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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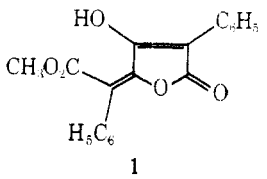
A regiospecific synthesis of vulpinic acid analogues substituted differently in each of the phenyl rings was developed. Treatment of the appropriate dimethyl phenyloxalacetate with the appropriate phenylacetyl chloride in the presence of triethylamine gave an enol ester. Excess triethylamine catalyzed 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-



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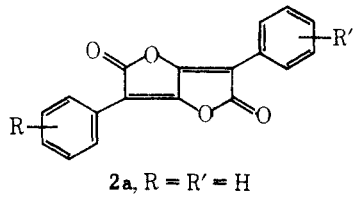
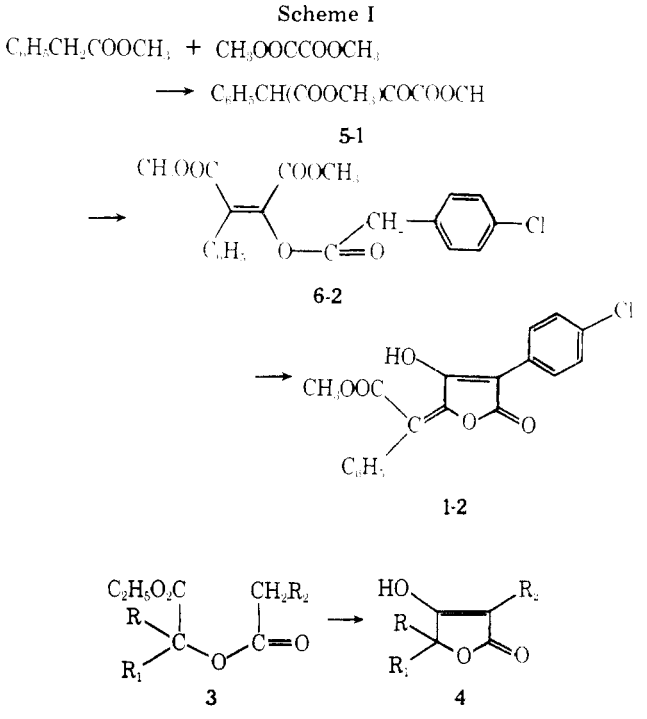


2a, R = R′ = H

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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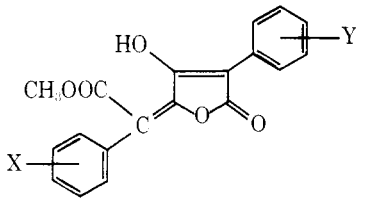
Table I. Vulpinic Acids Prepared by Scheme I



1-X

compd	registry no.	X	Y	mp °C	% yield from 10	recryst solvent[b]	formula[c]
1	521-52-8	H	H	148–149[a]	25	M	$C_{19}H_{14}O_5$
1-2	37542-22-6	H	4-Cl	160.0–161.5	25[d]	MA	$C_{19}H_{13}ClO_5$
1-3	68781-54-4	H	4-F	145.5–146.5[a]	22[d]	M	$C_{19}H_{13}FO_5$
1-4	68781-55-5	H	4-NO_2	220–221	11	MA	$C_{19}H_{13}NO_7$
1-5	68781-56-6	4-F	H	150–151[a]	14[d]	M	$C_{19}H_{13}FO_5$
1-6	68781-57-7	4-$(CH_3)_2CHO$	H	151–152.5	13	M	$C_{22}H_{20}O_6$
1-7	68781-58-8	3-CH_3O	H	160–160.5	16[d]	MA	$C_{20}H_{16}O_6$
1-8	38746-81-5	4-C_2H_5O	H	151.5–153.5[a]	11[d]	MA	$C_{21}H_{18}O_6$
1-9	68781-59-9	4-C_6H_5O	H	142–146	5	M	$C_{25}H_{18}O_6$
1-10	68781-60-2	4-$C_6H_5CH_2O$	H	184.5–186	15	MA	$C_{26}H_{20}O_6$
1-11	68781-61-3	4-CH_3O	4-Cl	167–168	19	MA	$C_{20}H_{15}ClO_6$
1-12	68781-62-4	4-C_2H_5O	4-Cl	169–170	23	MA	$C_{21}H_{17}ClO_6$
1-13	68781-63-5	4-C_2H_5O	4-F	166.5–167	24	M	$C_{21}H_{17}FO_6$
1-14	68781-64-6	4-C_2H_5O	3-CF_3	106–107	22	M	$C_{22}H_{17}F_3O_6$
1-15	68781-65-7	4-C_2H_5O	3,4-OCH_2O	171–171.5	5	A	$C_{22}H_{18}O_8$
1-16	68781-66-8	4-Cl	4-CH_3COO	142.5–144	15	MA	$C_{21}H_{15}ClO_7$

