sample of methyl ester (12 g. 0.066 mole) as dissolved in 150 ml. methanol and ozonized at −70°. When no more ozone was absorbed the solution was warmed at −10° and diluted with 100 ml. of water. Chlorine was slowly added at 0° until saturated. After standing overnight, the crude oxidate was isolated by washing, and removing the solvent. The residue, 6.8 g., was dissolved in ether, extracted with sodium bicarbonate solution to remove the soluble acids. Removal of the ether from the bicarbonate insoluble material gave a residue (4.5 g., 58%) (based on a 3:7 ratio of isomers), which was distilled, b.p. 104–106°/2 mm. By infrared spectral and vapor phase chromatographic analysis, the acid moiety, a keto acid, was identical to that obtained from the oxidation of the pinenic mixture obtained from pyrolysis of pinolic acid.

Acknowledgment. The authors wish to express their appreciation to Mr. L. E. Brown, Southern Utilization Research and Development Division, New Orleans, La., for elemental analyses reported in this paper.

OLUSTEE, FLA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY]

Ivalin, a New Sesquiterpene Lactone[1]

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The structure of ivalin, a new sesquiterpene lactone from *Iva microcephala* Nutt. and *Iva imbricata* Walt., is shown to be I.

The interesting connection which we established recently[2] between some sesquiterpene lactones of *Ambrosia* and *Parthenium* species made it desirable to investigate other genera related to *Ambrosia*. In the following, we report on the isolation and structure of a new sesquiterpene lactone from two *Iva* (marsh elder) species.

Extraction of flowers and leaves of *Iva microcephala* Nutt., an annual weed found in the Southern coastal plain, gave in 1.9% yield[3] a crystalline compound $C_{15}H_{20}O_3$, m.p. 130–132°, $[\alpha]^{23}D$ + 142°, which appeared to be new and which we have named ivalin. Ivalin was also obtained in somewhat lower yield from *Iva imbricata* Walt., but not from *Iva frutescens* L.

Ivalin (I) had a hydroxyl group (infrared bands at 3700 and 3500 cm.$^{-1}$, formation of an acetate, II) and two double bonds (infrared bands at 1600 and 1645 cm.$^{-1}$, hydrogenation). The remaining two oxygen atoms were presumably present as a γ-lactone (infrared band at 1750 cm.$^{-1}$) conjugated with one of the double bonds (λ_{max} 208 mμ, ϵ 11000). Ivalin is therefore bicyclic.

The nature of the two double bonds was inferred from the following. Ozonolysis of ivalin gave a 94% yield of formaldehyde, indicating the possibility of more than one exocyclic methylene group.[4] Partial hydrogenation of ivalin (palladium-on-calcium carbonate in ethanol) gave dihydroivalin (III) which still had one exocyclic methylene group (liberation of formaldehyde on ozonolysis, infrared band at 1645 cm.$^{-1}$), but no longer exhibited conjugation in the ultraviolet and whose lactone frequency had moved to 1770 cm.$^{-1}$ Hence ivalin contained two exocyclic methylene groups, one unconjugated and one conjugated with the lactone ring. This was also shown by the formation of a pyrazoline on treatment of ivalin with diazomethane. Hydrogenation of ivalin in acetic acid furnished tetrahydroivalin (V) which resisted ozonolysis and exhibited no double bond frequencies in the infrared.

The NMR spectra[5] of I, III, and V and their acetates completely verified these conclusions. I had two low-field doublets (367.4 and 336.7 c.p.s., J ~ 1.6 c.p.s.), each representing one proton, characteristic of the methylene group conjugated with a lactone.[6] These were absent in III and V. A second pair of doublets at somewhat higher field (291 and 271[7] c.p.s., J ~ 1.5–unconjugated >C=CH_2) was found in the spectra of I and III, but not in that of V. On the other hand, I had only one sharp signal at 57 c.p.s., (intensity three protons, tertiary methyl group). III exhibited this signal at 48 c.p.s. and had a new methyl doublet at 70 and 77 c.p.s. (methyl alpha to lactone). V had two split methyl signals (56, 64.5 and 73, 80 c.p.s.) one

(1) Supported in part by grants from the National Science Foundation (NSF G-14396) and the Eli Lilly Company.

(2) W. Herz and G. Högenauer, *J. Org. Chem.*, 26, 5011 (1961).

