dimethyl ketal identical with that reported.[13] The α-hydroxy ketal gave a colorless 3,5-dinitrobenzoate, mp 97–98° (lit.[13] 97–98°).

Also when a small crystal of *p*-toluenesulfonic acid was added to 1.5 g (9.4 mmol) of the hydroxy ketal, and the mixture was allowed to remain at room temperature for 24 hr, a crystalline material weighing 1.1 g (4.1 mmol, 87%) was isolated and identified as dodecahydro-4a,9a-dimethoxydibenzo-*p*-dioxin, mp 167–168° (lit.[14] mp 165°).

Reaction of 2-Chlorocyclohexanone (19) with 2.0 *M* Sodium Methoxide in Methanol.—A 100-ml solution of 2.0 *M* sodium methoxide in methanol was added to 5.0 g (37.5 mmol) of **19**, and the cloudy mixture was stirred for 45 min. The mixture was cooled, and 15 g (>0.2 mol) of glacial acetic acid in 50 ml of methanol was added. Methanol (100 ml) was removed by distillation through a Vigreux column. The moist solid that remained was mixed with 200 ml of pentane, and the inorganic precipitate was removed by filtration. The filter cake was washed several times with pentane, and the filtrate was concentrated by the distillations of pentane through a Vigreux column and methanol (40 ml) through a microware column packed with glass helices. The residue was applied to a slurry-packed (10% ether in hexane) silica gel (250 g) column and eluted as in the above experiment. Fractions (250 ml) 12–16 contained 2.83 g (17.7 mmol; 47%) of 2-hydroxycyclohexanone dimethyl ketal identical with that described above. There was no 2-methoxycyclohexanone detected.

(13) C. L. Stevens and J. Tazuma, *J. Amer. Chem. Soc.*, **76**, 715 (1954).
(14) M. Bergman and M. Gierth, *Justus Liebigs Ann. Chem.*, **448**, 48 (1926); R. Criegee and W. Schnorrenberg, *ibid.*, **560**, 144 (1948).

Registry No.—6 (X = Cl), 19054-51-4; 6 (X = Br), 19209-96-2; **7a**, 17245-79-3; **7b**, 17245-80-6; **8**, 37107-95-2; **8a**, 37107-96-3; **9**, 37107-97-4; **10**, 37107-98-5; **10** oxime, 37111-95-8; **11**, 37107-99-6; **12**, 37108-00-2; **13**, 37108-01-3; **17**, 37108-02-4; **19**, 822-87-7; 2-methoxy-4-methyl-*cis*-4-phenylcyclohexanone, 37108-03-5; 2-hydroxy-4-methyl-4-phenylcyclohexanone dimethyl ketal, 37111-97-0; 2-hydroxy-4-methyl-4-phenylcyclohexanone dimer, 37164-32-2.

Acknowledgment.—This work was supported by the National Science Foundation Grant No. GP 4208 and GP 7065.

Ivalbatin, a New Xanthanolide from *Iva Dealbata*[1a]

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Ivalbatin, a new xanthanolide, has been isolated from *Iva dealbata* Gray and its gross structure established as **2**. The stereochemistry of ivalbin and ivalbatin is discussed and formulas **23** (stereochemistry at C-2 still uncertain) and **26** (stereochemistry at C-6 questionable) are derived.

In an earlier communication[2] we derived a gross structure for ivalbin (**1**), a crystalline xanthanolide from *Iva dealbata* Gray. In the present paper we report isolation and structure determination of a second new xanthanolide (**2**) from *Iva dealbata*, which we have named ivalbatin, and discuss the stereochemistry of ivalbin and ivalbatin. For the former, formula **23** is deduced, although the stereochemistry at C-2 remains uncertain, for the latter formula **26**, with the stereochemistry at C-6 still in doubt.

As ivalbatin was obtained as an unstable oil and polymerized rapidly, it was purified by immediate conversion into the crystalline acetate **3**, $C_{17}H_{22}O_5$. The yield of **3**, based on the crude chloroform extract, was 16.8%, twice the amount of ivalbin; hence, ivalbatin is the major sesquiterpene lactone of this species.

Ivalbatin had $[\alpha]^{24}D$ −84°, uv end absorption at 210 nm (ε 13,400) and ir bands at 3450 (OH), 1755 (γ-lactone), 1705 (ketone), and 1655 cm^{-1} (C=C). A comparison of the nmr spectra of **2** and **3** revealed only one significant change, signals at 3.65 (>CHOH) and 3.40 ppm (>CHOH) being replaced by signals at 4.80 (>CHOAc) and 2.11 ppm (>CHOCOCH$_3$), respectively. Hence formula $C_{15}H_{20}O_4$ containing a secondary alcohol group could be assigned to ivalbatin. Other functional groups of **3** were the following: conjugated lactone as evidenced by ir bands at 1755 and 1655 cm^{-1}, uv end absorption at 209 nm (ε 13,800), and an nmr signal

