levels of saturation with boric acid (0.2, 0.3, 0.4, etc.) up to full saturation and finally with 5, 10, and 20% aqueous acetic acid displaced 1,4-anhydroribitol, followed by arabinitol and finally 1,4-anhydrolyxitol. All of these components overlapped but pure 1,4-anhydroribitol (210 mg) was obtained from the 0.3 and 0.4 times saturated boric acid eluents, and pure 1,4-anhydrolyxitol (115 mg) was obtained from the 5% acetic acid eluents. The syrupy benzoate had $[\alpha]^{25}D$ −42° indicating that the ribitol anhydride was 70% L and 30% D isomer; $[\alpha]^{25}D$ +107° (*c* 1.71, $CHCl_3$) for the D isomer has been reported.[23] From the syrup used to obtain the optical rotation 40 mg of crystalline 1,4-anhydro-DL-ribitol tribenzoate was isolated, mp 113–114°, undepressed on admixture with authentic material,[26] $[\alpha]^{26}D$ 0.0 ± 0.4° (*c* 2.0, $CHCl_3$). The lyxitol anhydride was at least 90% D isomer, its benzoate before purification had $[\alpha]^{25}D$ −32.2 (*c* 2.8, $CHCl_3$). The reported value for the crystalline 1,4-anhydro-D-lyxitol tribenzoate is −36.1° (*c* 1.73, $CHCl_3$), mp 117–118.[28] Crystalline material was obtained in good yield which had mp 115–116° and $[\alpha]^{25}D$ −34.0° (*c* 1.9, $CHCl_3$) in agreement with the reported values.

B. Ribitol and Xylitol.—The products present at 10 × $t_{1/2}$ were identified by gas chromatography of their trimethylsilyl ethers by comparison with known compounds. The product from ribitol gave a quantitative yield of a crystalline benzoate which was shown by comparison with authentic material to be 1,4-anhydro-DL-ribitol tribenzoate. The product from xylitol was shown to be the 1,4-anhydride by periodate oxidation (1 molar equiv of periodate consumed) and by conversion to a monotrityl derivative, mp 135–137°.[27]

1,4-Butanediol, 1,2,4-Butanetriol, 2-*O*-Methyl-1,2,4-butanetriol, 2-Methyl-1,4-butanediol, and 1,4-Pentanediol.—The products formed from these alcohols were identified by carrying out the dehydration using a 10% solution of the alcohol in D_2O–2 *N* sulfuric acid at 100° for 10 × $t_{1/2}$, the solutions were examined by nmr spectroscopy and the spectra obtained were compared with those obtained from known samples of the suspected product in similar solutions. In all cases the spectra were identical except for weak absorptions due to the small proportion of starting material still present.

***erythro*- and *threo*-1,2,4-Pentanetriol.**—The product was examined by nmr spectroscopy as described above and its identity inferred from the similarity of the absorptions to those observed for similar compounds such as 3-hydroxytetrahydrofuran and 2-methyltetrahydrofuran. A comparison of the spectra is presented in Table III.

Erythritol and Threitol.—That the product in each case was the 1,4-anhydride was established by preparation of the di-*O*-*p*-nitrobenzoyl derivative for comparison with authentic materials.[28]

1-Deoxy-D-arabinitol.—The product from the dehydration rapidly consumed 1 mole of periodate per mole of starting material. It contained only one component when examined as the acetate or trimethylsilyl derivative by gas chromatography.

2-Deoxy-D-ribitol.—The product did not consume periodate and appeared as a single component when examined as the acetate or trimethylsilyl derivative by gas chromatography.

First-order rate constants were calculated using the equation, $k = 2.303 \times$ slope. The slopes were calculated using the method of least squares.

Activation energy (E_a) was determined from the Arrhenius equation, $k = Se^{-E_a/RT}$, by plotting the logarithm of the first-order rate constant (k) against the reciprocal of the absolute temperature ($1/T$). The energy of activation was then calculated by use of the equation $E_a = -2.303R$ (slope). A hydrochloric acid strength of 2 *N* was used in obtaining these data.

The entropy of activation (ΔS^*) was calculated from the transition state theory[11] using the data obtained at 99° in 2 *N* hydrochloric acid. The second-order rate was used in calculating ΔS^*; it was derived from the experimental pseudo-first-order rate constant using the expression $K = k/H_0$ where K = second-order rate constant, k = pseudo-first-order rate constant, and H_0 = Hammett acidity function.

In calculating ΔS^* for ribitol and xylitol cyclization, their corresponding pseudo first-order rate constants were corrected by multiplying by one-half.

