THE JOURNAL OF Organic Chemistry®

VOLUME 44, NUMBER 5

MARCH 2, 1979

Acid-Catalyzed Cyclization of Cembrene and Isocembrol[1,2]

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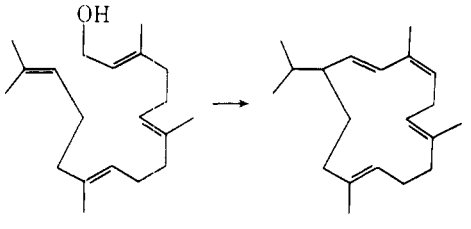
Received June 16, 1978

The acid-catalyzed ring closure of cembrene, a 14-membered ring diterpene, and its derivatives has been studied. The predominant reaction pathway yields a hydrophenanthrene ring system. Under mild conditions isomeric tricyclic compounds are formed, but under more forcing conditions aromatization of a ring occurs. The detailed mechanisms of these reaction processes have been evaluated.

In 1962, the structure of the macrocyclic diterpene cembrene (**2**) was established.[4] This new 14-membered ring compound, derived by the simple head-to-tail cyclization of geranylgeraniol (**1**), has since proved to be the prototype of a wide variety of natural products, many of which possess biological activity.[5,6] A few typical examples (**3**–**7**) of these cembrene derivatives will illustrate the nature of the various modifications the diterpene nucleus has undergone in nature.



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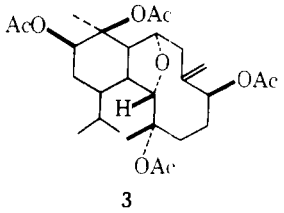
Two typical monocyclized cembrenes are eunicellin (**3**),[7] obtained from marine coral, and verticillol (**4**),[8] isolated from a conifer of the order cupressales. Bicyclized cembrenes are illustrated by taxicin II (**5**)[9] from the heartwood of the yew tree, by the cocarcinogen phorbol (**6**)[10] from the oil of *Croton tiglium*, and by **7**, "a constituent of the defense secretion of African termites."[11]



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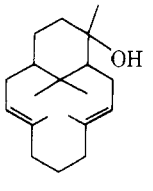

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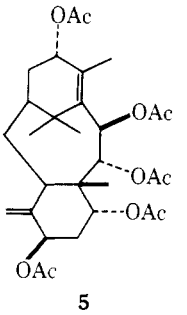

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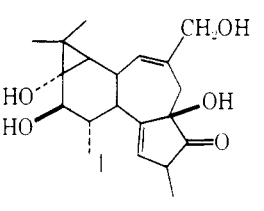

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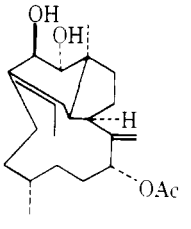

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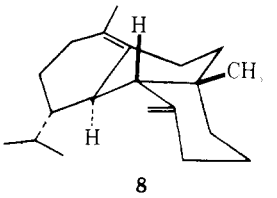
The occurrence of the cyclized cembrene nucleus in so many natural products prompted the study of the cyclization of cembrene and its derivatives. In the initial cyclization study, cembrene was subjected to the acidic conditions used in previous cyclization studies.[12] Under the conditions of 1 M perchloric acid in refluxing dioxane–water (80:20), there appeared after 1 h to be two major new components in the reaction mixture. The mixture was separated using a combination of column chromatography on silver nitrate impregnated silica gel, VPC collection, and fractional crystallization. One pure crystalline compound was obtained, and this material was shown by mass spectrometry to be isomeric with cembrene, by NMR spectroscopy to have one vinyl methyl group (δ 1.57), one quaternary (angular) methyl group (δ 0,87), two exocyclic vinyl protons (AB quartet at δ 4.46), and probably an isopropyl group [δ 0.85 (6 H, d, J = 6.5 Hz)], and by Raman spectroscopy to have two double bonds (1675 and 1645 cm^{-1}), one disubstituted and one tetrasubstituted. Thus, cembrene with one ring and four double bonds had been transformed into a compound with three rings and two double bonds. The complete structure was determined by crystal structure analysis and shown to be **8**.