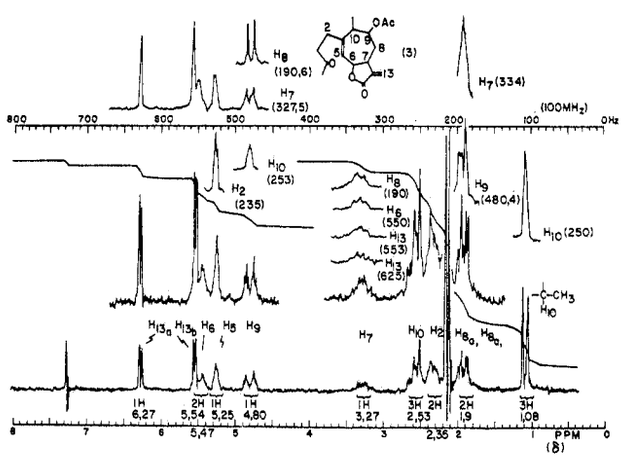


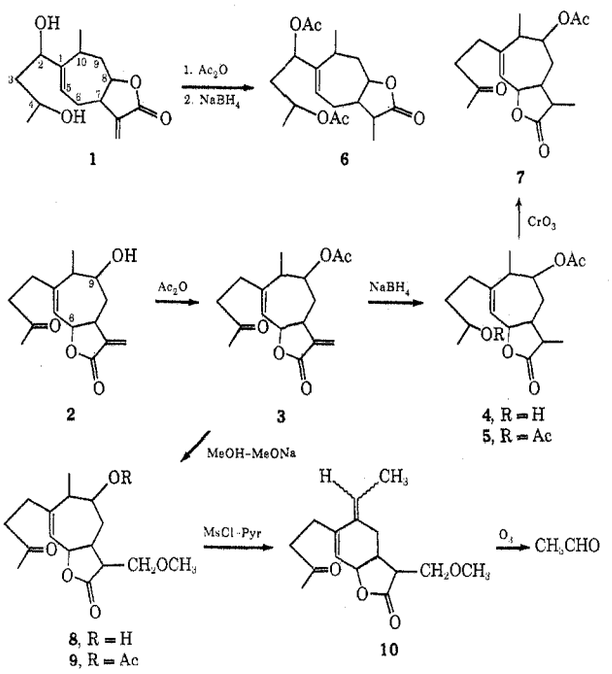
Figure 1.—Nmr spectrum and spin decoupling of acetylivalbatin (**3**).

characteristic of hydrogen under lactone at 5.47 ppm (Figure 1); methyl ketone (iodoform test, ir band at 1720 cm^{-1}, nmr signal at 2.17 ppm); secondary methyl (three-proton doublet at 1.08 ppm); trisubstituted double bond (one-proton broadened singlet at 5.25 ppm); and an exocyclic methylene group conjugated with the lactone group (two one-proton doublets at 5.54 and 6.27 ppm).

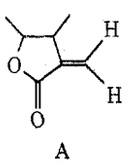
The presence of the exocyclic methylene group was confirmed by ozonolysis of **3** which yielded formaldehyde. Treatment of **3** with sodium borohydride gave an alcohol **4** which polymerized on standing and was converted into a diacetate **5** ($C_{19}H_{28}O_6$) (see Scheme I). The latter was not identical with diacetyldihydro-

(1) (a) Paper XIV: Constituents of *Iva* Species. For paper XIII, see G. D. Anderson, R. S. McEwen, and W. Herz, *Tetrahedron Lett.*, 4423 (1972). (b) Osaka University. (c) Florida State University. Work supported in part by a grant from the U. S. Public Health Service (CA-13121).
(2) W. Herz, H. Chikamatsu, N. Viswanathan, and V. Sudarsanam, *J. Org. Chem.*, **32**, 682 (1967).

SCHEME I



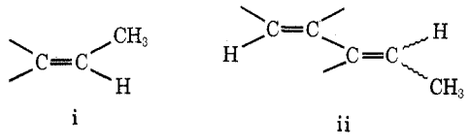
ivalbin (**6**). Oxidation of **4** with Jones reagent gave dihydroacetylivalbatin (**7**). That reduction of the exocyclic methylene group had taken place in **5** and **7** was indicated in the ir spectra by a shift of the γ-lactone band to higher wavenumber, in the uv spectra by a decrease in the end absorption, and in the nmr spectra by the disappearance of the two vinyl doublets and the appearance of a second methyl doublet. Further confirmation for the presence of partial structure A in ivalbatin was the formation of a noncrystalline



A

adduct **8**, characterized as the crystalline acetate **9** (nmr spectrum in Figure 3),[3] on treatment of **3** with sodium methoxide–methanol under mild conditions.

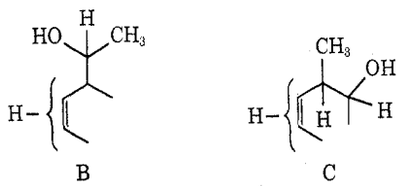
Dehydration of **8** with methanesulfonyl chloride–pyridine or treatment of **8** tosylate with lutidine gave a noncrystalline conjugated diene **10**, $C_{16}H_{22}O_4$, λ_{max} 239 nm (ϵ 11,550), whose nmr spectrum (Figure 4)[3] no longer exhibited the signal of a secondary methyl group, but had a new vinyl methyl doublet at 1.75 ppm obviously coupled to a new vinyl quartet at 5.86 ppm. This was confirmed by spin decoupling (Figure 4); the presence of partial structure i deduced in this manner was confirmed by ozonolysis of **10** which liberated acetaldehyde. Since the conversion of **8** into **10** had also resulted in the transformation of the broadened vinyl proton singlet of **8** at 5.15 ppm to a distinct doublet at lower field (5.46 ppm), the existence of partial structure ii, where the methyl-substituted



i ii

double bond is exocyclic (calcd λ_{max} 239 nm[4]), in **10** was assured.

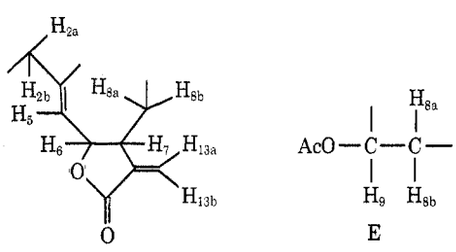
Although the dehydration reaction leading to **10** could be interpreted in terms of partial structure B, spin-decoupling experiments on **3** (Figure 1) established the presence of C rather than B in **3** and there-



B C

fore in **8**. Thus, irradiation at 2.53 ppm (H-10) collapsed the methyl doublet at 1.08 ppm to a singlet and the doublet of triplets at 4.80 ppm (hydrogen under acetate, H-9) to a broad singlet, while irradiation at the frequency corresponding to H-9 did not affect the methyl doublet. Hence dehydration of **8** was accompanied by rearrangement of the carbon skeleton.