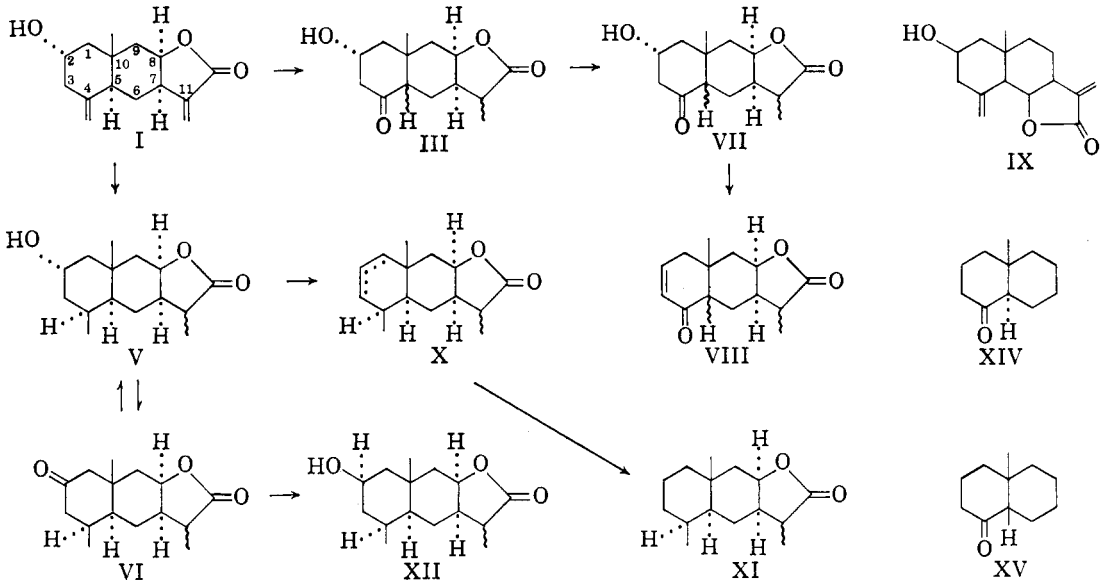
(3) The high yield of ivalin appears to be due to a fortuitous combination of circumstances, perhaps because of time and location of collection (see Experimental). This problem and the phytochemistry of other *Iva* species are being investigated further.

(4) The yields of formaldehyde, precipitated as the dinitrophenylhydrazone or dimedone derivative, generally are 30–50% per exocyclic methylene group in compounds of this type).

(5) Spectra were run by Mr. Fred Boerwinkle in deuteriochloroform solution at 60 mc., on a Varian HR-60 instrument, with tetramethylsilane as internal standard. Frequencies were determined by the side band technique.

(6) W. Herz, M. Miyazaki, and Y. Kishida, *Tetrahedron Letters*, 82 (1961).

(7) In the NMR spectrum of ivalin, this doublet was superimposed on the signal of the C-8 lactonic hydrogen (*vide infra*).



of which was superimposed on the tertiary methyl singlet (64.5 c.p.s.).

That the hydroxyl group was secondary was shown by the facile oxidation of V to dehydrotetrahydroivalin (VI) and the NMR. spectra (complex multiplet centered at 225–229 c.p.s., intensity one proton, which moved to 275 c.p.s. on acetylation and disappeared in the NMR. spectrum of VI). The new ketone group of VI appeared to be in a six-membered ring (infrared band at 1715 cm.$^{-1}$) and was flanked by at least one methylene group (band at 1430 cm.$^{-1}$, positive Zimmermann test).

Ozonolysis of dihydroivalin (III) furnished a norhydroxyketolactone $C_{14}H_{20}O_4$ (VII). The new keto group of VII was also in a six-membered ring (infrared band at 1715 cm.$^{-1}$). The Zimmermann test was dubious, but a band at 1420 cm.$^{-1}$ indicated the presence of an α-methylene group. Oxidation with chromium oxide–pyridine gave acidic material which was not further investigated. However, this result suggested that VII was a β-hydroxy ketone. This was confirmed when treatment of VII with methanesulfonyl chloride in pyridine resulted in the formation of an α,β-unsaturated ketone (VIII, infrared bands at 1780—γ-lactone—and 1680 cm.$^{-1}$). The ultraviolet (λ_{max} 225, 320 mμ, ϵ 8350, 50) and NMR spectrum (two narrowly split triplets at 363 and 372 c.p.s.—α-proton; two more widely split triplets at 411 and 420 c.p.s.—β-proton)[8] showed that the chromophore of VIII was unsubstituted and that two hydrogen atoms were attached to the γ-carbon.

The above evidence coupled with biogenetic considerations reduced the possible structures for ivalin to two—I (exclusive of stereochemistry) and IX. The NMR spectrum was not helpful in deciding between these, the lactonic hydrogen (H_8 in I) indicating its presence as a relatively narrow complex multiplet centered at 271 c.p.s. In the hope or resolving the issue by converting I to one of the known stereoisomeric desoxotetrahydrosantonins or tetrahydroalanto lactones, the mesylate of V was refluxed with lutidine. This resulted in the formation of an anhydro derivative (X)[9] hydrogenation of which gave a substance in all respects identical with an authentic sample of tetrahydroalanto lactone (XI).[11] This unequivocally established the structure of ivalin as a 2-hydroxyisoalanto lactone, the absolute stereochemistry at C-5, C-7, C-8 and C-10 being as shown in I.[12,13] Incidentally, comparison of the rotation of tetrahydroivalin with that of the triol prepared from it by lithium aluminum hydride reduction showed

(8) These appear to be the A and B components of an ABX_2 system (A, α-hydrogen; B, β-hydrogen; X, the two equivalent γ-hydrogens) where J_{AB} = 9, $J_{AX} \sim$ 3.5 and $J_{BX} \sim$ 2.1 c.p.s.

