural possibilities (see Table I).[7] In addition to the doublets of the exocyclic methylene group (absent in **2a**) ivalbin and **2a** exhibited signals for four deshielded protons, one at 5.85 and three clustered near 4.2 ppm. The former was clearly that of a vinyl proton (disappearance on hydrogenation) spin coupled to two adjacent hydrogens. Two of the three clustered signals were generated by the protons on carbon carrying the two secondary hydroxyl groups since conversion of **1a** and **2a** to **1b** and **2b** resulted in the characteristic downfield displacement to 5.25 and 4.85 ppm. Multiplicities indicated that the more deshielded proton was spin coupled to two equivalent hydrogens and perhaps a third and that the proton giving rise to the signal at 4.85 ppm was adjacent to one of the two methyl groups of ivalbin which were responsible for two methyl doublets. This would also account for the formation of a methyl ketone commented upon earlier. The proton generating the signal which remained constant near 4.3 ppm was undoubtedly attached to carbon carrying the lactone ether oxygen.

That these assignments were correct became evident when the nmr spectra of the α,β-unsaturated ketones and their transformation products were considered. Comparison of **1b** with **3b** revealed disappearance of one of the acetoxy protons, the remaining one being spin coupled to five equivalent protons. Simultaneously, the resonance of the vinyl proton had experienced a paramagnetic displacement to near 7 ppm, a chemical shift typical of a β hydrogen in an α,β-unsaturated ketone chromophore which because of its multiplicity had to adjoin a methylene group. The absence of other vinylic signals required substitution at the α carbon as in C. Lastly, conversion of **3b** and **4b** to **5** and **6**, respectively (C → D), resulted in spectra in



which the ABX_3 system of the crotonoyl residue could be clearly discerned.[8] In these spectra the α hydrogen of the α,β-unsaturated ketone system (H-3) displayed an unusually great chemical shift (~6.5 ppm). Comparison with the nmr spectrum of **8** where the shift of

(5) That the maxima of **4b** and **5b**, and those of analogous xanthumin derivatives (*vide infra*) are 12 and 5 mμ lower than those of the model compounds i (λ_{max} 244 mμ) and ii (λ_{max} 251 mμ)[6] is perhaps attributable to distortions imposed by the additional ring substituents.



i ii

(6) E. A. Braude and W. H. Forbes, *J. Chem. Soc.*, 2208 (1953).

(7) In order to show the relationship of ivalbin to guaianolides we have adopted the numbering system illustrated in formula **1a**.

(8) "N.M.R. Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, Spectrum No. 1,60,61.

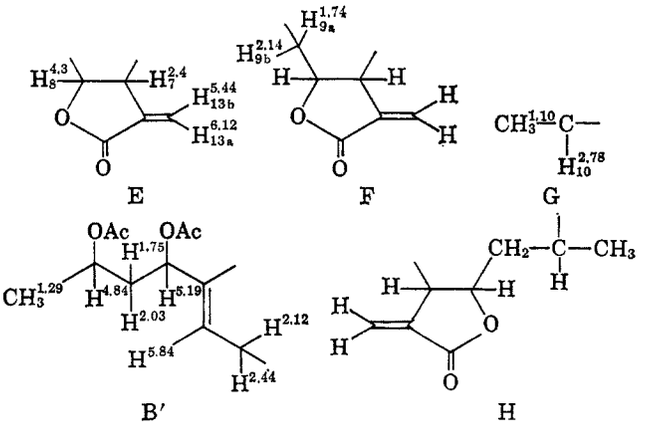
H-3 was more normal (6.1 ppm) and the presence of very strong *cisoid* bands near 1625 cm^{-1} in the infrared spectra of **5** and **6** prompted us to assign the conformation implicit in D to the cross-conjugated chromophore where H-3 experiences a time-averaged deshielding owing to the second double bond.

