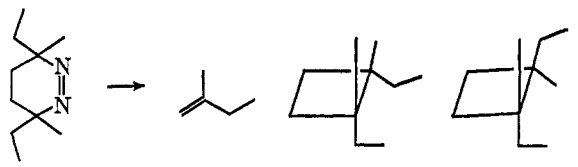
Product distributions obtained from thermolysis and direct and thioxanthone-sensitized photolyses are presented in Table I. All decompositions reported

**Table I.** Product Distributions for Decompositions of I[a-c]

| Isomer | Mode of decomposition | % III | % IV | % V | % retn of confgn in IV and V |
|---|---|---|---|---|---|
| *meso* | Thermal[d] | 49 | 43 | 2.5 | >98 |
| *d,l* | Thermal[d] | 51 | 3.5 | 42 | >98 |
| *meso* | Direct photolysis[e] | 61 | 35 | 3.5 | 95 |
| *d,l* | Direct photolysis[e] | 60 | 4 | 33 | 97 |
| *meso* | Thioxanthone sensitized[f] | 77 | 11.5 | 8 | 61 |
| *d,l* | Thioxanthone sensitized[f] | 75 | 8 | 12 | 65 |

[a] Analyses by vpc on a 150-ft didecyl phthalate capillary column with toluene internal standard and by nmr with anisole internal standard agreed within 2–3%. [b] I was 0.05–0.1 *M* in benzene. Results were the same in cyclohexane. [c] Decompositions were carried out in thoroughly degassed, sealed tubes. [d] Samples were heated at 145–148° for 5 half-lives. [e] Incident light was of wavelength longer than 330 mμ. [f] Thiozanthone was 0.05 *M* and absorbed over 97% of the incident light. It is known to be an effective triplet sensitizer: W. G. Herkstroeter and G. S. Hammond, *J. Am. Chem. Soc.*, **88**, 4769 (1966); W. G. Herkstroeter, A. A. Lamola, and O. S. Hammond, *ibid.*, **86**, 4537 (1964).

here were carried out either on 96% *meso*-I[12] containing 4% *d,l* contaminant or on 92% *d,l*-I containing 8% *meso*-I. Products were shown to be stable to the conditions of each mode of decomposition. Another product, which is as yet unidentified, was formed in less than 2% yield.



I III IV V

III was identified by comparison of spectra and vpc retention time with those of an authentic sample. V was identified by comparison with a sample prepared independently by hydrogenation of *trans*-1,2-divinyl-1,2-dimethylcyclobutane.[13] The structure of IV was assigned by elemental analysis and the similarity of its nmr and mass spectra to those of the *trans* isomer V. Every peak observed in the mass spectrum of IV was also observed in that of V, with small differences in the peak heights. The nmr spectrum of IV consisted of a six-proton triplet from δ 0.6 to 0.9, a six-proton singlet at δ 0.98, and an eight-proton multiplet from δ 1.2 to 1.7. That of V was essentially the same with the exception that the six-proton singlet was shifted down to δ 1.02. Decomposition of optically active I led to optically active V ([α] −29°), thus confirming its assignment as the *trans* isomer.

The use of benzophenone as a sensitizer led to negligible amounts of III, IV, and V but instead led to other unidentified products. Further work with this sensitizer and others is in progress.

For reasons only recently explained,[2] attempts to detect differences in the radical pairs from the singlet and triplet excited states of open-chained azo compounds have not been successful. Such differences, arising out of the greater lifetime of a radical pair having parallel rather than antiparallel electron spins, should show themselves in smaller cage effects and greater loss of configuration at the carbon atoms passing through the free-radical state from a triplet as compared to a singlet precursor. The differences recorded in Table I correspond to the expected longer lifetime of the "triplet" biradical from the cyclic azo compound I. In line with the explanation previously offered,[2] the cyclic azo triplet is unable to assume the skew conformation usual with acyclic azo compounds, and thus cannot undergo *trans–cis* isomerization, dissipate energy in internal degrees of freedom, or survive in a conformation unsuited to concerted radical-pair formation. The parallel spins in the biradical delay ring closure, allow rotation about all three single bonds separating the radical centers, and increase the cleavage to III relative to ring closure, since the eventual spin inversion which must precede reaction is now statistically likely to occur while the biradical is in a noncisoid conformation more favorable to cleavage than to ring closure.

The behavior of I presents a contrast to that of five-membered cyclic azo compounds,[7] where singlet mechanisms lead to preferred configurative inversion. The explanation offered in those cases[7] is consistent with the differences in geometry between 1,3 and 1,4 biradicals.