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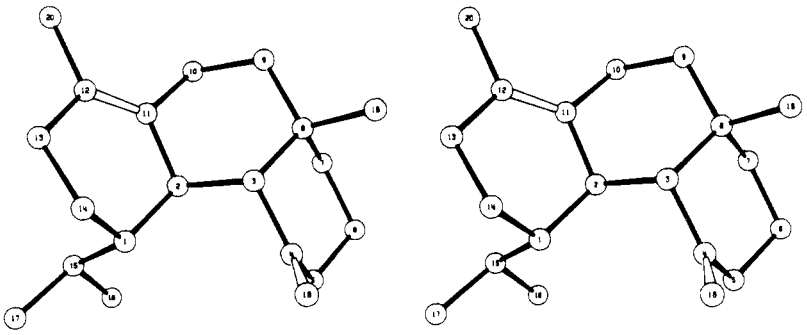


Figure 1. Stereoscopic drawing of compound 8.

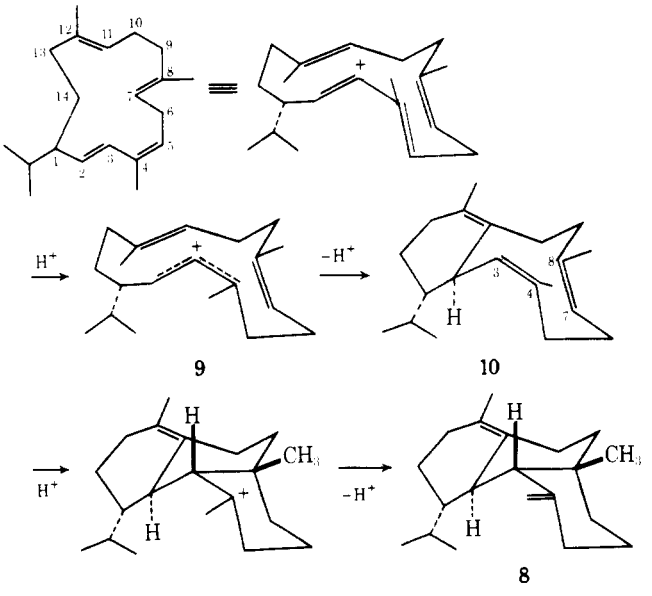
Table I. Distances and Estimated Standard Deviations (Å) from a Least-Squares Plane Fitted to C-2, C-12, C-13, and C-20 of the Cembrene Cyclization Product

atom	distance	atom	distance
C-2	0.0008 (7)	C-11	−0.0332 (31)
C-12	−0.0028 (24)	C-10	−0.2128 (61)
C-13	0.0006 (5)	C-14	−0.3291 (50)
C-20	0.0014 (12)	C-1	0.4273 (38)

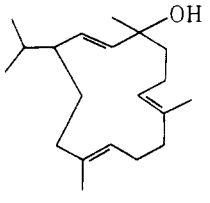
Crystals of the cyclization product are monoclinic with the symmetry of space group $P2_1$; the unit cell containing two molecules has parameters a = 9.1110 (4) Å, b = 11.3870 (10) Å, c = 8.9159 (6) Å, and cos β = −0.32575 (7) at 24 °C. The structure was solved from 2014 independent reflections measured on the Oak Ridge computer-controlled X-ray diffractometer by a Patterson search procedure.[13] The six carbon atoms of the tetrasubstituted double bond were selected as a known fragment in the Patterson search; however, the procedure actually yielded another fragment, a tetrasubstituted ethane near the center of the molecule. Extension by means of the tangent formula of the phases calculated for the selected reflections[14] developed the entire structure. After refinement of the atom parameters by the method of least squares, the value of $R(F)$ is 0.04. The stereoscopic view in Figure 1 of the carbon skeleton of the cyclized material is consistent with the known absolute configuration of cembrene.[4] It is worthy of note to call attention to the fact that C-10 is not coplanar with the other substituents of the tetrasubstituted bond (see Table I).

As in many other acid-catalyzed cyclizations of polyolefinic natural products, the overall ring closure process appears to be a stepwise process, involving two protonations.[2] A credible reaction pathway for the formation of tricyclic 8 from monocyclic cembrene (2) can be envisaged by examination of the conformation of cembrene in the crystal.[15] In this conformation the required carbon atoms for the ring closure of C-2 and C-11 are in the proper vicinity for bonding. It would be expected that the first protonation of cembrene would occur at the end of the diene system to yield the more stable allylic carbonium ion **9**.[16] In this allylic ion, the carbon atom at C-2 can readily cyclize with the 11,12 double bond and the resulting carbonium ion, in turn, can deprotonate to yield the bicyclic intermediate triene **10**. In this postulated intermediate triene **10** both the initial conformation of the tetraene as well as Dreiding models of the triene indicate that the newly formed 3,4 double bond should be cis to minimize steric repulsions in the molecule.