(9) The m.p. of this substance, 140–141°, resembles that of a somewhat impure Δ^2-isomer reported by Tanabe.[10] The NMR spectrum was difficult to interpret and suggested the possibility of a mixture of isomers.

(10) K. Tanabe, *Chem. Pharm. Bull.*, **6**, 219 (1958).

(11) We wish to thank Dr. K. Tanabe for supplying us with this material.

(12) K. Tsuda, K. Tanabe, I. Iwai, and K. Funakoshi, *J. Am. Chem. Soc.*, **79**, 5721 (1957); K. Tsuda and K. Tanabe, *J. Pharm. Soc. Japan*, **77**, 558 (1957); V. Benešova, V. Sýkora, V. Herout, and F. Šorm, *Chem. & Ind.*, 1359 (1958); W. Cocker and T. B. H. McMurry, *Tetrahedron*, **8**, 181 (1960).

(13) The absolute configuration of tetrahydroalanto lactone at C-11, although the subject of some argument, has not been established rigorously. Our formulas reflect this uncertainty. As V is stable to base, the C-11 methyl, like that of XI, must be in the stable configuration, most plausibly α or *cis* to the C-7 hydrogen.[14]

(14) W. G. Dauben, W. K. Hayes, J. S. P. Schwarz, and J. W. Farland, *J. Am. Chem. Soc.*, **82**, 2232 (1960); but see S. Nakazawa, *J. Am. Chem. Soc.*, **82**, 2229 (1960), for summation of the contradictory evidence.

that the Hydson-Klyne rule[15] is applicable in the ivalin series.

There remained the question of the orientation of the hydroxyl group at C-2. We attempted to settle this problem by reducing VI with sodium borohydride. The major, less strongly adsorbed, product (92%) was a new isomer (XII) epimeric at C-2. The minor, more strongly adsorbed, product (8%) was tetrahydroivalin. We assume that attack at the β-face of VI would be hindered even more severely than in 2-cholestanone where the axial (β) alcohol is formed predominantly.[16] Hence the hydroxyl group of XII should be axial and β, that of V, and ivalin, should be equatorial and α. The order of adsorption on alumina is in accord with this conclusion.

Further support for the proposed stereochemistry at C-2 was obtained in several ways although the usual infrared evidence[17] was inapplicable, the relevant regions being complicated by other bands. Treatment of V with phosphorus oxychloride–pyridine did not result in dehydration, but yielded a chloride—a mode of reaction characteristic of equatorial alcohols.[18] Furthermore, comparison of the rates of chromic acid oxidation[19] showed that XII was oxidized considerably faster than V because of the two severe diaxial —OH—CH_3 interactions present in XII. The results are given in Table I.

TABLE I

RATES OF OXIDATION

Compound	K_2 in 86.3% Acetic Acid and 10^{2-} Mole/NaOAc	K_2 in 90% Acetic Acid	K*
V	Stable	0.011	1.0
XII	0.035	0.62	110
5α-Cholestan-3β-ol	Stable	0.010	1.0
5α-Cholestan-2β-ol	0.0117	0.37	37

K_2 = [l. mole^{-1} min.$^{-1}$], K* = $K_{ROH}/K_{5\alpha\text{-cholestan-}3\beta\text{-ol}}$

Thirdly, the C-2 hydrogen atom of tetrahydroivalin gives rise to a complex NMR signal at 229 c.p.s. roughly of the type to be expected of an axial hydrogen spin-coupled to two more or less equivalent equatorial hydrogen atoms (dihedral angle $\sim$ 60°) and two axial hydrogens (dihedral angle $\sim$ 180°). By contrast, 2-epitetrahydroivalin (XII) with its C-2-hydrogen equatorial and therefore spin-coupled to 4 equivalent neighboring hydrogen atoms (dihedral angle $\sim$ 60°), should, and actually does, exhibit a quintuplet of approximate intensity 1,4,6,4,1 centered at 251 c.p.s. (J = 3). Ivalin is therefore satisfactorily represented by I. Incidentally, these observations also dispose of the possibility that the severe diaxial —OH—CH_3 and CH_3—CH_3 interactions present in the chair form of XII might have forced ring A to adopt the boat conformation.[20]