Double resonance experiments on **3** (Figure 1) allowed expansion of A to partial structure D. Irradiation at the frequencies of the exocyclic methylene group (H-13a and H-13b) caused simplification of the multiplet at 3.27 ppm (H-7). Conversely, irradiation at the frequency of H-7 collapsed not only the doublets at 5.54 and 6.27 ppm (H-13a and H-13b), but affected also the signals of the lactone proton (H-6) and a methylene group (H-8a and H-8b), the double doublet at 5.47 ppm (H-6) collapsing to a doublet, and the multiplet at 1.8–2 ppm (H-8a and H-8b) to a singlet.



D E

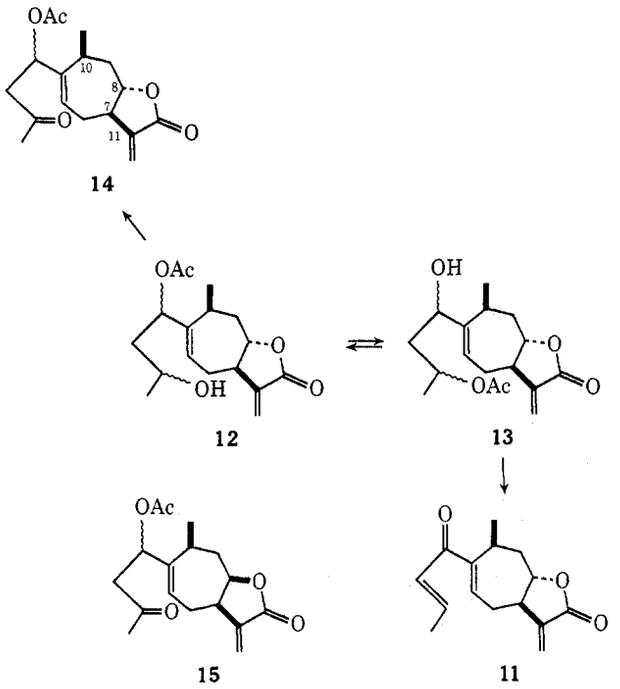
The chemical shift of the lactone proton in compounds of the ivalbatin series (5.50–5.32 ppm in **2**, **3**, **4**, **5**, **7**, **8**, and **9**) which appears at considerably lower field than the lactone proton (H-8) in the ivalbin series (4.3–4.2 ppm) indicated that this proton was allylic and that the lactone ring was closed to C-6 rather than C-8 as in ivalbin. This conclusion was verified as follows. (1) In the nmr spectrum of the product obtained by catalytic hydrogenation of **9**, the signal of H-6 is more complex and shifted to higher field (4.54 ppm). (2) Irradiation (Figure 1) at 2.35 ppm (H-2) collapsed the broad singlet of H-5 (5.25 ppm) to a doublet.[5] The J value (2.5 Hz) of this doublet was

(3) Nmr spectra and spin-decoupling data on compounds **9** (Figure 3) and **10** (Figure 4) will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth Street, N.W., Washington, D. C. 20036, by referring to code number JOC-73-585. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

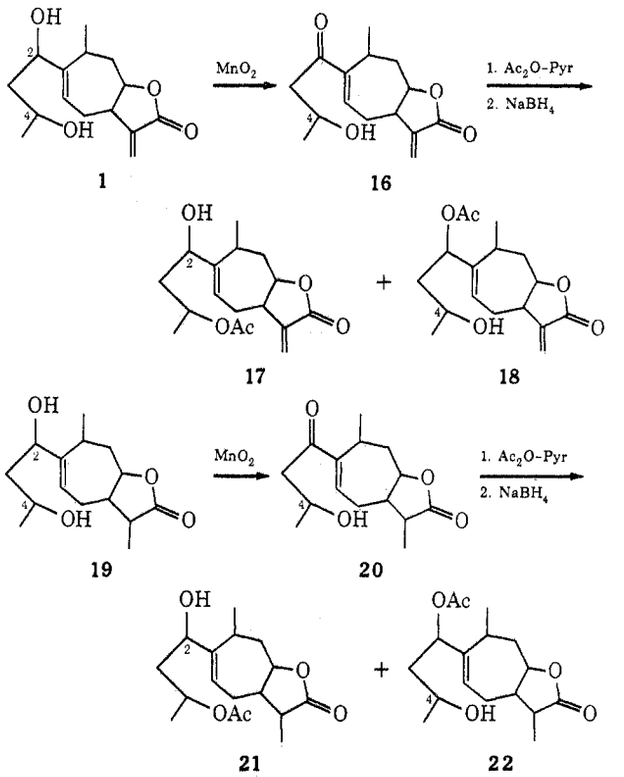
(4) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 17.

(5) Allylic coupling between H-2 and H-5 was also demonstrated in the ivalbin series.[2]

SCHEME II



SCHEME III



identical with one of the coupling constants of the lactone proton (H-6).

Partial structure D deduced in this manner was confirmed by spin-decoupling experiments carried out on **9** (Figure 3).

The presence of partial structure E in **3** was established by irradiation at the frequency of H-8a and H-8b (Figure 1). This caused simplification of the multiplet of H-7 and collapsed the doublet of triplets at 4.80 (H-9) to a doublet (J = 10 Hz); conversely, irradiation of the frequency of H-9 simplified the multiplet of H-8. Irradiation at the frequency of H-7 had no effect on H-9. Similar results were obtained by spin-decoupling experiments on **9** (Figure 3).