The second stage of the reaction must occur by protonation of the trans double bond at C-7, C-8 to yield the tricyclic product 8. It is of interest to note that to obtain the specific stereochemistry, the C-3, C-4 double bond must have been cis, the stereochemistry predicted above. Also, this cis stereochemistry minimizes the repulsions in the transition state for the final ring closure which leads to the methylene group and to the interesting axial orientation of the isopropyl group.



Some evidence for this proposed mechanism was gained by a study of the acid-catalyzed rearrangement of isocembrol



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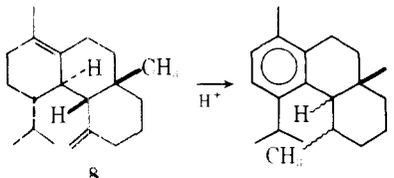
(11). Under the same conditions employed for the cyclization of cembrene, 1 M perchloric acid in refluxing dioxane–water (80:20), isocembrol rearranged to the same product mixture as that found starting with cembrene. Kinetic studies showed, however, that the tricyclic product 8 was formed directly from the alcohol and that cembrene was not an intermediate; i.e., the rate of conversion of isocembrol to 8 was faster than the rate of conversion of cembrene to 8.

When isocembrol was allowed to react under more forcing acid conditions, 0.02 M perchloric acid in refluxing acetic acid for 5 days, two compounds, **12** and **13**, which represented 75% of the hydrocarbon mixture (VPC analysis, 500 ft × 0.03 in. PPE), were formed in a ratio of 1:2. Analysis of the crude reaction mixture by NMR spectroscopy showed the very interesting feature of a singlet absorption at δ 6.84. These two major reaction products were purified by preparative VPC (20 ft × 0.25 in. SF-96). The spectral details of the structural

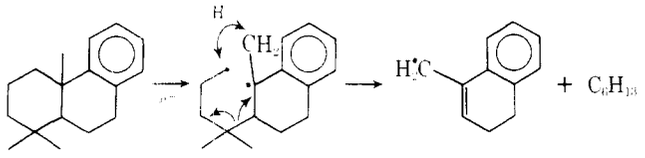
analysis of these two materials are given in the Experimental Section, and the results can be summarized as follows: compound **12** possessed an angular methyl group, a methyl group on an unsaturated carbon atom, an isopropyl group, and two aromatic protons; the UV spectrum [UV max 268 nm (ϵ 530)] indicated a benzene ring. The same groupings were indicated for compound **13**, both materials showed a parent peak in the mass spectrum at mass 270, and, except for slight intensity variations, the spectra were identical.

In view of the similarity of spectral properties the same hydrophenanthrene would be indicated, and since the two materials were derived from **8** it is suggestive that the two materials are the ring A aromatized variation of **8**. Evidence



8 **12** and **13**

for this postulated ring system was obtained by analysis of the mass spectra of the two compounds. Both **12** and **13** lose a C-5 unit from the parent ion (M = 270). Such a fragmentation is characteristic of tricyclic benzenoid diterpenes; i.e., the tricyclic compound **14** undergoes fragmentation with loss of



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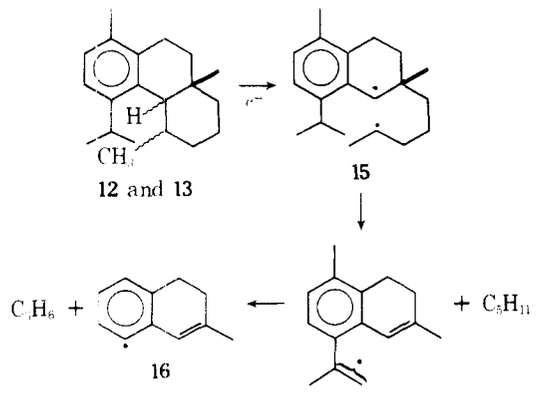
C_6H_3 as shown.[17] By application of this same mechanism, the hydrocarbons **12** and **13** would give the stabilized benzyl radical **15**. Hydrogen abstraction and fragmentation would lead to the loss of C_5H_{11}. Also as was found, a further loss of mass 42 could be explained by a further fragmentation to give the radical **16**. These suggested fragmentations are illustrated in Scheme I.