**Acknowledgments.** We thank Dr. P. S. Engel for helpful discussions and the National Science Foundation and the National Institutes of Health for predoctoral fellowships to N. A. P. and for grants in support of this work.

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*Received July 15, 1968*

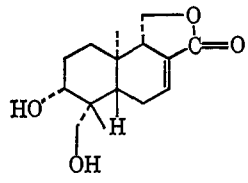
(12) The *meso* and *d,l* isomers could be easily distinguished by nmr.
(13) G. S. Hammond, W. Liu, and N. J. Turro, *J. Org. Chem.*, **28**, 3297 (1963).

## The Total Synthesis of Isoiresin, Dihydroiresin, and Isodihydroiresin

*Sir:*

The sesquiterpene iresin (**1**)[1,2] (*Iresine celosioides*) is the first sesquiterpene in which the presence of the bicyclofarnesol skeleton typical of di- and triterpenes was demostrated. Thus, in a certain sense, iresin represents the missing link between the lower and the higher terpenes. The excellent work of Djerassi[3,4] and his collaborators led to structure **1** for iresin and to **2** and **3a** for isoiresin and dihydroiresin, respectively, also constituents of *I. celosioides*. The substantial number of asymmetric centers present in these compounds (five, four, and six, respectively), together with

(1) C. Djerasi, P. Sengupta, J. Herran, and F. Walls, *J. Am. Chem. Soc.*, 76, 2966 (1954).
(2) C. Djerassi, W. Rittel, A. L. Nussbaum, F. W. Donovan, and J. Herran, *ibid.*, 76, 6410 (1954).
(3) C. Djerassi and W. Rittel, *ibid.*, 79, 3528 (1957).
(4) C. Djerassi, F. W. Donovan, S. Burstein, and R. Manli, *ibid.*, 80, 1972 (1958).



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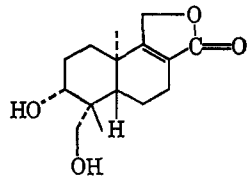

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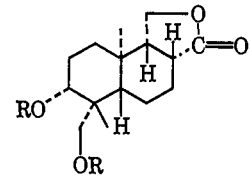
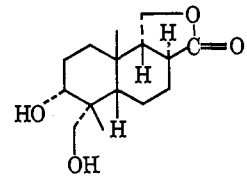


3a, R = H
b, R = Ac



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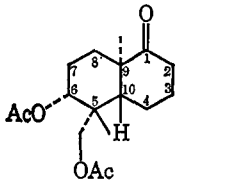

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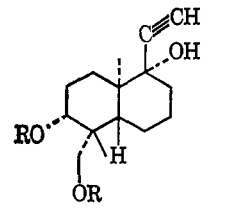
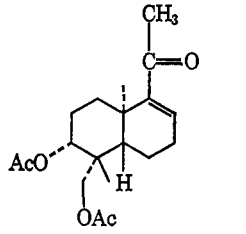


6, R = Ac
7, R = H



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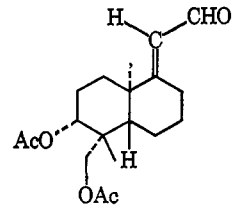

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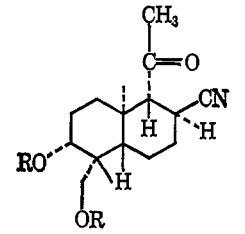
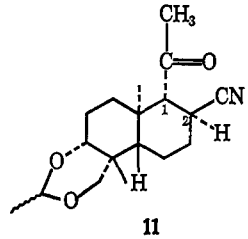


10a, R = H
b, R = Ac



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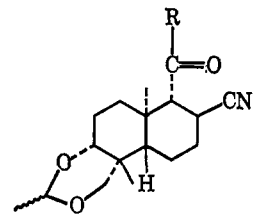
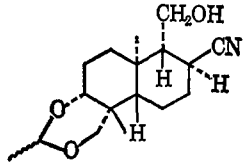


12a, R = OH
b, R = $OCH_3$
c, R = $O^-Na^+$
d, R = Cl



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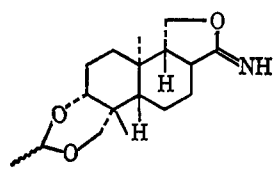

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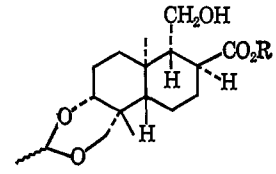


15a, R = H
b, R = $CH_3$

the particular arrangement of functional groups, probably accounts for the fact that a synthesis has not heretofore been reported. This paper reports the total synthesis of isoiresin (**2**), dihydroiresin (**3a**), and isodihydroiresin (**4**).