Combination of partial structures C, D, and E, which together account for 12 of the 15 carbon atoms of ivalbatin, with the methyl ketone function known to be present leads uniquely to formula **2** for ivalbatin, a ring-hydroxylated xanthanolide.

In the following we discuss the stereochemistry of ivalbin and ivalbatin. As regards the former, it has been correlated[6] through anhydrodehydroivalbin (**11**)[2] with xanthanol (**12**) and isoxanthanol (**13**) which in turn were correlated with xanthinin (**14**) as shown in Scheme II. Hence ivalbin has the same stereochemistry at C-7, C-8, and C-10 as xanthinin.

The absolute stereochemistry of xanthinin at C-10 has been established[6] by degradation to (−)-(*S*)-methylsuccinic acid. It has also been deduced[6] that xanthinin possesses a trans-fused γ-lactone ring because it differs from its stereoisomer xanthumin **15**. The latter also has a β-oriented C-10 methyl group and possesses a cis-fused γ-lactone ring.[7] Xanthumin has been correlated[8] with gafrinin for which a cis γ-lactone ring fusion has been deduced[9] independently by nmr analysis. If it be assumed that the absolute configuration of xanthinin and xanthumin at C-7 is the same as that of all other sesquiterpene lactones of established absolute configuration, *i.e.*, β, the absolute configuration of ivalbin at C-7, C-8, and C-10 is established as H-7 α, H-8 β, H-10 α.

The absolute configuration of ivalbin at C-2 and C-4 was investigated by means of Horeau's method[10] which has been found to be applicable to sesquiterpene lactones.[11] C-2 alcohols **17** and **21** and C-4 alcohols **16** and **20** were prepared from ivalbin (**1**) and dihydroivalbin (**19**), respectively (Scheme III). Acetylation of **17** and **21** gave ivalbin diacetate and dihydroivalbin diacetate, respectively, thus demonstrating that the configuration of **17** and **21** at C-2 was the same as that of ivalbin. Reaction of **16**, **17**, **20**, and **21** with excess (+)-α-phenylbutyric anhydride gave (−)-α-phenylbutyric acid in 21.0, 16.2, 15.0, and 10% optical yield, respectively. Hence the configuration at C-2 and C-4 should be *S*(2-OH α, 4-OH β).

Unfortunately, the nmr spectra of **17** and **21** showed that these substances were contaminated with C-4 alcohols **18** and **22**, respectively, as the result of partial migration of the acetyl group from C-4 to C-2 during the sodium borohydride reduction.[12] As a consequence the absolute configuration of ivalbin is as shown in **23** except for the situation at C-2 which requires further verification and is being investigated.

The absolute configuration of ivalbatin at C-9 was also deduced by application of Horeau's method. Reaction of ivalbatin and **8** with (±)-α-phenylbutyric anhydride gave (+)-α-phenylbutyric acid in 2.8 and 11.0% optical yield, respectively. The optical yield

(6) T. E. Winters, T. A. Geissman, and D. Safir, *J. Org. Chem.*, **34**, 153 (1969).

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

(8) L. A. P. Anderson, W. T. de Kock, W. Nel, and K. G. R. Pachler, *Tetrahedron*, **24**, 1687 (1968).

(9) W. T. de Kock and K. G. R. Pachler, *ibid.*, **24**, 1701 (1968).

(10) A. Horeau, *Tetrahedron Lett.*, 506 (1961); 965 (1962).

(11) W. Herz and H. B. Kagan, *J. Org. Chem.*, **32**, 216 (1967).

(12) A similar equilibrium was found to exist between **12** and **13**.[6]

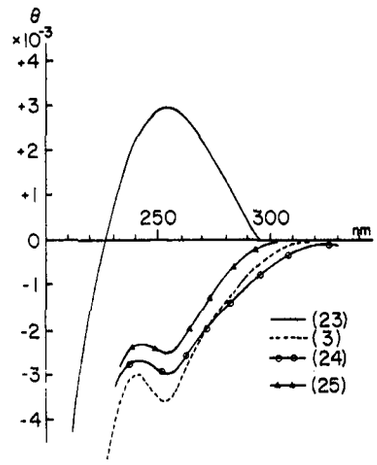


Figure 2.—CD curves of acetylivalbatin (**3**), ivalbin (**23**), parthemollin (**24**), and ivambrin (**25**).

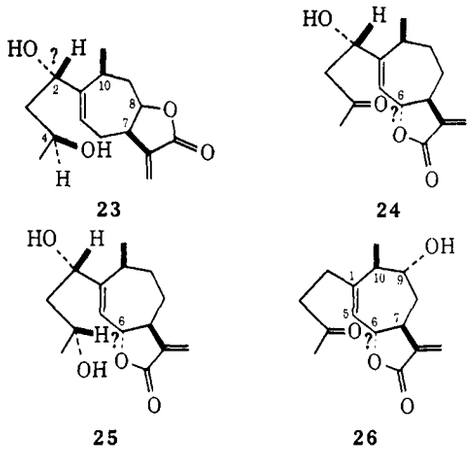
from **8** was sufficiently high to permit the conclusion that the configuration of ivalbatin at C-9 is *R* or OH α.

On biogenetic grounds it is plausible to assume that the C-10 methyl group of ivalbatin is β like that of ivalbin and all other xanthanolides and pseudoguaianolides isolated from related species. On this basis, H-9 and H-10 would be trans. The large value of $J_{H\text{-}9,H\text{-}10}$ (10 Hz) obtained from the spin-decoupling experiments on **3** and **9** is in accordance with this conclusion.