In view of the assumption that **12** and **13** arose from double bond rearrangements and dehydrogenation of **8**, the detailed course of the reaction processes was monitored. The process was most conveniently studied using isocembrol (**11**) as the starting material since the mild conditions of perchloric acid in refluxing dioxane–water could be employed. The course of the reaction was followed by VPC analysis (500 ft × 0.03 in. OV-17), and the course of the production of hydrocarbons is summarized in Table II. It is seen that after 48 h four major products were formed in a ratio of compound **18** (31%), compound **19** (11%), compound **20** (22%), and compound **21** (21%).

Scheme I



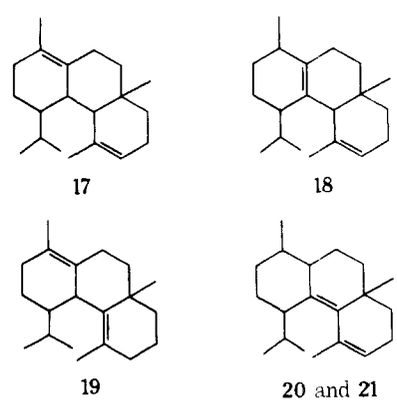
12 and **13** **15** **16**

Table II. Percent of Compound in Hydrocarbon Fraction from Isocembrol Reaction with Perchloric Acid in Dioxane–Water

	8	17	10	18	19	20	21
2.5 min	50	5	37				
5 min	49	8	34				
10 min	46	20	23				
20 min	46	22	22				
1 h	45	24		trace	trace	trace	
2 h	35	32		7	1	6	2
3 h	27	33		13	2	10	5
6 h	25	44		22	4	11	9
10 h	13	22		25	8	12	10
13 h	10	16		27	10	13	11
35 h	0	0		43	12	16	13
48 h	0	0		31	11	22	21

The kinetic study also showed early formation of hydrocarbon **10**, a material which reached its maximum yield in 2.5 min; no structural studies were conducted on this compound since isolation of the pure material could not be achieved due to the small amount of material found (at this stage of reaction, 90% of starting isocembrol remained). The data give the relative rate of appearance of the transformation products; however, the exact immediate precursor of each product cannot be stated with certainty. It should be noted that after 6 h, only 20% of the starting material had disappeared.

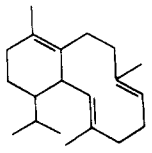
The reaction products were collected by VPC (980 ft × 0.03 in. OV-17), although the separation was difficult. Compounds **19–21** were collected in sufficiently pure form to permit the assignment of structure (data given in Experimental Section). Compound **17** was shown to be the other major product formed with **8** in the earlier study. Hydrocarbon **18** was obtained pure only in sufficient amount to allow for the determination of its mass spectrum; the structural assignment is based upon such data and upon the kinetic data. The structure assigned to hydrocarbon **19** agrees with the kinetic and NMR data, but the Raman bands for the tetrasubstituted double bonds require further evaluation. Also, the large intensity of mass peaks at *m/e* 220 and 205 still awaits explanation; the assigned structure is tentative.



17 **18** **19** **20** and **21**

The tricyclic compounds formed from isocembrol after 48 h under mild acid conditions show that double bond migration is extremely facile. When such a reaction mixture was subjected to reaction under more forcing acid conditions, again the only products formed were **12** and **13**.

Finally, attention must be given to hydrocarbon **10**, which is rapidly formed and also rapidly consumed. As pointed out earlier it was not possible to obtain spectral data to aid in the determination of its structure, but in view of the entire reaction sequence the bicyclic **10** would appear to be a reasonable assignment. In line with this structural assignment is the recent acid-catalyzed cyclization of ovatodiolide **22** to yield the



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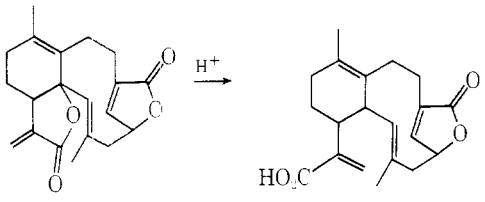
bicyclic **23**;[6] presumably the lactone ring adds sufficient stability to the cyclized product **23** to permit its isolation.