The free energy of activation (ΔF^*) was determined from the transition state theory using the data obtained at 99° in 2 *N* acid, and the equation $\Delta F^* = \Delta H^* - T\Delta S^*$, where $\Delta H^* = E_a - RT$.

TABLE III
CHEMICAL SHIFTS (τ VALUES) IN D_2O, 2 *N* WITH RESPECT TO H_2SO_4

Compound	Value for protons[a] C_2	C_5	C_3	C_4	CH_3
Tetrahydrofuran	6.20–6.60(m)		8.10–8.42(m)		
2-Methyl THF	5.72–6.57(m)		7.72–8.78(m)		1.22(2)
3-Hydroxy THF	5.88–6.32(m)		5.30–5.61(6)	7.46–8.25(m)	
Product from 1,2,4-pentanetriols	5.65–6.52(m)		5.40–5.65(6)	7.28–8.59(m)	1.25(2) 1.30(2)

[a] Numbers in parentheses indicate numbers of peaks; m indicates multiple peaks.

Registry No.—1,4-Butanediol, 110-63-4; 1,2,4-butanetriol, 3068-00-6; erythritol, 149-32-6; D-threitol, 2418-52-2; 2-*O*-methyl-1,2,4-butanetriol, 13942-68-2; 2-methyl-1,4-butanediol, 2938-98-9; 1,4-pentanediol, 626-95-9; DL-*erythro*-1,2,4-pentanetriol, 13942-71-7; DL-*threo*-1,2,4-pentanetriol, 13942-72-8; L-1,2,5-pentanetriol, 13942-73-9; ribitol, 488-81-3; xylitol, 87-99-0; D-arabinitol, 488-82-4; lyxitol, 13942-75-1; 2-deoxy-D-ribitol, 13942-76-2; 1-deoxy-D-arabinitol, 13942-77-3.

(26) D. L. MacDonald, J. D. Crum, and R. Barker, *J. Am. Chem. Soc.*, **80**, 3379 (1958).

(27) G. R. Gray, F. C. Hartman, and R. Barker, *J. Org. Chem.*, **30**, 2020 (1965).

(28) H. Klosterman and F. Smith, *J. Am. Chem. Soc.*, **74**, 5336 (1952).

Constituents of *Iva* Species. X. Ivangulin, a Novel *seco*-Eudesmanolide from *Iva angustifolia* Nutt.[1,2]

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The structure of two new sesquiterpene lactones from *Iva angustifolia* Nutt. has been elucidated. One of these, ivangustin, is the double bond isomer **2a** of asperilin. The second, ivangulin (**6**), represents a new structure type and is the methyl ester of a ring A *seco*-eudesmanolide.

In the course of our systematic study of the genus *Iva*,[1] we examined several collections of *Iva angustifolia* Nutt. (section *Linearbractea*), a species which is found mainly in Oklahoma and Texas.[3] This has led to the isolation of two new sesquiterpene lactones whose structure is discussed in the present paper.

(1) Previous paper, L. Farkas, M. Nogradi, V. Sudarsanam, and W. Herz, *Tetrahedron*, **23**, 3557 (1967).

(2) Supported in part by grants from the U. S. Public Health Service (GM-05814) and the National Science Foundation (GP-1962).

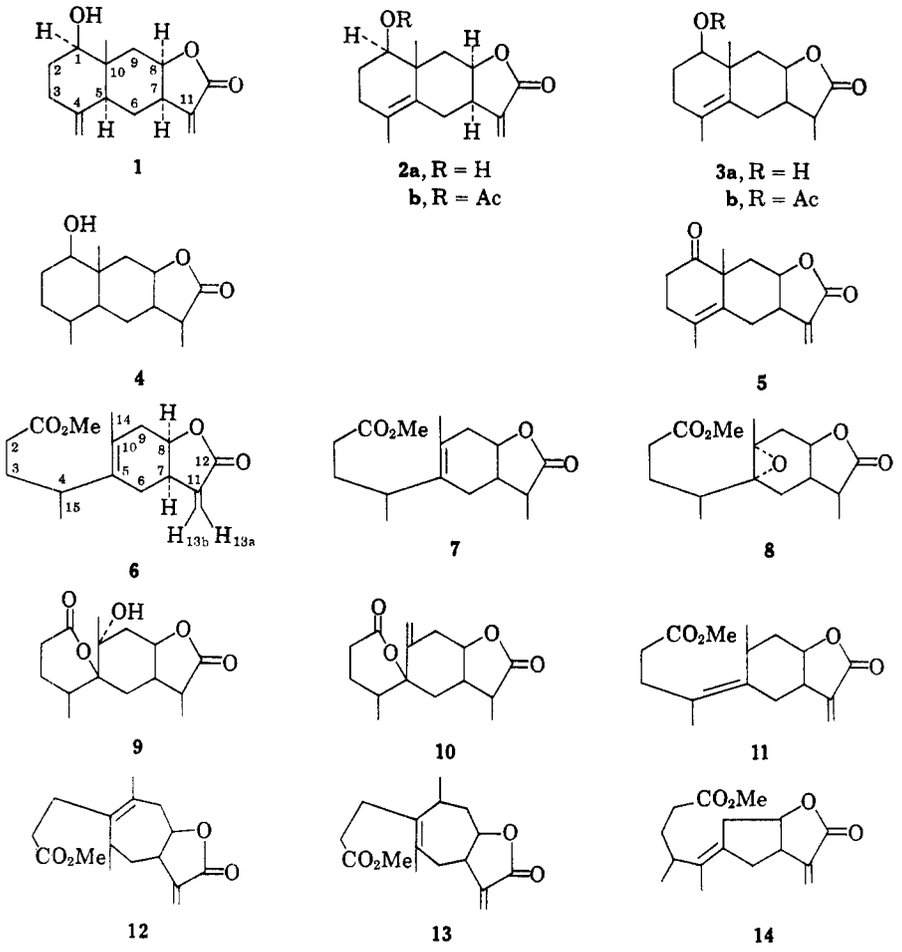
(3) R. C. Jackson, *Univ. Kansas Sci. Bull.*, **41**, 793 (1960).