Since partial formula A and B, none of whose atoms overlap, accounted for 12 of the 15 carbon atoms and since the nmr spectrum had revealed the presence of a second CH_3CH group, the monocyclic nature of ivalbin suggested that it was perhaps another member of the small class of sesquiterpene lactones such as xanthumin (**9**),[9] xanthinin (epimer of **9**),[10] and carabrone (**10**),[11] whose biogenesis presumably involves ring A cleavage of a guaianolide or guaianolide precursor,[12] and that ivalbin might be formulated as **1a**. However, none of its transformation products were identical with transformation products of xanthumin[9] or xanthinin[10,13] and several efforts to obtain useful and well-characterized smaller fragments by oxidative degradation of dihydroivalbin failed. Nevertheless unambiguous evidence for structure **1a** could finally be obtained from extensive spin-decoupling experiments on **1b** and **2b** which will now be discussed.[14]

In the nmr spectrum of **1b**, irradiation at 2.44 ppm (part of a complex four-proton multiplet in the range 2.1–2.9 ppm) collapsed the narrow doublets of the exocyclic methylene group to singlets and reduced the multiplet at 4.3 ppm (hydrogen under lactone oxygen) to a broad doublet. In accordance with previous experience,[15] this established the presence of partial structure E where δ_{H-7} = 2.4 ppm and δ_{H-8} = 4.3 ppm. H-8 in turn was coupled to two protons at 2.12 and 1.74 ppm, the latter part of a three-proton multiplet in the range 1.5–2.05 ppm. This permitted expansion of E to F.

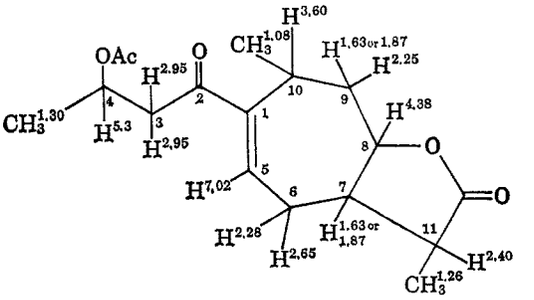
Double irradiation also established that the vinylic resonance at 5.84 ppm was split by coupling to two submerged protons at 2.37–2.45 (J = 10 cps) and 2.12 ppm (J = 4 cps), but was not coupled to any of the protons giving rise to signals in the range 1.5–2 ppm. The allylic methylene group of B′ (other chemical shifts assigned by additional spin-decoupling experiments which need not be described in detail) is therefore not identical with the methylene group of F.

B′, F, and the additional ethylidene group G (chemical shifts assigned by spin decoupling) together accounted for all atoms of diacetylivalbin $C_{19}H_{26}O_6$. Of the several structures which can *a priori* be formed by their combination, all but two could be dismissed by taking into account the observation that irradiation at 2.78 collapsed not only the methyl signal at 1.10, but also affected the resonances in the range 1.5–2.05 ppm. Other signals were not perturbed. The resonances in question are generated by the two methylene protons of B′, which clearly cannot be spin coupled to H-10 of **6**, and by H-9a of F. Hence F can be expanded to H.



Combination of B′ and H permits only **1b** and **11** as possible structures of diacetylivalbin. Of these, **11** was of course quite unlikely on biogenetic grounds, but was also not considered seriously because the starred doubly allylic proton at the junction of lactone and the seven-membered ring would have been expected to resonate at a field lower than the 2.4 ppm actually observed.

Conclusive evidence in favor of formula **1a** for ivalbin came from an examination of the nmr spectrum of **4b**. Because of the deshielding effect of the new ketone group on H-10, the latter's resonance had moved downfield to 3.60 ppm and was now clearly visible as a symmetrical multiplet which collapsed to a narrow *triplet* ($J_{H-10,H-9a} = J_{H-10,H-9b}$ = 2 cps), on irradiation at 1.08 ppm (C-10 methyl resonance). The chemical shift and behavior of this signal on irradiation was quite incompatible with H† in a formula based on **11** (R = H),[16] but was completely in accord with structure **4b** based on **1a**. The effect produced on the H-8 resonance (complex triplet at 4.38 ppm) by irradiation at 1.63, 1.87, and 2.21–2.36 ppm established the location of the H-7, H-9a, and H-9b signals,[17] as indicated in the formula below.



(9) H. Minato and I. Horibe, *J. Chem. Soc.*, 7009 (1965).