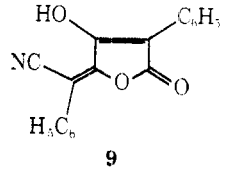
[a] Melting points[2] of compounds prepared via **2**: **1**, 148–149 °; **1-3**, 139–142.5 °C, **1-5**, 141–143.5 °C; **1-8**, 153–154 °C. [b] M, methanol; A, acetone. [c] Satisfactory analytical data (±0.4%) for C and H (and also N, F, and Cl in some instances) were reported for all new compounds listed in the table. [d] Yields obtained from **2**: **1-2**, 17 and 12% of 4-isomer; **1-3**, 13.5%;[e] **1-5**, 13%;[e] **1-8**, 27% plus 2.6% of the 4′-isomer; **1-7**, 0% pure plus 19% of the 3′-isomer. [e] By recrystallization of the tetrabutylammonium salt.

6-2 had peaks at 5.7 and 5.8 μm indicative of carbonyl functions and a peak at 6.2 μm consistent with an olefin. The NMR spectrum showed peaks at δ 3.59 corresponding to the benzylic protons and at δ 3.73 and 3.80 for the methyl protons of the ester groups. Both sodium methoxide and lithium diethylamide, the first of which converted **3** to **4**,[5] decomposed **6-2** to **5-1** and *p*-chlorophenylacetic acid. Treatment of **6-2** with 1,5-diazabicyclo[4.3.0]non-5-ene in refluxing toluene gave **1-2** in 2% yield. This was shown to be identical with **1-2** prepared by the classical route[2] and identified by ozonolysis[7] and by analysis of the NMR pattern.[8,9] Triethylamine in acetone at 60 °C was found to be a more efficient cyclization system.

The most convenient synthetic procedure involved reaction of **5** and the acid chloride in the presence of 1 mol of triethylamine in acetone at room temperature or below followed by cyclization using another mole of triethylamine at 60 °C in the same flask without removal of the salt formed in the first step. Using this procedure the vulpinic acids shown in Table I were obtained in up to 25% yield. Where available, yields of isolated products from **2** are indicated. It should be noted that in some instances pure isomers could not be obtained by us via **2**. The same process starting from the nitrile **8** gave vulpininonitrile **9**. By replacing the phenyl of **5** with other groups the tetronic

$C_6H_5CHCNCOCO_2C_2H_5$

8



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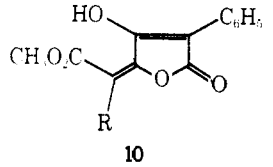
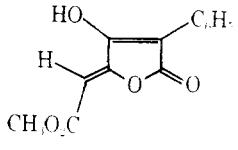


10

acids **10** shown in Table II were prepared. In each case the stereochemistry about the exocyclic double bond was established by infrared and NMR evidence for chelate type hydrogen bonding.[9]

In an attempt to form **10**, R = H, dimethyl oxalacetate was treated with phenylacetyl chloride and triethylamine in the manner described above. A yellow product was isolated in 20% yield which differed from the normal vulpinic acids in both its infrared and NMR spectra. Typical vulpinic acids have a strong IR band near 2400 cm^{-1} and a NMR peak near 13.8 ppm both due to the chelated hydroxyl. The product of this reaction had the corresponding IR band at 3150 cm^{-1} and NMR peak at 8.4 ppm indicating a nonchelated hydroxyl thus



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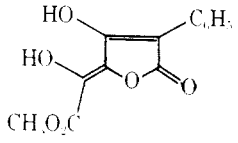

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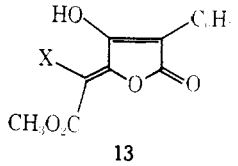
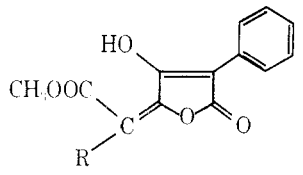


13

suggesting that the product was **11**. A similar inversion of the normal stereochemistry was previously observed in the 3-unsubstituted analogue of **11**.[10] Apparently chelation resonance energy by itself is not sufficient to maintain the hydroxyl and ester in a cis relationship; however, steric hindrance from even a methyl (**10**, R = CH_3) is sufficient assistance.