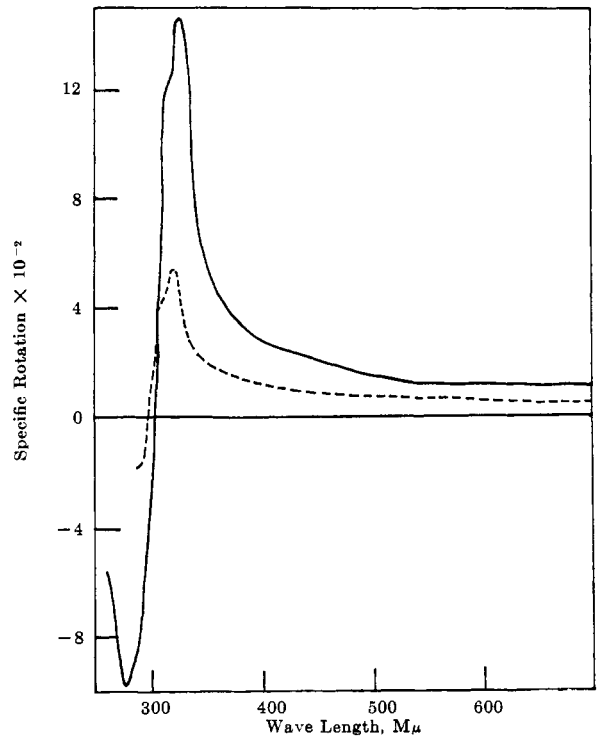


Fig. 1. Rotary dispersion curves of VI (——) and VII (- - - - -)

The optical rotatory dispersion curve of VI (Fig. 1) is similar to that of 2-cholestanone[21] and (+)-*trans*-8,9-dimethyl-3-decalone[22] in sign and magnitude of Cotton effect. This indicates that the *cis*-lactone ring exerts little influence on the shape of the molecule, the very slight lowering of the amplitude being perhaps due to the axial methyl group at C-4 as demanded by the octant rule.[23] On the other hand, the rotatory dispersion curve of the norhydroxyketo lactone VII (Fig. 1) is dif-

(15) W. Klyne, *Chem. & Ind.*, 1198 (1954); V. Sýkora and M. Romanuk, *Coll. Czech. Chem. Communs.*, **22**, 1909 (1957).

(16) W. G. Dauben, E. J. Blantz, J. Jiu, and R. A. Micheli, *J. Am. Chem. Soc.*, **78**, 3752 (1956).

(17) D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, **10**, 44 (1956).

(18) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(19) J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, **38**, 1529 (1955). We are greatly indebted to Drs. Schreiber and Eschenmoser, ETH, Zurich, for carrying out the experiments. The differences in the rate of oxidation of the two epimers were so great that it was necessary to measure rates in two different systems.

(20) This possibility was suggested by Dr. J. Levisalles, University of Strasbourg.

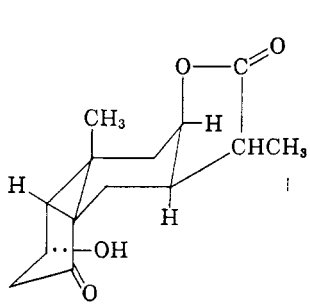
(21) C. Djerassi, W. Closson, and A. E. Lippman, *J. Am. Chem. Soc.*, **78**, 3163 (1956).

(22) C. Djerassi, L. A. Mitscher, and B. J. Mitscher, *J. Am. Chem. Soc.*, **81**, 947 (1959).

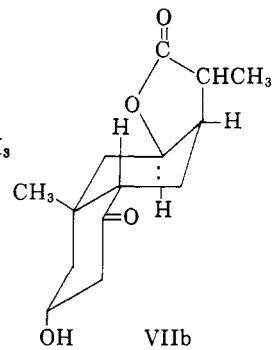
(23) C. Djerassi, *Optical Rotatory Dispersion*, McGraw Hill Book Company, 1960, p. 178. The contrast with the abnormally large positive Cotton effect of 2-ketomanoyl oxide is noteworthy, P. K. Grant, *J. Chem. Soc.*, 860 (1959); P. K. Grant and R. Hodges, *Chem. & Ind.*, 1300 (1960); R. Hodges, *Tetrahedron*, **12**, 215 (1961).

ficult to interpret if 4-cholestanone (XIII) or (+)-*trans*-10-methyl-1-decalone (XIV)[24] be taken as standards. Indeed, the sign of the Cotton effect is completely reversed, being positive for VII and negative for XIII and XIV.[24]

It is not clear whether such a large effect can and should be attributed to the equatorial hydroxyl group at C-2 which, being in the upper left quadrant, should make a positive contribution to the total dispersion picture, but would not be expected to alter the conformation of VII significantly from that of XIV. To explain the positive Cotton effect, one is therefore tempted to invoke epimerization at C-5 during the ozonolysis or the subsequent work-up. In this case, VII would have a *cis* rather than a *trans* A-B ring fusion and *cis*-10-methyl-1-decalone (XV) should serve as reference.[25] The Cotton effect of the appropriate enantiomer of XV is indeed positive and roughly of the same magnitude[26] as that of VII.



VIIa



VIIb

One might wonder why the possibility of epimerization should even be considered since in 10-methyl-1-decalones the *trans*-isomer appears to be somewhat more stable than the *cis*[24,27] and the introduction of an α-oriented hydroxyl group at C-2 would have the effect of exaggerating rather than minimizing this stability relationship in the "steroid-like"[28] cis conformation VIIa. However, in the nonsteroid-like *cis* conformation VIIb, diaxial interactions appear to be at a minimum. It is therefore quite possible that VII is the *cis* rather than the *trans* isomer. We hope to investigate this in more detail when additional supplies of ivalin become available.