(10) T. A. Geissman and P. J. Deuel, *J. Am. Chem. Soc.*, **79**, 3778 (1957); T. A. Geissman, *J. Org. Chem.*, **27**, 2692 (1962).

(11) H. Minato, S. Nosaka, and I. Horibe, *J. Chem. Soc.*, 5503 (1964).

(12) T. A. Geissman, R. J. Turley, and S. Murayama, *J. Org. Chem.*, **31**, 2269 (1966).

(13) L. Dolejs, V. Herout, and F. Šorm, *Collection Czech. Chem. Commun.*, **23**, 504 (1958).

(14) We wish to thank Dr. K. Hatada, Faculty of Engineering Science, Osaka University, for undertaking this work on a JNM-4H-100 spectrometer of the Japan Electron Optics Laboratory Co. The separation of signals and increased resolution obtained by operating at 100 Mc resolved ambiguities which became apparent in the course of preliminary spin-decoupling experiments kindly carried out by Professor R. W. King, Iowa State University, and Mr. J. J. Schmid, Florida State University, on Varian HA-60 nmr spectrometers. In a few instances the chemical shifts observed on the 100-Mc instrument differed slightly from the values given in Table I which were determined on a 60-Mc spectrometer.

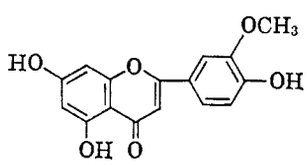
(15) W. Herz, S. Rajappa, M. V. Lakshmikantham, and J. J. Schmid, *Tetrahedron*, **22**, 693 (1966); W. Herz, S. Rajappa, S. K. Roy, J. J. Schmid, and R. N. Mirrington, *ibid.*, **22**, 1907 (1966).

(16) In the nmr spectra of **3b**, **4a**, **5**, and **6** (Table I), H-10 displays the same chemical shifts as in **4b**, but moves back upfield to 2.0 ppm in the nmr spectrum of **8** as predicted from formula **1a**.

(17) The shielded position of the H-7 resonance in **4b** also argues against a structure based on **11**, although a distinction was not made between H-7 and H-9a, the only protons resonating in the range 1.4–2.0 ppm. In the nmr spectrum of **5** (60 Mc), only one proton was found in this range and was identified as H-9a because it was spin coupled to H-10 and H-8.

The deshielding effect of the keto group also rendered evident H-3a and H-3b, formerly at 1.75 and 2.04 ppm, as the AB part of an ABX_3 system centered at 2.95 ppm which collapsed to an AB quartet on irradiation at 5.3 ppm (sextet of H-4 also coupled to methyl doublet at 1.36 ppm). Chemical shifts of H-6a, H-6b, and H-11 which together with H-9b were buried in a four-proton multiplet ranging from 2.1 to 2.75 ppm were determined in the usual manner.

The results described on the preceding pages require that ivalbin be formulated as the modified guaianolide **1a**, the first to be isolated from a member of the section *Cyclachaena* as defined by Jackson.[3] Members of this section which were investigated previously (*I. acerosa* Nutt., *I. nevadensis* M. E. Jones, and *I. xanthifolia* Nutt.) yielded only pseudoguaianolides,[18] a finding which at first appeared to distinguish them chemically from representatives of the sections *Linearbractea* and *Iva*.[19] The latter seem to specialize in the production of eudesmanolides and guaianolides, a conclusion which has now received additional support from an examination of *Iva cheiranthifolia* H. B. K. (section *Iva*). Extraction of this species whose distribution is limited to Cuba and the Bahama Islands furnished as the sole crystallizable constituents the eudesmanolide ivalin (**12**)[20] and the flavone chrysoeriol (**13**).