The first of these substances, a bicyclic hydroxylactone of formula $C_{15}H_{20}O_3$, mp 120–122°, $[\alpha]^{27}D$ +85°, which we have called ivangustin, was easily correlated with asperilin (**1**), a compound previously isolated from *Iva asperifolia* Less.[4] Partial reduction of ivangustin, which had the α,β-unsaturated lactone configuration typical of other constituents of *Iva* species[5] (strong ultraviolet absorption near 205 mμ, infrared bands at 1770 and 1670 cm^{-1}, slightly split nmr signals at 6.31 and 5.70 ppm, and formation of a pyrazoline), saturated the conjugated exocyclic methylene group (replacement of the vinyl proton resonances by the signal of a secondary methyl group at 1.22 ppm) and led to the formation of a noncrystalline dihydro derivative **3a** which was characterized as the solid acetate **3b**. Complete hydrogenation required the saturation of two double bonds and resulted in the formation of tetrahydroasperilin (**4**), thus establishing the location and orientation of the secondary hydroxyl group and the configuration of the ring skeleton.

The location of the second double bond was determined chemically by oxidation to **5** which did not have the properties of an α,β-unsaturated ketone and by an examination of the nmr spectra of ivangustin and its derivatives. Thus no resonances characteristic of vinyl protons appeared in the spectra of **3a**, **3b**, or **5**, but all compounds exhibited the signal of a vinyl methyl group near 1.6 ppm which on conversion to **4** was replaced by a methyl doublet. Simultaneously the signal of the angular methyl group, apparently somewhat deshielded by the proximity of the second double bond, moved upfield to a more normal position at 0.97 ppm. These observations require assignment of the second double bond to the Δ^4-position and formulation of ivangustin as **2a**.

The second substance, $C_{16}H_{22}O_4$, mp 84–85°, $[\alpha]^{27}D$ +109°, presented a somewhat more challenging problem. Its physical properties (high intensity absorption near 205 mμ, infrared bands at 1770 and 1670 cm^{-1}, nmr doublets at 6.25 and 5.70 and an apparent quintet at 4.88 ppm) revealed the presence of the usual conjugated lactone system. A sharp singlet at 3.64 ppm indicated that the "extra" carbon atom was that of a methoxyl group which, because of a second infrared carbonyl frequency at 1740 cm^{-1}, was presumably part of a carbomethoxy function, thus accounting for the remaining two oxygens of the empirical formula. A vinyl methyl group (nmr signal at 1.70 ppm broadened by long-range coupling) attached to a second completely substituted double bond and a secondary methyl (doublet at 0.95 ppm) completed the gross requirements for a satisfactory structural formula.

Catalytic hydrogenation under a variety of conditions resulted in the uptake of 1 or 2 mole equiv of



(4) W. Herz and N. Viswanathan, *J. Org. Chem.*, **29**, 1022 (1964).

(5) For references to sesquiterpene lactones isolated previously from other *Iva* species, see W. Herz, V. Sudarsanam, and J. J. Schmid, *ibid.*, **31**, 3232 (1966).

hydrogen, but the products were clearly mixtures of isomers. Sodium amalgam reduction under carefully defined conditions[6] eventually proved successful in reducing the conjugated lactone system selectively. The product, dihydroivangulin (**7**), had a new somewhat deshielded secondary methyl group and no longer exhibited the infrared frequency at 1670 cm^{-1} characteristic of the conjugated double bond. Conversion of **7** to an epoxide **8** put in evidence the presence of the isolated tetrasubstituted double bond; concomitant with the epoxidation the methyl singlet, now no longer broadened by long-range coupling, moved upfield to 1.31 ppm.