22 23

Thus, the rearrangement of cembrene (and isocembrol) under both mild and strong acid conditions leads to the formation of hydrophenanthrene ring compounds as final products. To date, no natural products possessing this substituted ring system have been found.

Experimental Section

Preparation of Tricyclic Hydrocarbon 8. A solution of 4.0 g of cembrene in 320 mL of dioxane and 80 mL of a solution of 72.9 g of 70% $HClO_4$ diluted to 100 mL in volume with water (the total reaction mixture was 1 N in $HClO_4$) was refluxed for 1 h under nitrogen. The cooled reaction mixture was poured into 2 N Na_2CO_3 solution, the organic material was extracted with hexane, and the extract was washed with water. The dried extract was rotary evaporated to yield 3.92 g of a yellow oil. This oil was dissolved in hexane, the solution was filtered through 30 g of alumina (Woelm, neutral, Act I), and the solvent was evaporated to yield 3.6 g of hydrocarbons.

The hydrocarbons were chromatographed on 120 g of silver nitrate–silica gel[18] using 125-mL portions of hexane as the eluant for the first 30 fractions and then using ether as the elutant. Fractions 15–19 crystallized upon evaporation of the solvent. These fractions were combined (415 mg, 10% yield based on starting cembrene), and the material, upon analysis by VPC on a 500 ft × 0.03 in. open tubular column coated with OV-101, was shown to be 75% of **8** and 25% of **17**.

The mixture was rechromatographed in the same manner to yield 232 mg of crystalline material of a purity of 90% (VPC analysis). This product was recrystallized from 95% ethanol. There was obtained 20 mg of a first crop, mp 64.5–66.0 °C, and a second crop of 86 mg, mp 60–61 °C. The concentrated mother liquor also crystallized. VPC analysis of the first two crops indicated a purity of 96%, and these combined fractions were recrystallized to give 64 mg of product, mp 65–66 °C, which still was only 96% pure. These crystals were used for the X-ray study.

A 21-mg portion of this crystalline material was kindly purified by preparative capillary column VPC by Dr. Roy Teranishi, and this material was 99.9% pure. All of the spectral data given in the text were obtained with this pure substance. The mass spectral data are listed in Table III.

Acid-Catalyzed Rearrangement of Isocembrol (11). (a) Isolation of 17. A solution of 2 g of isocembrol in 200 mL of the above aqueous dioxane–perchloric acid solution was refluxed for 2 h, and the reaction mixture was processed in the usual way to yield 1.5 g of crude material. This mixture was first separated by preparative VPC (10 ft × 0.25 in. OV-17), and the crude fraction of **17** was further purified by preparative capillary VPC (980 ft × 0.03 in. OV-17): Raman 1650, 1675 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 5.30 (m, 1), 1.68 (s, 3), 1.59 (s, 3), 0.87 (d, 3, J = 6.5 Hz), 0.82 (s, 3), 0.80 (d, 3, J = 6.5 Hz); high-resolution mass spectrum, m/e 272.2498 (calcd for $C_{20}H_{32}$, 272.2503); low-resolution mass spectrum, see Table III.

(b) Extended Time Study of Rearrangement. A solution of 5 g of isocembrol in 500 mL of the above aqueous dioxane–perchloric acid solution, under a nitrogen atmosphere, was refluxed for 48 h; samples were taken at various times and analyzed by VPC (500 ft × 0.03 in. OV-17). The reaction mixture was processed in the usual way to yield 2 g of a hydrocarbon mixture. This material was first separated by preparative VPC (10 ft × 0.25 in. OV-17), and the crude products were further purified by preparative capillary VPC (980 ft × 0.03 in. OV-17).

Table III. Low-Resolution Mass Spectra Relative Intensities

mass	relative intensities					
	8	17	18	19	20	21
272	100	94	100	99	100	100
257	15	20	32	70	25	46
229	11	59	90	73	61	65
173	3	7	23		22	28
159	2	10	30		28	33
147	12	25	40		32	36
145	4	9	26	32	27	38
133	8	12	14		22	24
131	3	8	15		18	26
121	21	42	11		9	15
119	14	22	19		26	31
109	78	57	21	34	18	21
107	37	100	13	29	12	16
105	37	34	36	50	42	44
95	15	35	14		18	22
93	19	35	13		15	18
91	17	37	21		26	31

Compound **19** had the following properties: Raman 1650 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 1.55 (s, 3), 1.51 (s, 3), 0.94 (s, 3), 0.94 (d, 3, J = 7 Hz), 0.88 (d, 3, J = 7 Hz); high-resolution mass spectrum (70 eV), m/e 272.2498 (calcd for $C_{20}H_{32}$, 272.2503); low-resolution mass spectrum, see Table III; other mass spectral bands not listed in the table are m/e 220 (20) and 205 (62).