(24) C. Djerassi and D. Marshall, *J. Am. Chem. Soc.*, **80**, 3986 (1958). The synthetic decalone obtained by these authors in stereochemically impure form had the opposite absolute configuration from that of XIII and expected for VII.

(25) For a discussion of why 4-coprostanone would probably not be a suitable analog, see ref. 24. Although the Cotton effect of 4-coprostanone is positive, the shape of its curve is quite different from that of VII.

(26) The curve given in ref. 24 is that of the enantiomer of opposite absolute configuration.

(27) F. Sondheimer and D. Rosenthal, *J. Am. Chem. Soc.*, **80**, 3995 (1958).

(28) For definition, see ref. 23, p. 76.

EXPERIMENTAL[29]

Isolation of ivalin. (a) Finely divided flower heads and leaves of *Iva microcephala* Nutt., wt. 1065 g., collected at the flowering stage on October 15, 1958, near Lake Seminole, Jackson County, Fla., were extracted in two large Soxhlet extractors with chloroform for 2 days. The extract was concentrated and the residue taken up in 250 ml. of hot ethanol, diluted with 250 ml. of hot water containing 10 g. of lead acetate and 3 ml. of acetic acid, and allowed to stand. After 2 days, the supernatant liquid was filtered and concentrated at reduced pressure. The gum was taken up in chloroform and dried. Removal of solvent yielded 33 g. of material which solidified on stirring with petroleum ether.

A solution of 27 g. of the crude product in 50 ml. of chloroform and 40 ml. of benzene was chromatographed over 220 g. of alumina (alcoa F-20). The first fraction, 150 ml. of benzene-chloroform (1:1) furnished 16 g. of green, somewhat gummy material which was crystallized from benzene–petroleum ether; yield 11.3 g. of colorless crystals. Fractions 2–7 (benzene-chloroform and chloroform) yielded an additional 6.7 g. of colorless material, total yield 19 g. (1.9%). One additional recrystallization raised the m.p. to 130–132°, $[\alpha]^{23}D$ + 142° (*c*, 1.03, $CHCl_3$), λ_{max} 208 mμ, (ϵ 11000), infrared bands at 3700 and 3500 (−OH), 1750 (γ-lactone), and 1640 cm.$^{-1}$ (rel. strong, shoulder at 1660—double bonds).

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.85; H, 8.20.

A collection of *I. microcephala* made on October 8, 1960 (beginning of flowering stage) in Taylor County, Fla., south of Perry, yielded only 7 g. of ivalin from 210 g. of crude gum obtained by extracting 29 lbs. of the whole plant including stems and some roots. There was also obtained a very polar substance whose properties are being investigated. A collection of *I. microcephala* from Grady, Lafayette County, Fla., on September 15, 1960 (before the flowering stage), yielded no ivalin, but the polar material and other substances now under study.

(b) Extraction of 1050 g. of leaves and flowerheads of *Iva imbricata* Walt., collected near Panama City, Fla., on August 8, 1958, and work-up in the usual manner furnished 13 g. of gum which was taken up in 30 ml. of benzene and chromatographed over 125 g. of alumina. The first two benzene fractions (100 ml. each) gave gums. Subsequent benzene and chloroform eluated yielded crystalline residues. The total weight of once-recrystallized material was 1.7 g. (0.17%), m.p. 127–130°, shown to be identical with ivalin by infrared spectrum and mixed m.p.

(c) Flowers and leaves of *Iva frutescens* L., collected near St. Marks, Fla., in July 1958, wt. 1000 g., were extracted in the usual way. The gum, wt. 10.5 g., was chromatographed over alumina, but no crystalline fractions were obtained.

Ozonolysis of ivalin. A solution of 0.1 g. of ivalin in 50 ml. of chloroform was ozonized at −70°. The mixture was steam distilled into an ethanolic solution of dimedone which was again steam distilled to remove organic solvents. Upon cooling there was obtained 0.9 g. (94%) of formaldehyde-dimedone derivative, m.p. 188–189°, mixed m.p. with an authentic sample undepressed.

Pyrazoline of ivalin. A solution of 0.1 g. of ivalin in 50 ml. of ethanol was treated with a solution of diazomethane in 50 ml. of ether. After allowing the mixture to stand in the refrigerator for 4 days, the solvents were removed *in vacuo*

(29) M.p.'s are uncorrected. Analyses by Dr. F. Pascher, Bonn, Germany. Ultraviolet spectra were determined by Mrs. M. Osmond and Mrs. P. DeTar in 95% ethanol solution on a Cary Model 14 spectrometer. Infrared spectra were run in chloroform solution, unless otherwise specified, on Perkin-Elmer Infracord or Model 221 instruments. Rotatory dispersion curves were run by Dr. M. O'Dwyer in dioxane solution on a Rudolph recording spectropolarimeter.

and the residue recrystallized from acetone–petroleum ether. The product melted at 170° (dec.).