Basic hydrolysis of ivangulin and dihydroivangulin resulted in the formation of mixtures of acidic γ-lactones which could be lactonized to mixtures of dilactones. This observation suggested that the tetrasubstituted double bond was γ,δ or δ,ϵ to the carbomethoxy group. More substantial evidence for this inference came from the isolation, on perchloric acid treatment of **8**, of a crystalline hydroxydilactone (**9**) whose infrared spectrum exhibited a new frequency at 1730 cm^{-1} characteristic of δ-lactones. The absence of new low-field nmr signals and the dehydration of **9**, albeit in low yield, to a substance **10** which contained a new exocyclic methylene group were consonant with the interpretation that the lactonization involved nucleophilic attack by the carbomethoxy group on a tertiary epoxidic carbon atom β to the tertiary methyl and δ to the carbomethoxy group.

Among the four biogenetically plausible formulas **6**, **11**, **12**, and **13** which satisfied the physical and chemical data,[7] **11** could be discarded because ozonolysis of **7** did not result in the liberation of levulinic acid, methyl levulinate, or, in fact, any low molecular weight fragment. Positive evidence in favor of **6** which, in view of the simultaneous presence of ivangustin in *I. angustifolia*, seemed considerably more likely than **12** and **13**, came from the 220-Mc nmr spectrum of ivangulin, which resolved most of the signals that were superimposed at 60 Mc, and from decoupling experiments at 100 Mc which allowed their identification. The results are given in Table I.[8,9]

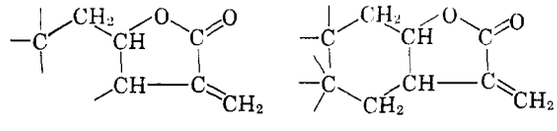
Frequencies corresponding to H-7, H-8, and H-13a and H-13b had already been identified by double irradiation at 60 Mc. Irradiation at the frequency corresponding to H-8 (4.86 ppm) collapsed a two-proton doublet at 2.36 ppm to a singlet, thus identifying a methylene group adjacent to H-8 whose protons (H-9a and H-9b) were not spin coupled to other protons. This observation eliminated **13** as a structural possibility, and led to partial structure A for ivangulin.

Irradiation at the frequency corresponding to H-7 (3.22 ppm) not only collapsed the H-8 quintet to a triplet and the H-13 doublets to singlets, but affected the AB part of an ABX system near 2.2 ppm which was partially superimposed on a two-proton triplet at 2.06 ppm. The A part was broadened by long-range coupling to the vinyl methyl group, but neither A nor B were coupled to other protons in the entire range of the spectrum. This permitted expansion of A to B, and eliminated **12** as a structural possibility.

TABLE I
220-Mc SPECTRUM OF IVANGULIN[a]

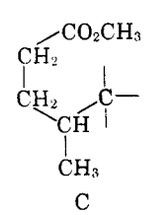
H-2a, 2b	2.06 (t)	$J_{2,3} = 7.5$
H-3a, 3b	1.5 (m)	$J_{3,2} = 7.5$, $J_{3a,4} = 8.5$, $J_{3b,4} = 5$
H-4	2.70 (m)	$J_{4,3a} = 8.5$, $J_{4,3b} = 5$, $J_{4,15} = 7$
H-15[b]	0.95	$J_{15,4} = 7$
H-6a	2.20 (ddbr)[c,d]	$\sim J_{6a,6b} = 15$, $J_{6a,7} = 7$
H-6b	2.01 (dd)[c,d]	$J_{6b,7} = 4.5$
H-7	3.22 (m)[d]	$J_{6a,7} = 7$, $J_{6b,7} = 4.5$, $J_{7,8} = 8.5$ $J_{7,13a} = 2.5$, $J_{7,13b} = 2$
H-8	4.86 (9)[e]	$J_{8,9a} = J_{8,9b} = 4.2$
H-9a, 9b	2.36 (d)	$J_{9,8} = 4.2$
H-14[b]	1.68 (br)[f]	
H-13a	6.25 (d)	$J_{13a,7} = 2.5$
H-13b	5.65 (d)	$J_{13b,7} = 2$
CH_3–O	3.64	

[a] Analyses were run in deuteriochloroform solution with the internal standard TMS. Frequencies are in parts per million, unmarked signals are singlets, doublet (d), triplet (t), apparent quintet (9), multiplet (m), slightly broadened singlet (br). Coupling constants were determined by inspection or by spin decoupling at 60 and 100 Mc; [b] three protons of methyl group; [c] AB part of ABX system; [d] H-6b signal partially hidden under H_2; [e] quintet resulting from superposition of two triplets; [f] broadened by long range coupling to H-6a.



