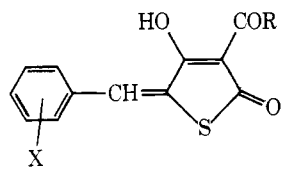
Vulpinic Acids as Potential Antiinflammatory Agents. 1. Vulpinic Acids with Substituents in the Aromatic Rings

F. R. Foden, J. McCormick, and D. M. O'Mant*

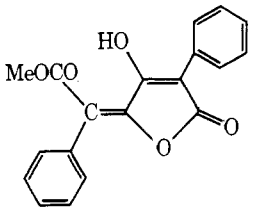
Imperial Chemical Industries Limited, Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, SK10 4TG, England.
Received May 3, 1974

The preparation of a series of vulpinic acids, substituted in either or both of the aromatic rings, is described. The compounds were found to be active in the adjuvant arthritis test in rats. High activity combined with an acceptable therapeutic ratio was confined to analogs with electron-withdrawing substituents in the meta positions of the rings.

In the search for other immunosuppressive agents related to the 3-acyl-5-arylidene-4-hydroxy-2-oxo-2,5-dihydrothiophenes (I)[1] one of our colleagues, Dr. R. W. Turner, submitted the natural product, vulpinic acid (II), for evaluation in the adjuvant-induced arthritis test in rats.[2] In



I



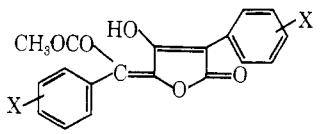
II

spite of its marked resemblance to the thiophenes, vulpinic acid was not immunosuppressive but was found to possess antiinflammatory properties. The therapeutic ratio was moderately good but the compound exhibited an unusual form of toxicity in causing hyperventilation which in many cases was followed by convulsions and death. Hyperventilation provoked by vulpinic acid was first observed by Soderberg[3] in cats and guinea pigs and was probably known to Eskimos, who used lichens containing vulpinic acid to poison wolves. Nevertheless, the antiinflammatory activity was considered interesting enough to pursue and we have synthesized and evaluated a series of vulpinic acids with various substituents in the two aromatic rings.

Chemistry. Symmetrically substituted vulpinic acids were synthesized from benzyl cyanides III by the route first described by Volhard[4] and later modified by Edwards[5] (Scheme I).

The so-called dinitriles IV were almost certainly of the imino lactone structure V, in which an enolic hydroxyl had ring closed with one of the cyano groups. Their infrared spectra invariably showed complex bands in the region of 3200–3500 cm^{-1}, indicative of N-H and -OH groups. The carboxylic acids VI, known as pulvinic acids, were not purified and usually contained some of the pulvinic lactone VII and the pulvinic amide VIII. The mixture was easily all converted in high yield to the pulvinic lactone by treatment with acetic anhydride. The infrared spectra of the vulpinic acids IX invariably showed a strong band at 2500 cm^{-1} due to the enolic hydroxyl group which was strongly bonded to the ester carbonyl.