A convenient starting material for this synthesis is the bicyclic diacetoxy ketone **5**, for which we have reported a stereoselective synthesis.[5] Treatment of **5** with sodium amide and acetylene in dry tetrahydrofuran gave a mixture of the diacetoxyethynylcarbinol **6**[6] (81%; mp 166–167; $\nu_{max}$ 3450, 3250, 2100, 1730, and 1720 $cm^{-1}$) and the triol **7** (5.4%; mp 203–204°; $\nu_{max}$ 3350, 3300, 3150, 3225, 2100 $cm^{-1}$) which was separated by chromatography over alumina. Brief treatment of **7** with acetic anhydride–pyridine gave **6** in 75% yield. Rearrangement[7] of **6** with refluxing formic acid[8] afforded the diacetoxy enone **8** (48%; mp 102–109°; $\nu_{max}$ 1740, 1730, 1650, 1625, 1240–1230 $cm^{-1}$; $\lambda_{max}$ (EtOH) 235 mμ (ε 9158)) and the α,β-unsaturated aldehyde **9** (12%).

(5) S. W. Pelletier, R. W. Chappell, and S. Prabhakar, *Tetrahedron Letters*, 3489 (1966); *J. Am. Chem. Soc.*, **90**, 2889 (1968).

(6) Although formulas of only one enantiomer are shown, unless otherwise indicated, they represent racemates. All new compounds gave satisfactory analytical data.

(7) W. S. Johnson, S. J. Gray, J. K. Crandall, and D. M. Bailey, *J. Am. Chem. Soc.*, **86**, 1966 (1964).

(8) J. D. Chanley, *ibid.*, 70, 244 (1948).

Treatment of **8** with a large excess of sodium cyanide in refluxing ethanol[9] yielded the cyanodiol **10a**, characterized as the diacetate **10b** (50%; mp 170–171°; $\nu_{max}$ 2225, 1725, 1708, 1250–1235 $cm^{-1}$). Condensation[10] of the diol **10a** with acetaldehyde in the presence of fused zinc chloride gave the acetylidene derivative **11**[11] (mp 233°; $\nu_{max}$ 2225, 1710 $cm^{-1}$).

Treatment of ketone **11** with sodium hypobromite[13] afforded cyano acid **12a**[14] (mp 266–268°; $\nu_{max}$ 3400–3000, 2225, 1700 $cm^{-1}$) in yields of 40–60%. Methylation of crude **12a** with diazomethane gave a single ester **12b** (72%; mp 221–222°; $\nu_{max}$ ($CHCl_3$)

(9) J. Romo, *Tetrahedron*, **3**, 37 (1958); R. H. Mazur and J. A. Cella, *ibid.*, 7, 130 (1959).

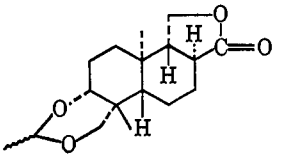
(10) M. P. Cava, W. R. Chaw, R. P. Stein, and C. R. Willis, *ibid.*, **21**, 2617 (1965).

(11) The nmr spectrum of **11** confirmed the *trans*-diaxial arrangement of the C-1 and C-2 hydrogens. Thus the C-1 proton of **11** appeared as a doublet at τ 7.43 strongly coupled[12] (*trans* diaxial, $J$ = 12 cps) with the adjacent proton. The C-2 proton was split by the adjacent protons into lines at τ 7.06 with $J_{2a,3a}$ = 12, $J_{2a,3e}$ = 4.5, $J_{1a,2a}$ = 12 cps, respectively. Decoupling of the C-2 proton upon irradiation 37 cps downfield to the center of the doublet caused the latter to collapse to a singlet.

(12) A. D. Cross and P. Crabbé, *J. Am. Chem. Soc.*, **86**, 1221 (1964).

(13) C. Djerassi and J. Staunton, *ibid.*, **83**, 736 (1961).