A

B



C

Irradiation at the frequency of the secondary methyl group (0.95 ppm) collapsed a multiplet at 2.70 ppm to a doublet of doublets. The same multiplet was strongly affected by irradiation at 1.5 ppm. Conversely, irradiation at 2.70 ppm collapsed the methyl doublet to a singlet and simplified a complex two-proton multiplet near 1.5 ppm but had no effect on the remaining part of the spectrum. Irradiation at 1.5 ppm also affected the two-proton triplet at 2.06 ppm, the latter remaining constant under irradiation at all other frequencies. The presence of partial structure C was thus indicated.

Combination of B and C in a formula which incorporates a tetrasubstituted double bond carrying a methyl group is possible in two ways, **6** and **14**, but only **6** accords with the chemical evidence cited in the previous paragraphs. The association with ivangustin renders this formula doubly persuasive since the parent acid can be visualized as having been formed from a eudesmanolide precursor by a cleavage

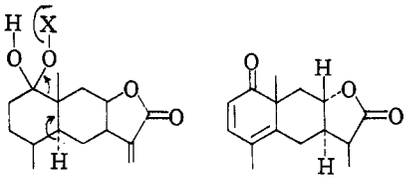
(6) W. Herz, A. Romo de Vivar, and M. V. Lakshmikantham, *J. Org. Chem.*, **30**, 120 (1965).

(7) The multiplicity of the signal at 4.88 ppm required that the proton under the lactone oxygen be spin-coupled to at least three protons. This was confirmed by irradiation of H-7 at 3.2 ppm which collapsed the doublets of the exocyclic methylene group to singlets and the signal at 4.88 ppm to a triplet.

(8) We are greatly indebted to Mr. R. S. Sudol and Dr. D. W. Ovenall, Plastics Department, Experimental Station, E. I. du Pont de Nemours and Company, Inc., who determined the 220-Mc nmr spectrum and undertook the decoupling experiments at 100 Mc, after it had become apparent that the signals at 60 Mc were not sufficiently resolved to permit unambiguous assignments.

(9) We have adopted the numbering system illustrated in structure **6** to show the relationship between ivangulin and eudesmanolides.

process D similar to the one proposed for the biogenesis of nyctanthic and dammarenolic acid.[10] Alternatively, ivangulin could arise by way of a reaction mimicking the photochemically induced fission of dehydroivangustin (**5**) or of its unknown 5,10-dihydro derivative in the presence of oxygen.[11] The laboratory photolysis of the ψ-santonin derivative **15** to a dehydro analog of ivangulin has been reported.[12]



D

15

The coupling constants listed in Table I support the relative configuration depicted in formula **6** which is also in accordance with our speculations concerning the derivation of ivangulin from a eudesmanolide precursor. In this connection it may be significant that extraction of a collection of *I. angustifolia* made earlier during the growing season than usual gave a very much smaller yield of ivangulin and a larger yield of ivangustin. However the factor of geographic variability cannot be dismissed at this time.

Experimental Section[13]

Extraction of *Iva angustifolia* Nutt. A.—Above-ground parts of *Iva angustifolia* Nutt. (7.7 kg) collected by Dr. N. Henderson on Oct 26, 1963, south of Hearn in Robertson County, Tex. (Henderson voucher 63-1839) were extracted with chloroform in the usual manner.[14] The crude gum (290 g) was dissolved in 500 ml of benzene and chromatographed over 1.3 g of silicic acid (Mallinckrodt 100 mesh), the eluate being collected in 500-ml fractions. Fractions 1–2 (benzene), 3–9 (benzene–chloroform 2:1) and 10–13 (benzene–chloroform, 1:2) gave gums only. Fractions 12–24 (benzene–chloroform, 1:1 and benzene–chloroform, 1:2) solidified and were combined. Recrystallization from benzene–ether furnished 9 g of crude ivangulin, mp 80–84°. The mother liquor was evaporated and rechromatographed over 120 g of silicic acid. This furnished an additional 3 g of ivangulin, mp 80–84°. Fractions 26–35 (benzene–chloroform, 1:2, 43 g of gum) were combined, dissolved in benzene, and rechromatographed over 500 g of silicic acid. Benzene and benzene–chloroform (5:1 and 2:1) gave gums. Part of the chloroform fraction furnished 2.7 g of crystalline material which after recrystallization from chloroform–petroleum ether yielded 1.8 g of ivangustin, mp 120–122°. Fractions 36, *et seq.* (chloroform–methanol; 99:1, 49:1, 19:1, and 9:1) gave gums.