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Experimental Section[21]

Isolation of Ivalbin.—*Iva dealbata* Gray (above-ground parts) was collected by Dr. N. C. Henderson on Sept 7, 1962, along U. S. Highway 62, 25 miles east of El Paso, Texas (Henderson voucher No. 62-1151) and again in Sept 1963. The powdered plant was extracted with chloroform in the usual manner.[20] In a typical run, 7.1 kg of the 1963 collection furnished 134 g of crude gum which was extracted with 50 ml of hot benzene. The benzene-soluble part, (93 g) was dissolved in 60 ml of ethyl acetate, diluted with petroleum ether, and chilled. The semicrystalline precipitate, (5.2 g) was recrystallized from ethyl acetate and furnished 3.6 g of ivalbin, mp 160–162°. The ethyl acetate–petroleum ether filtrate was evaporated, and the residue was taken up in benzene and chromatographed over 1 kg of silicic acid (Mallinckrodt 100 mesh), 800-ml fractions being collected. Fractions 1–6 (benzene), 7–15 (benzene–chloroform), and 16–30 (chloroform) eluted oils or noncrystallizable gums. Fractions 31–34 (chloroform–methanol, 20:1) eluted approximately 28 g of gum which partially polymerized on standing. Fractions 35–40 (chloroform–methanol, 20:1) eluted approximately 15 g of semicrystalline material which yielded 7.0 g of ivalbin after recrystallization from ethyl acetate. The more polar fractions (chloroform–methanol, 4:1) eluted gums. The benzene-insoluble material from three extractions (110 g) was chromatographed over 1 kg of silicic acid and furnished an additional 8.5 g of ivalbin, mp 160–162°, in the chloroform–methanol (20:1) eluates. The yield of ivalbin averaged 0.19%.

Pure ivalbin melted at 160–162°; $[\alpha]^{26}D$ −44.7° (*c* 1.835); infrared bands at 3750, 1760, 1660, and 1630 cm^{-1}; no λ_{max} [end absorption 203 mμ (ε 16,300)].

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33; O, 24.03. Found: C, 67.77; H, 8.10; O, 23.79.

Acetylation of 0.23 g of ivalbin with pyridine–acetic anhydride at room temperature and recrystallization of the crude product from ethanol–water furnished 0.21 g of ivalbin diacetate (**1b**) as colorless needles: mp 111–112°; $[\alpha]D$ −53.1° (*c* 1.83); infrared bands at 1770, 1728 (double strength), 1653, and 1600 cm^{-1}.

Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48; O, 27.40. Found: C, 65.25; H, 7.78; O, 27.40.

The di-*p*-bromobenzoate was prepared with benzoyl chloride–pyridine and recrystallized from ethanol–water, mp 132°.

Anal. Calcd for $C_{29}H_{28}Br_2O_6$: C, 55.10; H, 4.42. Found: C, 55.26; H, 4.62.

A solution of 0.2 g of ivalbin in 25 ml of acetic acid was reduced at atmospheric pressure with prereduced platinum oxide. Hydrogen uptake ceased after absorption of 2.85 molar equiv of hydrogen. The gummy product was chromatographed over alumina and silicic acid, but could not be obtained in crystalline form; infrared bands at 3600 and 1700 cm^{-1}; nmr signals at 4.2 m (H-8), 4.0 m (H-4), 1.20 d (7, six protons) and 0.98 d (7, three protons). Attempts to convert this material to crystalline diacyl derivatives failed. Oxidation of 0.15 g of the gum with 0.2 g of chromic acid in 3 ml of acetic acid and 0.5 ml of water resulted in gummy material which gave a positive iodoform test and was chromatographed over alumina; nmr signals at 4.2 c (H-8), 2.8 (three protons, methyl ketone), 1.23 d (7, C-11 methyl), and 0.98 dd (7, 2, C-10 methyl). The appearance of the last signal suggested the presence of a mixture.

A solution of 0.2 g of **1b** in 20 ml of acetic acid was ozonized at 0° for 1 hr, diluted with water, and steam distilled into a chilled saturated aqueous solution of dimedone. After standing there precipitated 0.1 g of the dimedone derivative of formaldehyde, mp 182–183°.

Dihydroivalbin (2a).—A solution of 0.39 g of **1a** in methanol was reduced with 50 mg of sodium borohydride at 0° and allowed to stand at room temperature for 2.5 hr, mixed with 1 ml of 2 *N* sulfuric acid, diluted with 10 ml of water, and extracted with chloroform. The washed and dried chloroform extracts were evaporated and the residue was recrystallized from ethyl acetate–petroleum ether: mp 128–129°; yield 60 mg; $[\alpha]^{28}D$ −16.2° (*c* 1.2); infrared bands at 3500 and 1770 and 1595 cm^{-1}; strong ultraviolet end absorption 203 mμ (ε 5800).

Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02; O, 23.85. Found: C, 67.14; H, 8.87; O, 24.12.

The yield was considerably improved by reduction with sodium amalgam. To a solution of 1 g of ivalbin in 40 ml of ethanol was added gradually with stirring over 1.5 hr 80 g of 3% sodium amalgam, the solution being maintained at a slightly acidic pH (phenolphthalein) by periodic addition of acetic acid. The solution was concentrated to small volume, diluted with water, and extracted with chloroform. The washed and dried chloroform extracts were evaporated and the residue was recrystallized from ethyl acetate–petroleum ether, yielding 0.68 g of **2a**, mp 126–127°.

A number of attempts to oxidize **1a** (potassium permanganate–aqueous acetic acid, ozone and oxidative work-up of the ozonide, peracetic acid, etc.) resulted in gummy acidic fractions which could not be characterized satisfactorily.

Diacetyldihydroivalbin (2b).—Reduction of 0.91 g of **1b** with 0.19 g of sodium borohydride in the manner described for **1a** resulted in 0.7 g of crude **2b** which was recrystallized from ethanol–water: mp 88.5–80.5°; $[\alpha]^{26}D$ −35.5° (*c* 2.01); infrared bands at 1770, 1725 (double strength), and 1650 cm^{-1}, identical with material prepared by acetylation of **2a**.

Anal. Calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 28.01; O, 27.41. Found: C, 64.72; H, 7.92; O, 27.00.

Hydrolysis of 0.97 g of **2b** with a 2% potassium hydroxide solution in boiling methanol for 1 hr, evaporation of solvent, dilution with water, acidification, and extraction with chloroform furnished 0.7 g of crude dihydroivalbin, mp 127–128° after recrystallization, yield 0.52 g. Attempts to hydrolyze one of the acetyl functions selectively did not succeed.

(18) L. Farkas, M. Nogradi, V. Sudarsanam, and W. Herz, *J. Org. Chem.*, 3228 (1966).

(19) Since ivalbin represented only a fraction of the total sesquiterpene lactone content of *I. dealbata* (see the Experimental Section) it would be premature to consider possible taxonomic implications of its discovery. We have not yet been successful in characterizing other constituents of *I. dealbata*.

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

(21) Melting points are uncorrected. Infrared spectra were run in chloroform, ultraviolet spectra were determined in 95% ethanol, rotations were taken in chloroform, nmr spectra were determined in deuteriochloroform using TMS as internal standard, unless otherwise specified. Petroleum ether was the fraction boiling point at 35–60°. Analyses were preformed by Dr. F. Pascher, Bonn, Germany.

Acetyldehydroivalbin (3b).—A mixture of 1.5 g of ivalbin and 6 g of activated manganese dioxide in 150 ml of benzene was stirred under reflux for 18 hr and filtered. The precipitate was washed with hot chloroform and the combined filtrate and washings were evaporated at reduced pressure. The residual oil was dissolved in chloroform and chromatographed over 27 g of silicic acid. Fractions were monitored by tlc. Fractions 5–12 (100 ml each) contained 0.3 g of **3a**. Fractions 13–30 (100 ml each) contained 0.7 g of recovered **1a**. Fractions 5–12 were combined and were acetylated with acetic anhydride–pyridine. The crude product was recrystallized from ethanol–water: yield 0.13 g; mp 89–90°; $[\alpha]^{26}D$ −116° (*c* 1.74); strong ultraviolet end absorption 203 mμ (ε 16,300); infrared bands at 1770, 1720, 1660, and 1620 cm^{-1}.

Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24; O, 26.11. Found: C, 66.85; H, 7.09; O, 26.04.