Anal. Calcd. for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found C, 66.39; H, 7.90; N, 9.37.

Acetylivalin. A mixture of 0.8 g. of ivalin, 5 ml. of pyridine, and 2 ml. of acetic anhydride was allowed to stand overnight. Dilution with water gave solid material which was recrystallized from benzene–petroleum ether, m.p. 150°, $[\alpha]^{24}D$ + 137° (*c*, 4.6, $CHCl_3$), infrared bands at 1750 (γ-lactone), 1730 (ester), 1660, and 1645 cm.$^{-1}$ (double bonds), NMR signals at 368.5 (spl.), 334.5 (spl.) (C-11 methylene), 294.5 (br.), 276 (br.) (C-4 methylene and H_2), 271 (br., H_3), 117 (acetate methyl), and 55 c.p.s. (C-10 methyl).

Anal. Calcd. for $C_{15}C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.35; H, 7.96.

The pyrazoline was prepared as described for ivalin, m.p. 154–155° (dec.).

Anal. Calcd. for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 65.82; H, 7.37; N, 8.04.

Dihydroivalin. A solution of 1 g. of ivalin in 50 ml. of ethanol was hydrogenated with 0.1 g. of palladium on calcium carbonate at barometric pressure. The solution was filtered and evaporated *in vacuo*. The residue was recrystallized from ethyl acetate–petroleum ether, yield 0.8 g. Two additional recrystallizations from the same solvent mixture gave the analytical sample, m.p. 150°, $[\alpha]^{23}D$ + 28.9° (*c*, 1.96, $CHCl_3$), only end absorption in the ultraviolet, infrared bands at 3610 and 3500 (−OH), 1770 (γ-lactone) and 1650 cm.$^{-1}$ (isolated double bond). Dihydroivalin was recovered from an attempted reaction with diazomethane.

Anal. Calcd. for $C_{15}H_{22}O_3.H_2O$: C, 67.13; H, 9.02; O, 23.85. Found: C, 67.48; H, 9.32; O, 23.60.

Acetyldihydroivalin. Acetylation of dihydroivalin in the usual manner with acetic anhydride-pyridine gave the acetate, m.p. 185–186°, after recrystallization from benzene-petroleum ether, infrared bands at 1770, 1735, and 1645 cm.$^{-1}$

Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27; O, 21.89. Found: C, 70.22; H, 8.19; O, 21.94.

Tetrahydroivalin. A solution of 3 g. of ivalin in 100 ml. of acetic acid was hydrogenated with 0.3 g. of platinum oxide. The solution was filtered and evaporated at reduced pressure. The residue was recrystallized from ethyl acetate–petroleum ether, wt. 2.55 g. The analytical sample melted at 152° (depression on admixture of dihydroivalin), $[\alpha]^{23}D$ + 7.6° (*c*, 3.1, $CHCl_3$), + 5.3° (*c*, 3.9, ethanol), transparent in the ultraviolet, infrared bands at 3610, 3500, and 1770 cm.$^{-1}$

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59; O, 19.02. Found: C, 71.35; H, 9.78; O, 18.79.

Lithium aluminum hydride reduction of tetrahydroivalin. A mixture of 1 g. of tetrahydroivalin, 0.4 g. of lithium aluminum hydride, and 70 ml. of *N*-ethylmorpholine was refluxed with stirring for 20 hr., cooled, decomposed cautiously with water, and acidified with dilute solfuric acid. Extraction with ether, drying, and removal of solvent furnished an oil which gradually solidified and then was recrystallized from ethyl acetate, yield 0.57 g., m.p. 168–169°, $[\alpha]^{22}D$ −11.6° (*c*, 5.1, ethanol).

Anal. Calcd. for $C_{15}H_{26}O_3$: C, 70.27; H, 11.01; O, 18.72. Found: C, 70.24; H, 10.97; O, 19.25.

Anhydrotetrahydroivalin. A chilled solution of 1.1 g. of tetrahydroivalin in 7 ml. of pyridine was treated with 2 ml. of methanesulfonyl chloride. After 12 hr. in the refrigerator, the mixture was poured on crushed ice. The solid, wt. 1.3 g., was recrystallized from benzene, m.p. 140°.

Anal. Calcd. for $C_{16}H_{26}O_5S$: C, 58.16; H, 7.93; O, 24.20; S, 9.71. Found: C, 58.06; H, 7.71; O, 23.93; S, 9.91.

A solution of 0.85 g. of the crude mesylate in 20 ml. of lutidine was refluxed for eight hr., cooled, and poured over crushed ice. The product, wt. 0.58 g., m.p. 135°, was recrystallized from ethanol and then melted at 140–141°, infrared bands at 1760 (γ-lactone) and 1645 cm.$^{-1}$ (weak, double bond).