Bromine and chlorine react rapidly with **11** in chloroform. Treatment of the reaction mixture with dilute alkali gave in each case **12** in about 70% yield. The stereochemistry was assigned by the lack of evidence for chelate hydrogen bonding in the infrared and NMR spectra. This product probably forms by addition of halogen to the exocyclic double bond of **11** followed by a base-catalyzed elimination of HX to form **13**.

Table II. Tetronic Acids Prepared by Scheme I



10-*X*

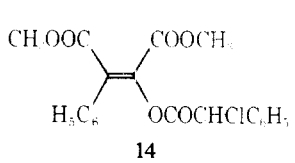
registry no.	compd	R	% yield[c]	mp, °C	recryst solvent[b]	formula[c]
68781-67-9	**10-1**	C_4H_3S[a]	3.5	119–120	M	$C_{17}H_{12}O_5S$
68781-68-0	**10-2**	CH_3	1	205–206.5	MA	$C_{14}H_{12}O_5$
68781-69-1	**10-3**	$C_6H_5CH_2$	6	158–159	MA	$C_{20}H_{16}O_5$
68781-70-4	**10-4**	C_6H_5O	7	181–183	E	$C_{19}H_{14}O_6$
68781-71-5	**10-5**	C_6H_5S	4	148–150	B	$C_{19}H_{14}O_5S$

[a] 2-Thienyl. [b] M, methanol; A, acetone; E, ethanol; B, 1-chlorobutane. Satisfactory analytical data (±0.4%) for C and H were reported for all compounds listed in the table. [c] Acylation and cyclization.

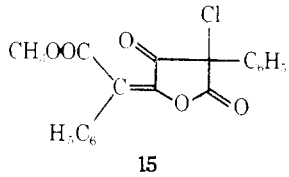
This in turn undergoes a hydroxyl–dehalogenation by an addition–elimination sequence involving hydroxide ion.

The generally low yields of vulpinic acids reported in Tables I and II was a matter of some concern. One rationalization of this concerns the conversion of **5** to **6**. In addition to two possible stereoisomers of **6** formed by *O*-acylation, *C*-acylation is also possible. The stereoisomer of **6** could give rise to a vulpinic acid whose stereochemistry about the exocyclic double bond is such that the ester and ring hydroxyl are trans, but such an isomer was not found except in the case of **11**. Another possible troublesome step is the cyclization of the anion of **6** to form **1**. In addition to the desired condensation with the ester group, the anion could undergo an elimination reaction to form the anion of **5** and the phenyl ketene. In general, **5** and the phenylacetic acid used to form **6** were present in the reaction mixture.

Another possible explanation for the low yields is that the anion of **6** forms with difficulty because the protons are not sufficiently acidic. In an attempt to overcome this, **5-1** was acylated with α-chlorophenylacetyl chloride to form **14** which was cyclized without isolation using excess triethylamine. Vulpinic acid (**1**) was formed in 22% yield which is about the same yield as obtained from phenylacetyl chloride and **5-1**.



14



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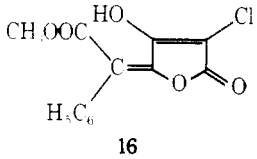

16

Presumably **15** is formed by the cyclization of **14**, but the chloride is lost in a base-catalyzed process. In a more useful example of this approach, **16** was obtained in 33% yield using dichloroacetyl chloride while chloroacetyl chloride gave a 14% yield of the same product. Thus in certain cases the acidity of the ester **6** may be a significant factor in the low yields of this tetronic acid synthesis.

Experimental Section

Melting points (uncorrected) were determined using a Thomas-Hoover capillary melting point apparatus. Mass spectra were determined using a Hitachi Perkin-Elmer RMN-6E spectrometer. NMR spectra were obtained on a Varian T-60 instrument and IR on a Perkin-Elmer 137 infracord. This work was carried out before the present general recognition of benzene as a hazardous solvent. We suggest that a suitable substitute be used.