Anhydrodehydroivalbin (5).—A solution of 0.14 g of **3b** in benzene was chromatographed over a column of basic alumina (Alcoa F-20). The eluate was evaporated and recrystallized from ethanol–water: yield 40 mg; mp 117–118°; $[\alpha]^{26}D$ −59.0° (*c* 0.915); infrared bands at 1770, 1650, and 1625 cm^{-1} (very strong, *cisoid* double bond).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37; O, 19.49. Found: C, 73.33; H, 7.24; O, 19.74.

Oxidation of Dihydroivalbin.—A solution of 1.75 g of **2a** in 150 ml of benzene was refluxed with 6 g of activated manganese dioxide for 19 hr. The product was worked up as described for **3a**. The residue (three spots on tlc) was dissolved in chloroform and chromatographed over 20 g of silicic acid, the fractions being monitored by tlc. Fraction 1, anhydrodehydrodihydroivalbin (**6**), crystallized on removal of solvent and was recrystallized from ethanol–water: mp 97–98°; $[\alpha]^{27}D$ −43.2° (*c* 0.821); infrared bands at 1770, 1655, and 1620 cm^{-1} (very strong, *cisoid* double bond); λ_{max} 246 mμ (ε 14,800).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12; O, 19.33. Found: C, 72.32; H, 8.00; O, 19.63.

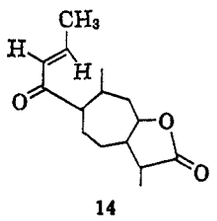
The second fraction, dehydrodihydroivalbin (**4a**), was an oil: 0.86 g; infrared bands at 3550, 1770, 1670, and 1630 cm^{-1}. The last fraction was starting material (0.46 g).

Acetylation of 0.8 g of **4a** with 1.5 ml of acetic anhydride and 6 ml of pyridine furnished 0.7 g of crude acetyldehydrodihydroivalbin (**4b**) which was recrystallized from ethanol–water: mp 97–98°; $[\alpha]^{27}D$ −78.0° (*c* 1.31); infrared bands at 1775, 1725, 1670, and 1625 cm^{-1}; λ_{max} 232 mμ (ε 11,300).

Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85; O, 25.94. Found: C, 66.51; H, 7.89; O, 25.62.

A solution of 0.1 g of **4b** in benzene was chromatographed over basic alumina. The eluate was concentrated and the residue (60 mg) was recrystallized from ethanol–water, mp 93–94°, identical with **6** obtained from the oxidation experiment.

Anhydrotetrahydroivalbin (8).—A solution of 0.3 g of **4b** in 20 ml of ethanol was reduced at atmospheric pressure with 0.22 g of 5% palladium–barium carbonate catalyst. Hydrogen uptake ceased after the absorption of 1 molar equiv. Filtration and removal of solvent yielded 0.29 g of viscous oil (**7**, one spot on tlc); infrared bands at 1765, 1725, and 1715 cm^{-1}. A solution of 0.2 g of **7** in 10 ml of benzene was chromatographed over 6 g of basic alumina. Chloroform eluted a viscous oil: homogeneous on tlc; 90 mg; bp 140–150° (0.3 mm); $n^{25}D$ 1.500, $[\alpha]^{25}D$ +23.8° (*c* 1.325); infrared at 1765, 1690, 1660 (weak, *transoid* (double bond), 1625 cm^{-1} (strong *cisoid* double bond); λ_{max} 227 mμ (ε 28,500). The presence of two double-bond frequencies and the splitting of the H-4 and C-10 methyl signals in the nmr spectrum suggested the possible presence of two conformers (**8** and **14**) in chloroform solution. The dinitrophenylhydrazone, prepared, in the usual fashion, was recrystallized from ethyl acetate–ethanol and melted sharply at 198–199°, λ_{max} 373 mμ (ε 17,000).



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Anal. Calcd for $C_{21}H_{26}N_4O_6$: C, 58.59; H, 6.09; N, 13.02. Found: C, 58.37; H, 6.17; N, 12.73.