B.—*Iva angustifolia* (8.6 kg) collected by Mr. M. Cramer in late Oct 1964 in the vicinity of Austin, Tex., gave 160 g of crude gum which was chromatographed over 1 kg of silicic acid. Fractions 1–6 (benzene–petroleum ether, 1:1), 7–12 (benzene–petroleum ether, 2:1), and 13–18 (benzene) gave mobile oils, fractions 19–25 (benzene–chloroform, 4:1) and 26–32 (benzene–chloroform, 3:1) gave gums, fractions 33–40 (benzene–chloroform, 2:1) gave a gum which after trituration with petroleum ether and recrystallization from hexane furnished 4.0 g of ivangulin, mp 82–84°. Fractions 41–47 (benzene–chloroform, 1:1) gave gummy matter, fractions 48–54 (benzene–chloroform, 1:1) gave semisolid material which was extracted with a large volume of hot heptane. Concentration of the filtered extract yielded 5.0 g of ivangustin, mp 122°. Subsequent fraction eluted only gums.

C.—A collection of *I. angustifolia* (18.1 kg) made by Dr. C. S. Wallis in mid-Sept 1966 in the vicinity of Ft. Gibson, Warner, Porum and Sallisaw, Muskogee, and Sequoyah Counties, Okla., gave 260 g of gum which was chromatographed over 1.5 kg of silicic acid in the usual way. The yield of ivangulin was disappointingly small (1.5 g), but the yield of ivangustin was enhanced (23 g).

Ivangustin (2a).—Ivangustin, when recrystallized from chloroform–petroleum ether, had mp 120–122°, $[\alpha]^{27}D$ +85° (*c* 1.05), high intensity absorption at 205 mμ, infrared bands at 3600, 3500 (bonded and nonbonded –OH), 1770 (γ-lactone), 1670 and 1640 cm^{-1} (two double bonds), nmr signals at 6.30 (d, three protons) and 5.61 (d, J = 3, H-13a and H-13b), 4.47 (m, H-8), 3.5 (t, J = 8.5, H-1), 1.58 (C-4 methyl), and 0.92 ppm (C-10 methyl).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12; O, 19.31. Found: C, 72.47; H, 8.04; O, 19.07.

Acetylation of 50 mg of **2a** with pyridine–acetic anhydride in the usual fashion gave a gum which was chromatographed over 4 g of silicic acid. The benzene–chloroform (1:1) eluate **2b** was an oil which was homogeneous on tlc but could not be induced to crystallize. The acetate **2b** had infrared bands at 1770 (γ-lactone) and 1735 cm^{-1} (acetate) and was converted to the pyrazoline by treatment with ethereal diazomethane. After 3 days the solution was evaporated and the residue recrystallized from heptane. The pyrazoline melted at 139–141°, λ_{max} 326 mμ (ϵ 170).

Anal. Calcd for $C_{18}H_{24}O_4N_2$: C, 65.04; H, 7.28. Found: C, 65.21; H, 7.22.

Dihydroivangustin (3a).—A solution of 0.125 g of **2a** in 30 ml of ethanol was shaken with 30 mg of palladium on a calcium carbonate catalyst in an atmosphere of hydrogen until the calculated amount of hydrogen (11.5 ml) had been absorbed. The mixture was filtered and evaporated, and the residue was chromatographed over 14 g of silicic acid. The chloroform eluate contained **3a** which was homogeneous on tlc but could not be induced to crystallize: nmr signals at 4.58 (c, H-8), 3.45 (t, J = 8, H-1), 1.65 (C-4 methyl), 1.22 (d, J = 7, C-11 methyl), and 1.09 ppm (C-10 methyl). Acetylation of **3a** with pyridine–acetic anhydride in the usual fashion furnished a gum which was chromatographed over silicic acid. The fraction eluted with benzene–chloroform (1:1) solidified on trituration with petroleum ether. Recrystallization from heptane furnished 25 mg of **3b**, mp 149–150°, $[\alpha]^{27}D$ +69° (*c* 0.875); nmr signals showed peaks at 4.75 (t, J = 8, H-1), 4.47c (H-8), 2.07 (acetate), 1.67 (C-4 methyl), 1.26 (d, J = 7, C-11 methyl), and 1.16 ppm (C-10 methyl; infrared bands at 1790 (γ-lactone) and 1740 cm^{-1} (acetate).

Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27; O, 21.89. Found: C, 69.82; H, 8.37; O, 21.69.