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46; O, 13.66. Found: C, 76.71; H, 9.32; O, 14.08.

Tetrahydroalantolactone. A solution of 0.31 g. of anhydrotetrahydroivalin in ethanol was hydrogenated with 0.03 g. of palladium on charcoal, yield of crude product quantitative. Recrystallization from ethanol raised the m.p. to 142°, $[\alpha]^{23}D$ −12° (*c*, 3.0, $CHCl_3$), infrared band at 1770 cm.$^{-1}$, no depression on admixture of an authentic[14] sample of m.p. 142°.[30]

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24; O, 13.54. Found: C, 75.78; H, 10.02; O, 13.95.

Ozonolysis of dihydroivalin. A solution of 0.1 g. of dihydroivalin in 50 ml. of chloroform was ozonized at −70°. The mixture was worked up as described in the ozonolysis of ivalin; yield of formaldehyde-dimedone condensation product 20%. The aqueous solution remaining after the steam distillation was evaporated to dryness. The colorless residue was recrystallized from acetone–petroleum ether, yield 50%, m.p. 178–179°, infrared bands at 3610 and 3500 (−OH), 1775 (γ-lactone), 1715 (ketone), and 1420 cm.$^{-1}$, ultraviolet spectrum λ_{max} 282.5 mμ, ε 35, optical rotatory dispersion curve in dioxane (*c*, 0.511) $[\alpha]_{700}$ +55°, $[\alpha]_{589}$ +51°, $[\alpha]_{319}$ +532°, $[\alpha]_{312}$ +432° (infl.), $[\alpha]_{279}$ −203°.

Anal. Calcd. for $C_{14}H_{20}O_4.H_2O$: C, 62.20; H, 8.20; O, 29.59. Found C, 61.71; H, 8.11; O, 29.49.

A solution of 0.12 g. of VII in 0.5 ml. of pyridine and 5 ml. of acetic anhydride was allowed to stand at room temperature for one day. Dilution with water gave a precipitate which was recrystallized from ethyl acetate–petroleum ether, yield 0.08 g., m.p. 209°, infrared bands at 1775 (γ-lactone), 1735 (double strength—ester and ketone) and 1425 cm.$^{-1}$, NMR signals at 310 (septuplet centered at this position, H_2), 272.5, 268, 265.5, 261 (H_3), 167 (sextuplet centered at this frequency—two H_3), 124 (acetate methyl), 77.5, 70.5 (C-11 methyl), and 54.5 c.p.s. (C-10 methyl).

Anal. Calcd. for $C_{16}H_{22}O_5$; C, 65.29; H, 7.53; 7.53; O, 27.18. Found: C, 64.94; H, 7.38; O, 27.36.

Dehydration of VII. A solution of 0.2 g. of VII, 5 ml. of pyridine and 1 ml. of methanesulfonyl chloride was kept in the refrigerator overnight and then poured over ice. Extraction with chloroform followed by washing and drying gave 0.23 g. of crude VIII. Crystallization from benzene and then ethanol gave crystals melting at 181–182°, infrared bands at 1780 (γ-lactone), 1680 (conjug. ketone) and 1430 cm.$^{-1}$ In addition to the vinyl protons discussed previously, the NMR spectrum had signals at 275.5, 273.5 (H_3), 79, 72.5 (C-11 methyl), and 59 c.p.s. (C-10 methyl).

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74; O, 20.49. Found: C, 71.95; H, 7.63; O, 20.78.

Dehydrotetrahydroivalin. A solution of 2 g. of tetrahydroivalin in 40 ml. of acetic acid was allowed to stand overnight with 0.77 g. of chromic acid in 50 ml. of acetic acid. A few drops of methanol were added, the acetic acid was removed at reduced pressure, and the residue was extracted repeatedly with hot benzene. The extracts were concentrated and the residue triturated with petroleum ether. There was obtained 1.15 g. of crude ketone, m.p. 183–187°. Chromatography over alumina (benzene-chloroform) and recrystallization raised the m.p. to 195–197°, $[\alpha]^{29}D$ + 73.2° (*c*, 2.47, $CHCl_3$), infrared bands at 1770 (γ-lactone), 1715 (ketone), and 1430 cm.$^{-1}$ Optical rotatory dispersion curve in dioxane (*c*, 0.513) $[\alpha]_{700}$ +113°, $[\alpha]_{589}$ +113°, $[\alpha]_{323}$ + 1454°, $[\alpha]_{315}$ +1216° (infl.), $[\alpha]_{278}$ −986°.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; O, 19.17. Found: C, 71.52; H, 8.76; O, 19.62.

(30) The properties of tetrahydroalantolactone as given in the literature vary somewhat, the m.p. being in the range 141–148° and the rotation in the range 10–16°. See K. Tsuda, K. Tanabe, I. Iwai, and K. Funakoshi, *J. Am. Chem. Soc.*, **79**, 5721 (1957).