Dimethyl Phenyloxalacetate (5-1).[6] A solution of 203 g (1.5 mol) of dimethyl oxalate was refluxed in 600 mL of benzene using a Dean-Stark trap to remove water (6 mL). Then 235 g (1.5 mol) of methyl phenylacetate was added and the refluxing continued to remove final traces of water. This was cooled and added to a suspension of 81.2 g (1.5 mol) of sodium methoxide in 700 mL of benzene and the mixture brought to reflux slowly. After 10 min a white solid appeared which stopped the stirrer; then 500 mL of benzene and 750 mL of methanol were added and the reflux was continued for 45 min with the Dean-Stark trap used to slowly remove the methanol. The solid which formed was collected by filtration, washed with benzene, and then dissolved in 2 L of water. After acidification with HCl, the solution was extracted twice with ether and the ether washed with water, dried, and concentrated to give 136.4 g (38.6%) of a pale yellow oil which was used without further purification: NMR ($CDCl_3$) δ 3.50 (s, 1, 0.33 of CH_3O), 3.71, 3.78 (s, 5, CH_3O), 5.34 (s, 0.8, $C_6H_5CH(CO)_2$), 7.30 (s, 5, phenyl **H**), 12.73 (br s, 0.2, –**OH** chelated). This indicates that this compound is 20% in the enol form in $CDCl_3$ solution.

Dimethyl 2-Phenyl-3-phenylacetoxymaleate (6-1). A solution of 23.6 g (0.1 mol) of **5** in 250 mL of acetone was treated with 10.1 g (0.1 mol) of triethylamine to give a yellow solution. Then 15.35 g (0.1 mol) of phenylacetyl chloride was added at 0–10 °C to give an immediate white precipitate. After standing at room temperature for 18 h approximately half of the reaction mixture was diluted with water, acidified, and extracted with ether. The ether was washed several times with dilute HCl, dilute sodium carbonate, and then water. Drying with $MgSO_4$ and evaporation of the ether gave a yellow oil: IR 5.76, 5.82, and 6.20 μm; NMR (CCl_4) δ 3.56 (s, 2 $CH_2C{=}O$), 3.65 (s, 3 OCH_3), 3.70 (s, 3, OCH_3), 7.12 (br s, 10, phenyl **H**). Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.70; H, 5.24.

Vulpinic Acid (1-1) by Cyclization of 6-1. The remaining half of the above reaction mixture was treated with 30 mL (0.3 mol) of triethylamine and held at 56 °C for 18 h. It was then cooled, diluted with 300 mL of water, and acidified with HCl to give a red oil. This was extracted with ether, washed several times with dilute HCl, and evaporated to dryness. The residual oil was triturated with 20 mL of methanol to give 4.0 g (25%) of yellow crystals, mp 148–149 °C, whose IR was identical with that of authentic vulpinic acid.

Vulpinic Acid from Dimethyl Phenyloxalacetate and α-Chlorophenylacetyl Chloride. A solution of 2.36 g (0.01 mol) of **5-1** and 1 g (0.01 mol) of triethylamine in 25 mL of acetone was treated with 1.89 g (0.01 mol) of α-chlorophenylacetyl chloride keeping the temperature below 25 °C. After 15 min 4.5 mL (0.022 mol) of additional triethylamine was added and the reaction mixture stored at 50 °C for 18 h. The reaction mixture was diluted with water, acidified with HCl, and chilled to precipitate 2.2 g of a brown semisolid product. This was triturated with methanol to give 0.8 g (22%) of yellow plates whose IR was identical with that of authentic vulpinic acid.

(*E*)-5-(1′-Carbomethoxybenzylidine)-3-chlorotetronic Acid ((*E*)-16). A cooled acetone (200 mL) solution of 23 g (0.1 mol) of **5-1** and 10.1 g (0.1 mol) of triethylamine was treated with 11.1 g (0.1 mol) of chloroacetyl chloride. After stirring at 25 °C for 1 h 28 mL (0.2 mol) of triethylamine was added and the reaction mixture held at 60 °C

for 18 h. The reaction mixture was poured into 600 mL of ice and water, acidified with HCl, and extracted with ether. The ether was extracted with 5% Na_2CO_3 and the aqueous layer acidified with HCl. Extraction with ether followed by washing the ether with water, drying over $MgSO_4$, and evaporation gave a solid which on recrystallization from chlorobutane gave 4.0 g (14.4%) of yellow crystals. Recrystallization from methanol gave yellow crystals: mp 158–159 °C; IR (Nujol) 4.20 (chelated OH), 5.65, 5.97, and 6.28 μm. Anal. Calcd for $C_{13}H_9ClO$: C, 55.63; H, 3.23. Found: C, 55.90; H, 3.42.