Dehydroivangustin (5).—A solution of 0.105 g of **2a** in 3 ml of pyridine was added to 0.5 g of chromic oxide in 6 ml of pyridine at 0°, stirred at 0° for 2 hr, and left overnight at room temperature. After decomposing the excess oxidizing agent by adding a few drops of methanol, the mixture was poured over ice and extracted with ether. The washed and dried ether extracts were evaporated and chromatographed over 7 g of silicic acid. The chloroform–methanol (100:1) eluate solidified on trituration with petroleum ether. Three recrystallizations from heptane furnished 25 mg of **5**, mp 98.5–100.5°, λ_{max} 204 mμ (14000), infrared bands at 1780 (γ-lactone), 1720 (ketone), 1680 (double bond), and 1450 cm^{-1} (–CH_2C=O), nmr signals showed peaks at 6.31 (d) and 5.70 (d, J = 2, H-13a and H-13b), 4.45 (m, H-8), 1.83 (C-4 methyl), and 1.25 ppm (C-10 methyl).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.17; H, 7.32; O, 19.51. Found: C, 73.27; H, 7.32; O, 19.29.

Tetrahydroasperilin (4).—A solution of 50 mg of ivangustin in 30 ml of acetic acid was shaken with 50 mg of platinum oxide at a hydrogen pressure of 30 psi. The solvent was removed, the residue was taken up in chloroform and washed, dried, evaporated, and chromatographed over 3 g of silicic acid. The chloroform–methanol (100:1) eluate solidified on trituration with petroleum ether. Three recrystallizations from chloroform–petroleum ether gave 20 mg of tetrahydroasperilin, mp

(10) D. Arigoni, D. H. R. Barton, R. Bernasconi, D. Djerassi, J. S. Mills, and R. E. Wolff, *J. Chem. Soc.*, 1900 (1960).

(11) G. Quinkert, *Angew. Chem.*, **77**, 229 (1965). We have not yet discovered suitable laboratory conditions for reducing this proposed reaction to practice.

(12) W. G. Dauben, D. A. Lightner, and W. K. Hayes, *J. Org. Chem.*, **27**, 1897 (1962).

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

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

149–150°, $[\alpha]^{26}D$ +13.4° (*c* 0.85), nmr signals (after D_2O exchange) at 4.5 (m, H-8), 3.25 (m, H-1), 1.30 (d, J = 6.5, C-11 methyl), 1.17 (d, J = 6.5, C-4 methyl), and 0.97 ppm (C-10 methyl), identical in all respects with authentic tetrahydroasperilin (nmr and infrared spectra and mixture melting point).

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59; O, 19.02. Found: C, 71.50; H, 9.45; O, 19.10.

Ivangulin (6).—Ivangulin when recrystallized from benzene–ether or heptane had mp 84–85°, $[\alpha]^{27}D$ +109°, high intensity absorption at 205 mμ, infrared bands at 1770 (γ-lactone), 1740 (ester), 1670 and 1640 cm^{-1}, nmr signals (60 Mc) at 6.25 (d) and 5.70 (d, J = 3, H-13a and H-13b), 4.88 (quint, J = 5, H-8), 3.64 (methoxyl), 1.70 (br, C-10 methyl), and 0.95 (d J = 7, C-4 methyl).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.06; H, 7.91; O, 23.02. Found: C, 60.10; H, 8.09; O, 22.71.

Reduction of ivangulin with lithium aluminum hydride in tetrahydrofuran gave a gum which could not be induced to crystallize. The infrared spectrum indicated the disappearance of both carbonyl functions. Benzoylation with benzoyl chloride–pyridine gave a gum which was chromatographed over silicic acid. The benzene eluate furnished the noncrystalline benzoate whose nmr spectrum indicated that the methoxyl group of **5** had been reduced to $-CH_2OH$ and benzoylated. Ivangulin was recovered from an attempt to carry out a reduction with zinc and acetic acid.

Catalytic hydrogenation of ivangulin (PtO_2 or Pd–C) at atmospheric pressure in ethanol gave a mixture whose nmr spectrum indicated the presence of partially reduced and isomerized products, the disappearance of doublets characteristic of a conjugated exocyclic methylene group, a new vinyl methyl signal at 1.85, and a secondary methyl signal at 1.10 ppm. This mixture could not be resolved satisfactorily by chromatography. Catalytic reduction in acetic acid resulted in the uptake of 2 mole equiv of hydrogen and the saturation of both double bonds (nmr spectrum), but the gummy mixture of isomers could not be separated chromatographically.