Extraction of *Iva Cheiranthifolia* H. B. K.—The plant was collected on Nov 1, 1964, by Dr. Sidney McDaniel and Mr. John Schmiederer, 3 miles southeast of Freeport, Grand Bahamas Island, along the edge of a pine ridge behind the beach. The above-ground parts (2.75 kg) were extracted in the usual fashion[20] with chloroform, yield of crude gum being 50 g. It was chromatographed over 250 g of silicic acid, 400-ml fractions being collected. Fractions 1–18 (benzene) gave gums (mixture containing more than four constituents by tlc). Fractions 19–21 (chloroform–benzene, 1:4) and 22–26 (chloroform–benzene, 1:3) also eluted mixtures (at least three components). Fractions 27–32 (chloroform–benzene, 1:2) eluted a mixture which contained one major component. Fractions 33–37 (chloroform–benzene, 1:1), 38–42 (chloroform–benzene, 1:2), 43–47 (chloroform–benzene, 1:3), and 48–55 (chloroform) gave mixtures containing at least three components. Fractions 56–60 (chloroform–methanol, 99:1), 61–64 (chloroform–methanol, 40:1), 65–69 (chloroform–methanol, 19:1), and the more polar eluates yielded dark greens gums which gave streaks on tlc.

Rechromatography of fractions 27–32 over 50 g of silicic acid (eluates benzene, benzene–ether in various proportions, and ether) indicated partial purification in the benzene–ether (6:1) fraction. The gummy residue was dissolved in hexane containing the minimum amount of ether and was allowed to evaporate slowly at room temperature. The solid which separated was recrystallized from ether–hexane: mp 132–134°; yield 0.2 g; infrared bands at 3700, 3500, 1765 (γ-lactone), 1665, and 1645 cm^{-1} (double bonds); nmr signals at 6.07 d and 5.57 d (conjugated $=CH_2$), 4.8 d (one proton of $=CH_2$), 4.5 c (two protons, second proton of $=CH_2$ superimposed on proton under lactone oxygen), 3.75 c (*H*COH), and 0.81 (singlet methyl) ppm. The material was identified as ivalin by direct comparison with authentic material;[20] the mixture melting point was undepressed.

Fractions 65–69 were triturated with chloroform. The solid which separated was recrystallized from methanol–acetonitrile and from methanol. The yellow flavonoid (15 mg) had mp 326–328° (Kofler); nmr signals (deuteriodimethyl sulfoxide) at 13.2 (chelated hydroxyl), 7.7 c (H-2′ and H-6′ superimposed), 7.1 d (9, half of AB system, H-5′), 6.95 (H-3), 6.66 d (2, H-8), 6.33 d (H-6) ppm, methoxy submerged under water signal. Acetylation of 8 mg of flavone with acetic anhydride–sodium acetate at reflux temperature and chromatography of the crude product over silicic acid furnished 8 mg of a triacetate: mp 220–222°; nmr signals at 7.4 d (J = 9 cps, half of AB system, H-6′), 7.35, 7.2 (H-2′ and H-8), 7.12 d (J = 9 cps, half of AB system, H-5′), 6.81 d (J = 2 cps, H-6), 6.60 (H-3), 3.88 (methoxyl), 2.42 (acetate), and 2.32 ppm (two acetates). These data suggested that the flavone from *I. cheiranthifolia* was chrysoeriol (lit.[22] mp 330–331°), mp of acetate 220–221°. Direct comparison of the flavone with an authentic sample of synthetic chrysoeriol[23] (melting point, mixture melting point, and infrared spectrum) established its identity.

Rechromatography of the other fractions failed to yield homogeneous solid material.

Registry No.—**1a**, 7544-65-2; **1b**, 7544-66-3; **2a**, 7544-67-4; **2b**, 7561-75-3; **3b**, 7544-68-5; **4a**, 7544-69-6; **4b**, 7544-70-9; **5**, 7544-71-0; **6**, 7561-76-4; **8**, 7544-72-1; **1b** di-*p*-bromobenzoate, 7550-94-9; chrysoeriol, 491-71-4; **14**, 7550-95-0; **8** dinitrophenylhydrazone, 7544-73-2.

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(22) J. Gripenberg in "The Chemistry of Flavonoid Compounds," T. A. Geissman, Ed., The MacMillan Co, New York, N. Y., 1962, p 422.

(23) We wish to thank Dr. R. M. Horowitz for supplying this material.