A similar experiment using dichloroacetyl chloride instead of chloroacetyl chloride gave **16** in 33% yield.

Pulvinonitrile (9). A solution of 21.7 g (0.1 mol) of ethyl 3-cyano-3-phenylpyruvate and 10.1 g (0.1 mol) of triethylamine in 200 mL of acetone was treated with 15.35 g (0.1 mol) of phenylacetyl chloride. After 1 h at room temperature 30 mL (0.2 mol) of triethylamine was added and the yellow mixture held at 60 °C for 18 h. The red reaction mixture was diluted with water and acidified and the oil taken up in ether. The ether was washed with dilute HCl and then with water. Evaporation gave an orange oil which immediately crystallized. After trituration with 25 mL of hot chlorobutane, cooling, and filtration 15 g of a yellow solid was obtained. Recrystallization from chlorobutane gave pale yellow needles, mp 195.5–196.5 °C (lit.[4] mp 189–191 °C; lit.[11] mp 193–194 °C, soften 190 °C). Anal. Calcd for $C_{18}H_{11}NO_3$: C, 74.73; H, 3.83; N, 4.84. Found: C, 74.59; H, 3.79; N, 4.85.

(*Z*)-5-Carbomethoxymethylidine-3-phenyltetronic Acid (11). A suspension of 36.4 g (0.2 mol) of the sodium salt of dimethyl oxalacetate in dry acetone was treated with 30.9 g (0.2 mol) of phenylacetyl chloride. After 1 h at room temperature 28 mL (0.2 mol) of triethylamine was added and the reaction mixture stored at 50 °C for 20 h. The cooled solution was diluted to 2 L with water and acidified and the yellow solid was collected by filtration, washed with water, and dried to give 10.0 g (20.3%) of product. Recrystallization from chloroform gave yellow needles: mp 182.5–184.5 °C dec; IR (Nujol) 3.1, 5.7, 6.0, and 6.3 μm; NMR (CD_3COCD_3–CD_3SOCD_3) δ 3.84 (s, 3, OCH_3), 6.70 (s, 1, $CH=$), 7.30 (m, 3, 3,4,5-phenyl H), 7.62 (m, 2, 2,6-phenyl **H**), 8.42 (br s, 1, **OH**). Anal. Calcd for $C_{13}H_{10}O_5$: C, 63.42; H, 4.09. Found: C, 63.62; H, 4.23.

(*E*)-5-(1′-Hydroxycarbomethoxymethylidene)-3-phenyltetronic Acid (12). A suspension of 3.8 g (0.0155 mol) of **11** in 50 mL of $CHCl_3$ at 10 °C was treated with a solution of 2.74 g (0.017 mol) of bromine in 5 mL of $CHCl_3$ to give a clear orange solution. After 10 min the solution was treated with, and then extracted by, 3% aqueous NaOH. The aqueous layer was washed with ether and acidified with concentrated HCl to give 3.0 g (74%) of a yellow solid. Recrystallization from acetone–chloroform and then acetone–chlorobutane gave pale yellow needles: mp 215–216.5 °C dec; IR (Nujol) 3.0, 3.8, 5.9, 6.1, and 6.2 μm; NMR (CD_3COCD_3–CD_3SOCD_3) δ 4.00 (s, 3, OCH_3), 7.43 (m, 3, 3,4,5-phenyl **H**), 7.95 (m, 2, 2,6-phenyl **H**), 8.80 (br S, 2, **OH**). Anal. Calcd for $C_{13}H_{10}O_6$: C, 59.55; H, 3.84. Found: C, 59.22; H, 4.21.

Dimethyl 2-Oxo-3-phenoxysuccinate. A mixture of sodium methoxide (26.4 g, 0.488 mol), dimethyl oxalate (79 g, 0.672 mol), and methyl phenoxyacetate (74.5 g, 0.488 mol) in 400 mL of dry benzene was refluxed for 2 h. It was then cooled, poured into an ice-water mixture, and extracted with ether. The aqueous layer was acidified with dilute HCl and this extracted twice with ether. The organic layer was dried over $MgSO_4$ and concentrated to give 52 g (42%) of product whose NMR was consistent with the structure. This was used without further purification to prepare **10-4**.

A similar procedure was used to prepare **dimethyl 2-oxo-3-phenylthiosuccinate** in 62% yield and **dimethyl 2-oxo-3-benzylsuccinate** in 42% yield. These products were used without further purification to prepare **10-5** and **10-3**.

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