(14) That no stereochemical change had occurred during the conversion of **11** to **12a** was indicated by the nmr spectrum of **12a** in which the C-2 proton was again split into six lines at τ 7.04, $J_{1a,2a}$ = 12, $J_{2a,3a}$ = 12, and $J_{2a,3e}$ = 4 cps, respectively.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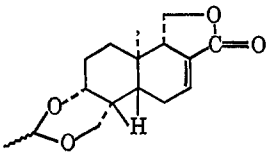
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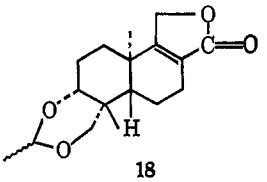
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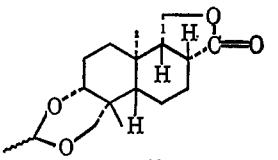
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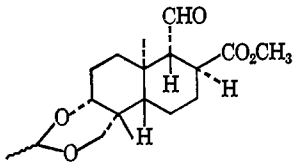
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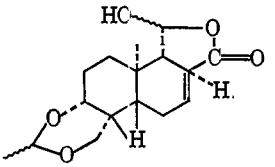
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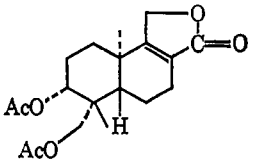
22

2225, 1730 $cm^{-1}$). The crude acid chloride **12d** obtained by the action of oxalyl chloride[15] on the sodium salt **12c** was reduced[16] with lithium tri-*t*-butoxyaluminum hydride in dry tetrahydrofuran to give a mixture of the cyano alcohol **13** ($\nu_{max}$ 3490, 2225 $cm^{-1}$) and an imino lactone[17] (presumably **14**, $\nu_{max}$ 3350, 3200, 1680, 1625 $cm^{-1}$). Alkaline hydrolysis of the crude mixture gave the hydroxy acid **15a** (51%; $\nu_{max}$ 3220, 2650, 1700 $cm^{-1}$). Methylation of **15a** with diazomethane afforded the methyl ester **15b** (mp 165–169°; $\nu_{max}$ 3450, 1725 $cm^{-1}$). Lactonization of **15a** either thermally or with DCC–pyridine[18] afforded (+)-acetylideneisodihydroiresin (**16**); mp 240–242°; $\nu_{max}$ ($CHCl_3$) 1770 $cm^{-1}$. The infrared spectra ($CHCl_3$) of **15b** and **16** were identical with those of the corresponding optically active compounds prepared from iresin as described below.

(±)-Acetylideneiresin[3] (**17**) (mp 282–284°; $\nu_{max}$ 1750, 1690 $cm^{-1}$; $[\alpha]D$ ($CHCl_3$) +64.1°) was hydrogenated in ethyl acetate in the presence of 5% Pd–C to give a mixture of acetylideneisoiresin (**18**) (mp 230–233°; $\nu_{max}$ 1740, 1670 $cm^{-1}$; $\lambda_{max}$ (EtOH) 219 mμ (ε 25,610); $[\alpha]D$ ($CHCl_3$) −24.2°) and acetylidenedihydroiresin (**19**) (mp 199–200°; $\nu_{max}$ 1770 $cm^{-1}$; $[\alpha]D$ ($CHCl_3$) +26.5°; τ 9.15 (3 H, singlet, $\geqslant CCH_3$), 8.80 (3 H, doublet, $-CHCH_3$, $J$ = 5 cps), 8.70 (3 H, singlet, $-OCH_2CCH_3$), 5.12 (1 H, quartet, $-CHCH_3$, $J$ = 5 cps)) which was separated by careful column chromatography. On exposure to the action of 5% methanolic potassium hydroxide for 42 hr, **19** was converted to the optically active hydroxy acid **15a** ($\nu_{max}$ 3225, 2625, 1700 $cm^{-1}$). Methylation of **15a** with diazomethane gave the (+)-methyl ester **15b**, mp 160–164°; $\nu_{max}$ 1725 $cm^{-1}$; $[\alpha]D$ ($CHCl_3$) +31.25°; τ 9.05 (3 H, singlet, $\geqslant CCH_3$), 8.72 (3 H, doublet, $-CHCH_3$, $J$ = 5 cps), 8.65 (3 H, singlet, $-OCH_2C(CH_3)<$), 8.14 (broad singlet, $CH_2OH$, disappearing upon deuteration), 6.32 (3 H, singlet, $CO_2CH_3$), 6.7–5.84 (multiplet), 5.04 (1 H, quartet, $J$ = 5 cps). Thermal or DCC-induced lactonization of **15a** gave (+)-acetylideneisodihydroiresin (**16**), mp 270–272°; $\nu_{max}$ 1760 $cm^{-1}$; $[\alpha]D$ ($CHCl_3$) +28.6°; τ 9.02 (3 H, singlet, $\geqslant CCH_3$), 8.87 (3 H, doublet, $J$ = 5 cps, $-CHCH_3$), 8.69 (3 H, singlet, $-OCH_2CCH_3<$), 5.77–6.67 (complex multiplet), 5.08 (1 H, quartet, $-CHCH_3$, $J$ = 5 cps).