Just as in the case of parthemollin (**24**),[13] knowledge of the coupling constants involving H-5, H-6, and H-7 was not sufficient to decide unambiguously between cis and trans fusion of the lactone ring. The strong positive Cotton effects exhibited by ivalbin (**23**) (Figure 2) and its acetate (λ_{max} 257 nm, θ +2960 and λ_{max} 255 nm, θ +3090, respectively) are in agreement with the generalization[14] that, regardless of structural type, cis-fused α-methylene-γ-lactones closed to C-8 exhibit negative Cotton effects and that in trans-fused lactones closed to C-8 the Cotton effect is positive, whereas the reverse situation prevails in lactones closed to C-6.[15] On this basis, acetylivalbatin (**3**) which displays a strongly negative Cotton effect at 255 nm, and therefore invalbatin itself, would be trans-fused lactones and invalbatin would be **26**.

However, applicability of the rule to ivalbatin is suspect due to our ambiguous results[13] with parthemollin (**24**) which exhibited a negative Cotton effect indicative of a trans-fused lactone ring, although application of the Hudson–Klyne rule suggested cis fusion.[16]

The CD curves of acetylivalbatin (**3**), parthemollin (**24**), and ivambrin (**25**)[18] are compared in Figure 2.



The similarity is striking, each displaying a hump near 242 nm. Subtraction of the curve of **25** from the curve of **24** gives a good minimum at 287 nm (θ −1730) which can be ascribed to the Cotton effect of the ketone group present in **24**, but not in **25**. This suggests that the curve of **24** is a composite of a relatively weak negative Cotton effect near 290 nm (ketone) superimposed on a stronger negative Cotton effect near 250 nm (n,π^* transition of conjugated lactone) which in turn is superimposed on strongly negative Cotton effects due to the π,π^* transitions. The very similar curve of **3**, slightly modified by the presence of a much weaker ketone Cotton effect as expected,[15] indicates that the fusion of the lactone ring in ivalbatin and parthemollin is the same, although the configuration at C-6 remains in doubt.

Experimental Section[19]

Isolation of Ivalbatin.—*Iva dealbata* Gray was collected by Dr. Norlan C. Henderson on Aug 14 and 15, 1967, along Texas Ranch Road 2317 just south of the intersection with US 62-180 in Cornudas, Hudspeth County, Tex. In the usual manner[2] 160 lb of powdered plant (above-ground part) was extracted with chloroform to give 1500 g of crude gum.

In a typical run, 157 g of crude gum was extracted with 500 ml of hot chloroform–benzene (2:1). The soluble part was chromatographed over 1500 g of silicic acid (Mallinckrodt 100 mesh), 800-ml fractions being collected in the following order: 1–6 (chloroform–benzene, 2:1), 7–18 (chloroform), 19–21 (chloroform–methanol, 40:1), 22–29 (chloroform–methanol, 100:3.0). Fractions were monitored by tlc. Fractions 11–20 contained ivalbatin; fractions 21–26 contained semicrystalline material which yielded 13.65 g of crude ivalbin after filtration. The mother liquor (7 g) was combined with fractions 11–20 and taken up in ethyl acetate. The material soluble in ethyl acetate (59 g) was dissolved in 400 ml of benzene, rechromatographed over 220 g of neutral alumina (Woelm activity III), and eluted with benzene, 500-ml fractions being collected. Fractions 2 and 3 eluted 42 g of green gum (crude ivalbatin). Fraction 4–7 eluted 2 g of pale yellow gum which showed only one spot by tlc and was pure ivalbatin (**2**): $[\alpha]^{24}D$ −84.04° (*c* 2.586, chloroform); $n^{20}D$ 1.5263; uv spectrum (ethanol) 210 nm (end absorption) (ϵ 13,400); ir bands (liquid) at 3450 (OH), 1755 (γ-lactone), 1705 (C=O), and 1655 (C=C); nmr signals of 1.19 ($HCCH_3$, d, J = 7.5), 2.16 ($COCH_3$, s), 3.40 (OH, disappeared on addition of D_2O), 3.65 (HCOH, broad d, J = 10), 5.20 (C=CH, s), 5.50 (HCO, dd, J = 10 and 2.5), 5.63 and 6.24 (exocyclic methylene, d, J = 2.5); bp 150° (0.001 mm) (dec). As ivalbatin easily polymerized on standing without solvent, a

(13) W. Herz, S. V. Bhat, and A. L. Hall, *J. Org. Chem.*, **35**, 1110 (1970).

(14) W. Stöcklin, T. G. Waddell, and T. G. Geissman, *Tetrahedron*, **26**, 2397 (1970).

(15) The CD curves of xanthinin (**14**) and xanthumin (**15**) are composites of four contributions: double bond, π,π^* of lactone, n,π^* of conjugated lactones (maximum near 250 nm), and ketone. Comparison of the CD curve of **3** (Figure 2 of present paper) with the curves of **14** and **15** (Figure 3 of ref 14) suggests that the ketone chromophore of xanthinin and xanthumin is positive. The ketone Cotton effect of ivalbatin, whatever its sign, would be expected to be considerably weaker because of the absence of a substituent on C-2.

(16) Such difficulties seem to arise most commonly when the lactone ring is closed to an allylic position,[17] a situation which can easily affect the chirality of the unsaturated lactone chromophore.

(17) W. Herz and S. V. Bhat, *J. Org. Chem.*, **37**, 906 (1972).

(18) H. Yoshioka, A. Higo, T. J. Mabry, W. Herz, and G. D. Anderson, *Phytochemistry*, **10**, 401 (1971).

(19) Melting points are uncorrected. Nmr spectra were determined on a JNM-4H-100 spectrometer in $CDCl_3$ with TMS as internal standard. Coupling constants are expressed as hertz, s = singlet, d = doublet, t = triplet, q = quartet, sx = sextet, dd = double doublet, dt = doublet of triplet, and m = multiplet. Tlc was carried out with silica gel G as adsorbent.

satisfactory elemental analysis could not be obtained. It was stored in a refrigerator as a solution in benzene.