2-Epitetrahydroivalin. A solution of 0.25 g. of dehydrotetrahydroivalin in 20 ml. of 95% ethanol was allowed to stand with 0.04 g. of sodium borohydride for several hours. A few drops of acetic acid were added, solvent was removed at reduced pressure, and the residue diluted with water, made slightly alkaline with sodium bicarbonate, and extracted with benzene. The benzene extracts yielded 0.27 g. of solid, m.p. 157–166°. By crystallization from benzene, there was obtained 0.16 g. of 2-epitetrahydroivalin, m.p. 168–170°. Further recrystallization did not change the m.p. The mother liquors were chromatographed over 6 g. of acid-washed alumina, eluent benzene-chloroform (7:3). The first fraction consisted of 0.07 g. of slightly less pure 2-epitetrahydrovalin, m.p. 165–168° (total yield 0.23 g. or 92%), the second fraction was 0.02 g. (8%) of slightly impure tetrahydroivalin, m.p. 141–144°. 2-Epitetrahydroivalin had $[\alpha]^{26}D$ +29° (*c*, 4.5, $CHCl_3$), infrared bands at 3600, 3500 and 1770 $cm.^{-1}$

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59; O, 19.02. Found: C, 71.73; H, 9.40; O, 19.29.

2-Chlorotetrahydroalantolactone. A solution of 0.37 g. of tetrahydroivalin in 5 ml. of pyridine was treated with 0.3 ml. of phosphorus oxychloride and allowed to stand at room temperature for 24 hr. The mixture was poured over ice and the precipitate, wt. 0.27 g., recrystallized from ethanol, m.p. 160–162°, $[\alpha]^{26}D$ + 95.5° (*c*, 3.2, $CHCl_3$). The analysis indicated that the substance was contaminated by a small amount of olefin.

Anal. Calcd. for $C_{15}H_{23}O_2Cl$: C, 66.90; H, 8.53; O, 11.81; Cl, 13.09. Found: C, 67.42; H, 8.87; O, 11.44; Cl, 12.60.

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TALLAHASSEE, FLA.

[CONTRIBUTION FROM THE SECTION OF EXPERIMENTAL MEDICINE, THE UNIVERSITY OF TEXAS M. D. ANDERSON HOSPITAL & TUMOR INSTITUTE]

Estrogens. IV. The Synthesis of 2- and 4-Alkylestrones[1-3]

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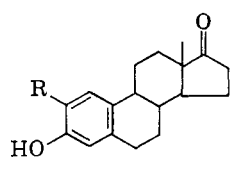
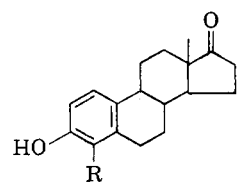
The synthesis of 2- and 4-alkylestrones *via* the Claisen rearrangement of estrone 3-allyl ether and estrone 3-crotyl ether is reported. The structural assignments are based on the infrared and ultraviolet spectra of the products and their mononitro derivatives.

During an investigation concerned with the effect of structural changes on the estrogenic activity of estrone, it was desirable to synthesize several 2- and 4-alkylestrones in which the alkyl groups were larger than methyl. The Claisen rearrangement of estrone allyl ether (I) offered a convenient method to synthesize these compounds. Although Miescher and Scholz reported this reaction, the only crystalline product described was a benzoate which was identified as the benzoate of 2- or 4-allylestrone.[4] The separation and identification of the two isomers formed during this rearrangement were reported recently in a brief communication.[5] It is the purpose of this paper to record this work in greater detail, to submit additional data in support of the structural assignments which were originally made on the basis of infrared spectra, to report the synthesis of other steroids from these products, and to describe the product which was formed during the Claisen rearrangement of the crotyl ether of estrone.

When a solution of I in diethylaniline was heated at reflux temperature in an atmosphere of nitrogen, two isomeric phenolic products were formed. They were separated by chromatography on a column of alumina. The higher melting isomer, 2-allylestrone (II), was eluted with benzene; then the second product, 4-allylestrone (III), was eluted with a solution of 9 parts benzene and 1 part ether. About 35% of unrearranged I was recovered; the yields of the products based on unrecovered ether were 28% II and 58% III. Each of the isomeric allylestrones formed a monoacetate.





II. R = CH_2=CH—CH_2— III. R = CH_2=CH—CH_2—
IV. R = CH_3—CH_2—CH_2— V. R = CH_3—CH_2—CH_2—

The hydrogenation of II over 5% palladium-on-charcoal gave 2-*n*-propylestrone (IV) in 80–85% yields. Similarly, III was hydrogenated to 4-*n*-propylestrone (V) in 75–80% yields. While

(1) Part III of this series appeared in *J. Org. Chem.*, **26**, 1677 (1961).

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(3) Presented before the Division of Medicinal Chemistry, American Chemical Society, 139th National Meeting, St. Louis, Mo., March 1961.

(4) K. Miescher and C. Scholz, *Helv. Chim. Acta*, **20**, 1237 (1937).

(5) T. L. Patton, *Chem. & Ind.* (London), 1567 (1960).