Compound **20** had the following properties: UV max (cyclohexane) 247 nm (ϵ 22 000); NMR (100 MHz, $CDCl_3$) δ 5.20 (m, 1), 1.54 (s, 3), 2.95 (septet, 1, J = 7 Hz), 0.96 (d, 6, J = 7 Hz), 0.80 (s, 3), 0.74 (d, 3, J = 7 Hz); high-resolution mass spectrum (70 eV), m/e 272.2492 (calcd for $C_{20}H_{32}$, 272.2503); low-resolution mass spectrum, see Table III.

Compound **21** had the following properties: UV max 247 nm (ϵ 13 000); NMR (100 MHz, $CDCl_3$) δ 5.17 (m, 1), 1.51 (s, 3), 0.96 (d, 6, J = 7 Hz), 0.77 (s, 3), 0.73 (d, 3, J = 7 Hz); high-resolution mass spectrum (70 eV), m/e 272.2500 (calcd for $C_{20}H_{32}$, 272.2503); low-resolution mass spectrum, see Table III.

Compound **18** was only analyzed by low-resolution mass spectrometry (see Table III).

Preparation of Compounds 12 and 13. A solution of 10 g of isocembrol in 860 mL of glacial acetic acid containing 1.5 mL of 70% perchloric acid was refluxed for 5 days, poured into 1000 mL of water, and extracted with ether. The ethereal solution was processed in the usual manner to yield 2.5 g of monomeric hydrocarbon material. The material was purified by preparative VPC (20 ft × 0.25 in. SF-96) to give **12** and **13**.

Compound **12** had the following properties: IR 3077 cm^{-1}; UV max 268 nm (ϵ 530); NMR (100 MHz, $CDCl_3$) δ 6.84 (s, 2), 1.97 (s, 3), 1.20 (d, 3, J = 7 Hz), 1.16 (d, 3, J = 7 Hz), 0.76 (d, 3, J = 7 Hz), 0.68 (s, 3); high-resolution mass spectrum (70 eV), m/e 270.2345 (calcd for $C_{20}H_{30}$, 270.2345); low-resolution mass spectrum (70 eV), m/e (rel intensity) 270 (93), 255 (31), 227 (13), 212 (19), 201 (46), 200 (52), 199 (98), 173 (35), 159 (52), 157 (100), 145 (43).

Compound **13** had the following properties: IR 3077 cm^{-1}; UV max 268 nm (ϵ 250); NMR (100 MHz, $CDCl_3$) δ 6.84 (s, 2), 3.17 (septet, 1, J = 7 Hz), 2.15 (s, 3), 1.27 (d, 3, J = 7 Hz), 1.02 (d, 3, J = 7 Hz), 0.75 (s, 3), 0.65 (d, 3, J = 7 Hz); high-resolution mass spectrum (70 eV), m/e 270.2340 (calcd for $C_{20}H_{30}$, 270.2347); low-resolution mass spectrum (70 eV), m/e (rel intensity) 270 (100), 255 (16), 227 (19), 199 (93), 159 (33), 157 (87), 145 (25).

Acknowledgment. The authors are greatly indebted to Dr. Roy Teranishi of the U.S. Department of Agriculture, Albany, Calif., for his contributions to this entire study. The Raman spectra were kindly determined by Saima Kint of the same laboratory.

Registry No.—**8**, 68782-07-0; **11**, 25269-17-4; **12**, 68782-12-7; **13**, 68782-13-8; **17**, 68782-08-1; **18**, 68782-09-2; **19**, 68782-10-5; **20**, 68782-11-6; cembrane, 1898-13-1.