Acetylivalbatin (3).—A 44-g sample of ivalbatin (fractions 2–7 of the second chromatography on alumina described above) was acetylated with 80 ml of Ac_2O and 140 ml of pyridine to give 36 g of crude acetate after washing with cold ether. Recrystallization from ethanol afforded 26.4 g of pure acetate **3** (16.8% from the extract of plant): mp 127–128°; $[\alpha]^{20}D$ −136° (*c* 1.99, chloroform); uv spectrum 209 nm (end absorption) (ϵ 13,800) (ethanol); ir bands (chloroform) at 1755 (γ-lactone), 1730, 1240, and 1015 (acetate), 1720 (C=O), and 1655 (C=C); nmr signals at 1.08 ($HCCH_3$, d, J = 7.5), 2.11 ($OCOCH_3$, s), 2.17 ($COCH_3$, s), 4.80 (HCOAc, dt, J = 10 and 2.5), 5.25 (C=CH, s), 5.47 (HCO, dd, J = 10 and 2.5), 5.54 and 6.27 $C=CH_2$, each d, J = 2.5); CD (methanol) λ 320 (θ 0), 300 (θ −268), 255 (θ −3561), 242 (θ −2934), 202 (θ −49,060), and 198 mμ (θ −47,100).

Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.59; H, 7.10.

The 2,4-dinitrophenylhydrazone was recrystallized from ethanol, mp 140–141°.

Anal. Calcd for $C_{23}H_{26}O_8N_4$: C, 56.78; H, 5.39; N, 11.52. Found: C, 56.63; H, 5.40; N, 11.66.

Ozonolysis of 3.—A solution of 500 mg of **3** in 25 ml of chloroform was ozonized at 0° for 40 min. After evaporation of the solvent *in vacuo*, the ozonide was decomposed with water. The reaction mixture was steam-distilled into a chilled saturated aqueous solution of dimedone to afford the dimedone derivative of formaldehyde (110 mg, 23%), mp 188–189° (from methanol and water), undepressed on admixture with authentic material.

Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.71; H, 8.28.

Reduction of 3 with Sodium Borohydride.—To a solution of 2.00 g of **3** in 20 ml of methanol was added with stirring 125 mg of $NaBH_4$ during 20 min at room temperature. Stirring was continued for 1.5 hr, the reaction mixture was acidified with 5 ml of 2 *N* H_2SO_4, diluted with 100 ml of water, and extracted with chloroform. The washed and dried extract was evaporated. The residual oil **4** (2.0 g) easily polymerized. It had ir bands (oil) at 3400 (OH), 1760 (γ-lactone), 1730, 1230, and 1020 (acetate and 1650 (C=C); nmr signals at 1.10 ($HCCH_3$, d, J = 7.5), 1.20 ($HCCH_3$, d, J = 7.5), 2.10 ($COCOCH_3$, s), 3.37 (COH, s), 3.80 (HCOH, sx, J = 6), 4.80 (HCOAc, dt, J = 10 and 2.5), 5.32 (HCO, m), and 5.40 (C=CH, broad s).

Acetate 5.—Acetylation of **4** with Ac_2O and pyridine immediately after evaporation of solvent gave crystalline acetate **5**: mp 129–131° (from ethanol and water); $[\alpha]^{22}D$ −54.1° (*c* 1.5, chloroform); uv spectrum (ethanol) 207 nm (end absorption) (ϵ 6800); ir bands (KBr) at 1760 (γ-lactone), 1725, 1230, and 1020 (acetate), and 1650 (C=C); nmr signals at 1.06 ($HCCH_3$, d, J = 7.5), 2.03 ($COCOCH_3$, s), 2.07 ($COCOCH_3$, s), 4.75 (HCOAc, dt, J = 10 and 2.5), 4.90 (HCOAc, sx, J = 7), and 5.38 (C=CH, and HCO, d, J = 2.5; 2 protons).

Anal. Calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.58; H, 7.92.

Dihydroivalbatin Acetate (7).—To a solution of 1.86 g of alcohol **4** (obtained from 1.95 g of **3**) in 20 ml of acetone was added dropwise during 1 hr 2.1 ml of 8 *N* Jones reagent under cooling with an ice bath. After filtration, the filtrate was concentrated *in vacuo*, water was added, and the mixture was extracted with ether. The washed and dried extract was evaporated; the residue (1.56 g) crystallized on standing: mp 88–88.5° (from petroleum ether–ether); $[\alpha]^{22}D$ −108.5° (*c* 1.24, chloroform); uv spectrum 207 nm (end absorption) (ϵ 4400); ir bands (chloroform) at 1760 (γ-lactone), 1730, 1240, and 1015 (acetate), and 1650 (C=C); nmr signals at 1.10 ($HCCH_3$, m), 1.23 ($HCCH_3$, d, J = 7.5), 2.09 ($COCOCH_3$, s), 2.18 ($COCH_3$, s), 4.82 (HCOAc, m), 5.31 (C=CH, s), and 5.35 (HCO, overlap with vinyl proton).

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

The 2,4-dinitrophenylhydrazone was recrystallized from ethanol–ethyl acetate.

Anal. Calcd for $C_{23}H_{28}O_8N_4$: C, 56.55; H, 5.78; N, 11.47. Found: C, 56.25; H, 5.84; N, 11.54.