Dihydroivangulin (7).—To a solution of 0.1 g of **6** in 10 ml of ethanol was added 10 g of 3% sodium amalgam in small portions, the solution being kept acidic by periodic addition of acetic acid. The solution was concentrated and diluted with water. The solid product **7** was recrystallized from acetone–petroleum ether to yield 75 mg, and had mp 75–77°, $[\alpha]^{27}D$ +71 (*c* 1.7), positive tetranitromethane reaction, high ultraviolet intensity at 205 mμ, infrared bands at 1770 (γ-lactone), 1740 (ester) and 1640 cm^{-1} (double bond), nmr signals at 4.55 (q, J = 5, H-8), 3.58 (methoxyl), 1.62 (br, C-10 methyl), 1.18 (d, J = 7, C-11 methyl), and 0.97 (d, J = 7, C-4 methyl).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.57; H, 8.57; O, 22.85. Found: C, 68.48; H, 8.49; O, 22.99.

A solution of 0.5 g of **7** in 100 ml of methanol was ozonized at −70°, reduced catalytically, and worked up in the usual way to yield 0.5 g of neutral, colorless oil. Vpc analysis indicated the absence of methyl levulinate; fractional distillation gave no material which boiled below 170° (0.2 mm).

Hydrolysis of **7** with 10% sodium hydroxyde in methanol at room temperature gave an acidic fraction which could not be induced to crystallize and was a mixture of two components apparently epimeric at C-11. It had nmr signals at 4.8 (c, H-8), 1.75 (vinylic methyl at C-10), 1.30 (d, J = 7, ⅓ intensity) and 1.22 (d, J = 7, ⅔ intensity, epimeric C-11 methyls), and 0.99 (d, J = 7, C-4 methyl). Treatment of this material with 50% sulfuric acid gave a mixture of hydroxylated γ, δ-dilactones (infrared spectrum) which could not be separated satisfactorily by chromatography.

Dihydroivangulin Epoxide (8).—A solution of 0.1 g of **7** in 2 ml of chloroform was mixed with 0.1 g of *m*-chloroperbenzoic acid, allowed to stand overnight, and worked up in the usual fashion. The solid product **8** was recrystallized from acetone–petroleum ether and then melted at 100–101°, yield 70 mg, $[\alpha]^{27}D$ +35° (*c* 0.8), negative tetranitromethane test, infrared bands at 1770 (γ-lactone) and 1740 cm^{-1} (methyl ester), nmr signals at 4.45 (quint, J = 4, H-8), 3.68 (methoxyl), 1.31 (C-10 methyl), 1.17 (d, J = 8, C-4 methyl), and 1.04 (d, J = 7, C-11 methyl).

Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.86; H, 8.11; O, 27.03. Found: C, 64.55; H, 8.19; O, 27.01.

A solution of 0.2 g of **8** in 2 ml of 70% perchloric acid was allowed to stand overnight at 5°, poured into ice water, and extracted with chloroform. The organic layer was washed, dried, and evaporated, and the residue was recrystallized from acetone–petroleum ether. The yield of **9** was 0.15 g, mp 167–169°, infrared bands at 3650 and 3500 (bonded and nonbonded hydroxyl), 1780 (γ-lactone) and 1730 cm^{-1} (γ-lactone), nmr signals at 4.69 (q, J = 6, H-8), 1.43 (C-10 methyl), 1.21 (d, J = 7, six protons, C-4 and C-11 methyl). Repeated analyses of two separate preparations of this substance gave erratic results, apparently due to rapid absorption of moisture.

Treatment of 0.15 g of **8** with thionyl chloride–pyridine at 0° followed by the usual work-up and chromatography of the crude gum over 10 g of silicic acid gave, in the benzene–ether (19:1) eluate, a small amount of solid which was recrystallized from acetone–ether–hexane and then melted at 151–153° to yield 15 mg of pure material. The same substance was obtained in somewhat lower yield by treatment of **8** with methanesulfonyl chloride. Its infrared spectrum (absence of hydroxyl bands, presence of γ-lactone at 1770, γ-lactone at 1725, double bond at 1650 and 900 cm^{-1}) was appropriate for formula **10** as was the nmr spectrum which had signals at 5.07 (br, two protons, $=CH_2$), 4.5 (c, H-8), 1.16 (d, J = 7), and 1.11 (d, J = 7, C-4 and C-11 methyls).

Anal. Calcd (mass spectrum) for $C_{15}H_{20}O_4$: mol wt, 264. Found: mol wt, 264.

Registry No.—**2a**, 14164-59-1; **2b**, 14164-60-4; **3a**, 14164-61-5; **3b**, 14164-62-6; **4**, 14170-40-2; **5**, 14164-63-7; **6**, 14271-37-5; **7**, 14164-64-8; **8**, 14271-38-6; **9**, 14164-65-9; pyrozoline ($C_{18}H_{24}O_4N_2$), 14164-66-0; **10**, 14171-87-0.