Supplementary Material Available: Tables containing final parameters of the carbon atoms and hydrogen atoms, bond distances, and valence angles (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) This work was supported in part by National Science Foundation Grant MPS 73-04662 and by the Hoffmann-La Roche Foundation and in part by the Division of Material Sciences, U.S. Department of Energy, under contract W-7405-eng-26 with the Union Carbide Corp.
(2) A preliminary publication covering a portion of this study has appeared previously: W. G. Dauben, *J. Agric. Food Chem.*, **22**, 156 (1974).
(3) On leave from Givaudan Research Corp. Ltd., Dübendorf, Switzerland.
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A Regiospecific Synthesis of Substituted Vulpinic Acids

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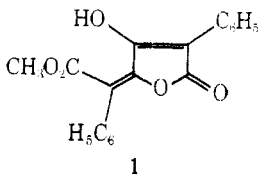
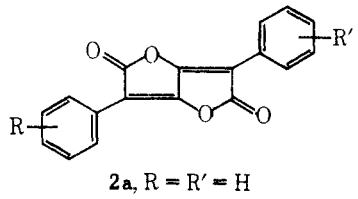
Received July 27, 1978

A regiospecific synthesis of vulpinic acid analogues substituted differently in each of the phenyl rings was developed. Treatment of the appropriate dimethyl phenyloxalacetate with the appropriate phenylacetyl chloride in the presence of triethylamine gave an enol ester. Excess triethylamine catalyzed cyclization to the desired substituted vulpinic acid. This approach also was successful in certain instances when one of the phenyls was replaced by another substituent.

Interest in the anti-inflammatory properties of vulpinic acid **1**, a lichen metabolite,[1] prompted the synthesis for pharmacological evaluation of a series of compounds in which various substituents were placed in one or both of the aromatic rings of vulpinic acid.[2] The classical procedure[2,3] for the synthesis of vulpinic acid requires ring opening of the dilactone **2a**, and a more recent method[4] using azidoquinones proceeds from 2,5-diphenyl-1,4-benzoquinone, which is also symmetrical. Ring opening of **2** when R and R′ are not identical gives a mixture of isomers, and in our hands attempts to control the isomer ratio by varying solvents or reaction temperature were not very successful. For most substituents the isomers are not readily separable by chromatography, although frequently they may be separated by fractional crys-



1

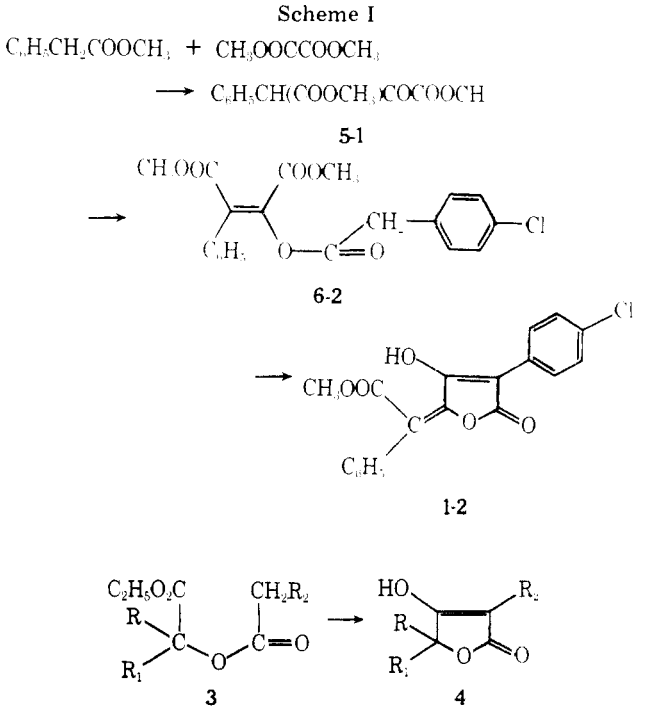


2a, R = R′ = H

tallization[2] at a considerable cost in material and time. Vulpinic acids **1-*X*** where neither R nor R′ are hydrogen are previously unreported, probably because of the difficulty of separation and identification of the isomers.

An approach to a regiospecific synthesis of aryl-substituted vulpinic acid isomers was suggested by the Haynes and Stanners[5] tetronic acid synthesis involving base cyclization of α-acyloxy ester **3** where R, R_1, and R_2 were hydrogen, methyl, or phenyl. In order to adapt this process to vulpinic acid synthesis, the procedure shown in Scheme I was followed. Methyl phenylacetate and dimethyl oxalate were condensed using sodium methoxide in ether to obtain **5-1**.[6] Reaction of this with *p*-chlorophenylacetyl chloride using triethylamine as the base gave the enol ester **6-2**. The infrared spectrum of

Scheme I



5-1

6-2

1-2

3 **4**

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