Methanol Adduct 8.—To a solution of 500 mg of **3** in 25 ml of absolute methanol was added a solution of sodium methoxide–MeOH (prepared from 0.07 g of sodium and 5 ml of methanol). After 4 days in a refrigerator Dry Ice was added carefully, and the solvent was evaporated at room temperature *in vacuo*. The residue was dissolved in water, acidified with 2 *N* H_2SO_4, and extracted with chloroform. Evaporation of the washed and dried extract yielded a viscous oil (0.5 g): $n^{24}D$ 1.5107; $[\alpha]^{24}D$ −62.82° (*c* 0.5, chloroform); ir bands (chloroform) at 3450 (OH), 1750 (γ-lactone), 1705 (C=O), and 1645 (C=C); nmr signals at 1.13 ($HCCH_3$, d, J = 7.5), 2.11 ($CCOCH_3$, s), 2.28 (OH), 3.29 (OCH_3, s), 3.55 (HCOH, m), 3.59 (CH_2O, m), 5.15 (C=CH, s), and 5.34 (HCO, dd, J = 10 and 2.5).

The *p*-bromobenzoate was recrystallized from ethanol, mp 97° (from ethanol), $[\alpha]^{20}D$ −29.67° (*c* 0.728, chloroform).

Anal. Calcd for $C_{23}H_{27}O_6Br$: C, 57.63; H, 5.67; Br, 16.67. Found: C, 57.72; H, 5.87; Br, 16.79.

The acetate **9** was recrystallized from ethanol–water: mp 90–91°; $[\alpha]^{25}D$ −149.9° (*c* 0.926, chloroform); ir bands (KBr) at 1760 (γ-lactone), 1720, 1240, and 1025 (acetate), 1710 (C=O), and 1650 (C=C); nmr signals at 1.07 ($HCCH_3$, d, J = 7.5), 2.08 ($COCOCH_3$, s), 2.14 ($CCOCH_3$, s), 3.36 (OCH_3, s), 3.61 (CH_2OCH_3, octet, J = 5), 4.76 (HCOAc, dt, J = 10 and 3), 5.25 (C=CH, broad s), and 5.40 (HCO, dd, J = 8.5 and 3).

Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.88; H, 7.74. Found: C, 63.93; H, 7.70.

The 2,4-dinitrophenylhydrazone was recrystallized from ethanol, mp 122–123°.

Anal. Calcd for $C_{24}H_{30}O_9N_4$: C, 55.59; H, 5.83; N, 10.81. Found: C, 55.67; H, 5.88; N, 10.80.

Catalytic Reduction of Acetate 9.—A solution of 750 mg of **9** in 50 ml of ethanol was reduced at atmosphere pressure with 210 mg of 10% Pd/C. Hydrogen uptake ceased after absorption of about 1 molar equiv of hydrogen. The gummy product was chromatographed over silicic acid to remove the less polar fraction (which showed no absorption in the lactone region of the ir spectrum) and afforded 110 mg of a mixture of diastereomeric (at C-1) dihydro derivatives of **9**. Vpc showed two partially resolved peaks at 2.5 and 2.7 min in the ratio of 1:2 (10% SE-30, 1 m, 250°). The ir spectrum (chloroform) exhibited bands at 1760 (γ-lactone), 1720, 1245, and 1015 (acetate), and 1715 (C=O). The nmr spectrum exhibited absorption for three protons at 0.85 ($HCCH_3$, d, J = 7.5) and 0.95 ($HCCH_3$, d, J = 7.5) in the ratio 2:1, 2.08 ($COCOCH_3$, s), 2.12 ($COCH_3$, s), 3.34 (OCH_3, s), 3.61 (CH_2O, m), 4.54 (HCO, m) and 4.84 (HCOAc, m). Although the material was homogeneous on tlc, a satisfactory elemental analysis could not be obtained.

Dehydration of 8. 1. With Methanesulfonyl Chloride and Pyridine.—A solution of 570 mg of **8** in 5 ml of pyridine and 1 ml of MsCl was heated at 70° for 2 hr. After addition of ice–water the reaction was extracted with chloroform. Evaporation of washed and dried extract afforded a red oil (420 mg) which was dissolved in benzene and purified by passing it through a column of 5 g of neutral alumina (activity III). Bulb-to-bulb distillation yielded 230 mg of diene **10**, bp 140–170° (0.01 mm).

2. *Via* **the Tosylate.**—To a solution of 980 mg of **8** (purified by chromatography over silicic acid) in 6 ml of pyridine was added 1 g of *p*-TsCl. After 2 days at room temperature and addition of ice–water, the mixture was extracted with chloroform. Evaporation of the washed and dried extract afforded 1.19 g of crude tosylate as a viscous oil which was dissolved in 20 ml of 2,6-lutidine and refluxed at 150° for 15 hr. The lutidine was evaporated *in vacuo*, water added to the residue, and the mixture extracted with chloroform. Evaporation of the washed and dried extract *in vacuo* afforded 530 mg of red oil which was dissolved in benzene and purified by chromatography over 10 g of alumina. Bulb-to-bulb distillation afforded 300 mg of diene **10**: bp 140–155° (0.01 mm); $n^{20}D$ 1.5192 (The material was homogeneous by vpc and tlc criteria. The mass spectrum showed a molecular ion peak at m/e 278; however, the carbon content of the elemental analysis was slightly outside theoretical limits); $[\alpha]^{18}D$ −3.57° (*c* 1.68, chloroform); ir bands (oil) at 1760 (γ-lactone, 1710 (C=O), 1635, and 1615 (C=C); uv spectrum (ethanol) 239 nm (ϵ 11,550); nmr signals at 1.75 (>C=$CHCH_3$, d, J = 7.5), 2.15 ($COCH_3$, s), 3.36 (OCH_3, s), 3.65 (CH_2O, d, J = 5), 5.03 (HCO, dd, J = 7.5 and 2.5), 5.46 (C=CH, d, J = 2.5), and 5.86 (>C=$CHCH_3$, q, J = 7.5).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04, H, 7.97. Found: C, 68.45; H, 7.91.