Oxidation[19] of (+)-**15b** with DCC–DMSO gave an excellent yield of the aldehyde ester **20** (mp 155–158°, homogeneous on tlc; $\nu_{max}$ ($CCl_4$) 1740, 1725 $cm^{-1}$; τ 9.08 (3 H, singlet, $\geqslant CCH_3$), 8.80 (3 H, doublet, $CHCH_3$, $J$ = 5 cps), 8.68 (3 H, singlet, $-CH_2C(CH_3)<$), 7.54 (1 H, doublet, presumably $-CHCHO$, $J$ = 11 cps), 6.42 (3 H, singlet, $CO_2Me$), $\tau_A$ 6.05, $\tau_B$ 6.65 (AB quartet, $J$ = 11 cps, $-CCH_AH_BO-$), 5.08 (1 H, quartet, $CHCH_3$, $J$ = 5 cps), 0.18 ($J$ = 0.6 cps, $-CHCHO$)). Hydrolysis with aqueous methanolic $K_2CO_3$ under nitrogen gave the γ-hydroxy-γ-lactone **21** (mp 210–253; $\nu_{max}$ 3280, 1770 $cm^{-1}$; $\lambda_{max}$ (EtOH) 206 mμ (ε 204)) which without purification was pyrolyzed[20] at 235° with pyridine-impregnated alumina (2% v/w; neutral, Woelm, activity 1). Chromatographic purification of the product afforded an α,β-unsaturated lactone (mp 230–233°; $\nu_{max}$ 1740, 1670 $cm^{-1}$; $\lambda_{max}$ (EtOH) 219 mμ (ε 25,730)) whose richly detailed infrared spectrum (Nujol) and mobility on thin layer chromatoplates were identical with those of (−)-aceylideneisoiresin (**18**). Acid hydrolysis of **18** followed by acetylation of the product, chromatography, and crystallization from acetone–hexane yielded (−)-isoiresin diacetate[21] (**22**), mp 136–137°; $\nu_{max}$ 1750, 1675, 1240 $cm^{-1}$; $[\alpha]D$ ($CHCl_3$) −73.0°. Since natural isoiresin diacetate has been reduced to dihydroiresin diacetate (**3b**),[21] this work constitutes a formal synthesis of dihydroiresin diacetate also.

**Acknowledgment.** This work was supported in part by grants from the National Institutes of Health, U. S. Public Health Service, and the National Science Foundation. We thank Professor Carl Djerassi for a generous sample of natural iresin.

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(16) H. C. Brown and P. M. Weissman, *Israel J. Chem.*, **4**, 430 (1963); R. Breslow, J. Lockhart, and A. Small, *J. Am. Chem. Soc.*, **84**, 2793 (1962).
(17) The formation of the imino lactone, 3,3-ethylenedioxy-11β,17α-dihydroxy-18-nor-D-homoandrost-5-ene-13β-carboimidic acid 13β,11β-lactone, by sodium borohydride reduction of 13β-cyano-3,3-ethylenedioxy-17α-hydroxy-11-oxo-18-nor-D-homoandrost-5-ene has been reported: W. Nagata, M. Narisada, and T. Sugusawa, *J. Chem. Soc., C*, 648 (1967).
(18) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger, and W. N. Hubbard, *J. Am. Chem. Soc.*, **82**, 1255 (1960); R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierskad, *Tetrahedron*, 2, 1 (1958).
(19) K. E. Pfitzner and J. G. Moffat, *J. Am. Chem. Soc.*, **87**, 5670 (1965).
(20) E. J. Corey and A. G. Hartmann, *ibid.*, **87**, 5763 (1965); H. C. Barrett and G. Büchi, *ibid.*, **89**, 5665 (1967); E. Von Rudloff, *Can. J. Chem.*, **39**, 1860 (1961).
(21) P. Crabbé, S. Burnstein, and C. Djerassi, *Bull. Soc. Chim. Belges*, **67**, 632 (1958).

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