Ozonolysis of 10.—A solution of 850 mg of **10** in 20 ml of chloroform was ozonized at 0° for 1 hr. The solvent was evaporated *in vacuo* at room temperature. The residue was mixed with 50 ml of water and steam-distilled directly into a chilled 50% aqueous ethanolic solution of 1 g of dimedone. After standing, there precipitated 275 mg of the dimedone derivative

of acetaldehyde. Chromatography of a solution of the precipitate in benzene over 3 g of silica gel yielded 120 mg of adduct, mp 139–140° (from ethanol and water), which was identical with an authentic sample by mixture melting point, ir, and nmr spectrum.

Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.50; H, 8.52.

Dehydroivalbin (16).—Oxidation of 2.08 g of ivalbin with MnO_2 and purification of the product by chromatography over silicic acid[2] gave 0.8 g of **16** as an oil, $n^{22}D$ 1.5244, $[\alpha]^{23}D$ −44.2° (*c* 1.11, chloroform).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.93; H, 7.73.

4-Acetylivalbin (17) and 2-Acetylivalbin (18).—A solution of 240 mg of dehydroivalbin acetate[2] in 5 ml of methanol was reduced with 20 mg of $NaBH_4$ at 0° for 20 min. The reaction mixture was acidified with 1 *N* H_2SO_4, diluted with water, and extracted with chloroform. The washed and dried extract was evaporated. When the residual oil was purified by chromatography over silicic acid, 160 mg of homogeneous material as determined by tlc was obtained as an oil: $n^{27}D$ 1.5045; $[\alpha]^{19}D$ −33.85° (*c* 0.774, chloroform). The nmr spectrum displayed absorptions totaling one proton at 3.84 (HC_4OH, m), and 4.13 HC_2OH, t, J = 7.5) in the ratio 1:2, totaling one proton at 4.93 (HC_4OAc, sx, J = 7.5) and 5.33 (HC_2OAc, t, J = 7.5) in the ratio 2:1, and totaling one proton at 5.7–6.0 (C=CH, m). On the basis of these data, the reduction product was a mixture of 4-acetylivalbin (**17**) and 2-acetylivalbin (**18**) in the ratio 2:1.

Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 65.91; H, 7.67.

Acetylation of the mixture of **17** and **18** with Ac_2O and pyridine afforded ivalbin diacetate, mp 106–107° (from ethanol and water), $[\alpha]^{26}D$ −47.1° (*c* 0.9, chloroform).

Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 64.93; H, 7.51.

Dehydrodihydroivalbin (20).—Oxidation of 2.4 g of dihydroivalbin with manganese dioxide and chromatography over silicic acid, as described previously,[2] gave 569 mg of **20** as an oil, $n^{24}D$ 1.5207, $[\alpha]^{23}D$ −26.56° (*c* 0.24, chloroform). The material was homogeneous by tlc criteria, but the carbon content was slightly low.

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.13; H, 8.33.

4-Acetyldihydroivalbin (21) and 2-Acetyldihydroivalbin (22).—A solution of 3.5 mg of dihydrodehydroivalbin acetate[2] in methanol was treated with 38 mg of $NaBH_4$ at 0°. The product was worked up in the same manner as in the reduction of dehydroivalbin acetate. Purification by chromatography over silicic acid gave 280 mg of a homogeneous material, as determined by tlc, as an oil, $n^{24}D$ 1.4967, $[\alpha]^{24}D$ −15.7° (*c* 0.668, chloroform). The carbon content was slightly below theoretical limits. The nmr spectrum displayed absorptions totaling one proton at 3.82 (HC_4OH, m) and 4.12 (HC_2OH, t, J = 7.5) in the ratio 1:2, totaling one proton at 4.97 (HC_4OAc, sx, J = 7.5) and 5.32 (HC_2OAc, t, J = 7.5) in the ratio 2:1, and totaling one proton at 4.72 and 4.92 (C=CH, each q, J = 5) in the ratio 2:1. On the basis of these data, the product was a mixture of **21** and **22** in the ratio 2:1.

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.29; H, 8.43.

Acetylation of the mixture of **21** and **22** with Ac_2O and pyridine afforded dihydroivalbin diacetate, mp 88–89° (from ethanol and water), $[\alpha]^{23}D$ −33.8° (*c* 0.368, chloroform).

Anal. Calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.79; H, 8.06.

Asymmetric Esterifications by the Horeau Method.—The purity of the α-phenylbutyric acid isolated from the esterification was checked by nmr spectroscopy. In all instances the esterification yield was estimated by nmr spectroscopy of the neutral extract and appeared to be practically quantitative.

A typical run for dehydroivalbin (**16**) follows. **16** (107.95 mg, 4.1×10^{-4} mol) was esterified with 365.4 mg (1.18×10^{-3} mol) of (±)-α-phenylbutyric anhydride in 4 ml of pyridine. The resultant mixture was worked up by the standard procedure.[20] The recovered α-phenylbutyric acid (yield 220.5 mg) showed $[\alpha]^{20}D$ −4.26° (*c* 4.41, benzene). A fully stereospecific esterification should give $[\alpha]^{20}D$ −20.25°. Therefore the optical yield was 21.04%.

The same procedure was applied to the other compounds.

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Registry No.—**2,** 37163-90-9; **3,** 37163-91-0; **3** DNP hydrazone, 37163-92-1; **4,** 37392-67-9; **5,** 37392-68-0; **7,** 37392-69-1; **7** DNP hydrazone, 37392-70-4; **8,** 37392-72-6; **8** *p*-bromobenzoate, 37392-71-5; **9,** 37392-73-7; **9** DNP hydrazone, 37413-06-2; **10,** 37392-74-8; **16,** 37163-93-2; **17,** 37163-94-3; **18,** 37163-95-4; **20,** 37392-75-9; **21,** 37392-76-0; **22,** 37392-77-1; ivalbin diacetate, 37163-96-5; dihydroivalbin diacetate, 7561-75-3.