Table I. Symmetrically Substituted Vulpinic Acids

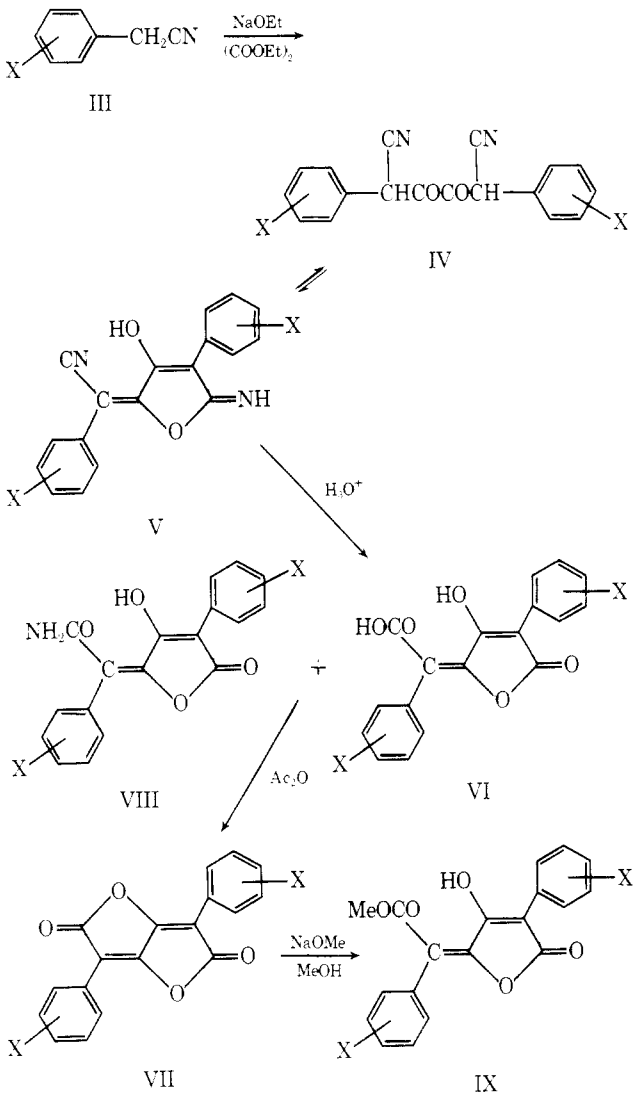


IX

Compd no.	X substituent	% yield	Recrystn solvent	Mp, °C	Formula	Analyses	Act. in rat arthritis test: Toxic dose, mg/kg	Act. in rat arthritis test: Min active dose, mg/kg
1	4-Me–	81	AcOH	194–195	$C_{21}H_{18}O_5$	C, H	N.A.[a] 100	
2	3-Me–	62	AcOH	123–124	$C_{21}H_{18}O_5$	C, H	100	25
3	2-Me–	79	Et_2O	70–72	$C_{21}H_{18}O_5$	C, H		50
4	4-Ph–	64	Dioxane–H_2O	206–208	$C_{31}H_{22}O_5$	C, H	100	25
5	4-Cyclohexyl–	88	AcOH	216–218	$C_{31}H_{34}O_5$	C, H		25
6	4-MeO–	73	AcOH	179–181[b]	$C_{21}H_{18}O_7$	C, H		100
7	3-MeO–	86	AcOH	164–165	$C_{21}H_{18}O_7$	C, H		50
8	3,4-$(MeO)_2$–	53	BuOH	193–195	$C_{23}H_{22}O_9$	C, H	100	25
9	4-HO–	90		360–362[c]	$C_{19}H_{14}O_7 \cdot 0.5H_2O$	C, H	N.A. 50	
10	4-Cl–	34	BuOH	183–185[d]	$C_{19}H_{12}Cl_2O_5$	C, H, Cl	25*	>5
11	3-Cl–	86	Toluene	178–180	$C_{19}H_{12}Cl_2O_5$	C, H, Cl	100	5
12	3-I–	71	AcOH	220–221	$C_{19}H_{12}I_2O_5$	C, H, I	100	10
13	3-CF_3–	69	MeOH	147–148	$C_{21}H_{12}F_6O_5$	C, H, F	25	>10
14	2-F–	81	MeOH–H_2O	136–140	$C_{19}H_{12}F_2O_5$	C, H	N.A. 100	
15	3,5-$(Cl)_2$–	95		191–192	$C_{19}H_{10}Cl_4O_5$	C, H, Cl[e]	50	20
Phenylbutazone							250	20
Vulpinic acid							75*	5

*Hyperventilation observed. [a]N.A. = neither active or toxic. [b]F. Kögl and H. Becker, *Justus Liebigs Ann. Chem.*, 465, 243 (1928), give mp 174.5°. [c]Prepared by Kogl and Becker,[6] no melting point. [d]Karrer[8] gives mp 214–216°. [e]Cl: calcd, 30.9; found, 30.3.

Scheme I



That this was an intramolecular bond rather than an intermolecular one was shown by its persistence in dilute solution in polar solvents, such as dioxane. The presence of such an intramolecular bond showed that the vulpinic acids existed in that geometrical isomer about the exocyclic double bond illustrated (IX).

One of the vulpinic acids (IX, X = 4-Cl) was also prepared by direct conversion of the nitrile IV to the vulpinic acid with methanol and dry hydrogen chloride. However, the yield was relatively poor.

4,4′-Dihydroxyvulpinic acid (IX, X = 4-OH) was prepared from 4,4′-dimethoxypulvinic lactone (VII, X = 4-OMe) by hydrolysis and demethylation with HI and HOAc. The dihydroxypulvinic acid (VI, X = 4-OH) so produced was acetylated and ring closed with Ac_2O to 4,4′-diacetoxypulvinic lactone (VII, X = 4-OAc). The lactone was methanolyzed and deacetylated with methanol and sodium hydroxide to dihydroxyvulpinic acid. The compound has been prepared by Kögl and Becker[6] by a different route, but no melting point or analysis was given.

Asymmetrically substituted vulpinic acids were prepared by the procedure described by Akermark[7] and Edwards[5] (Scheme II). A mixture of two imino lactones (XI and XII) was produced by the reaction of an aryl cyanopyruvate X with a substituted benzyl cyanide and base. The mixture of nitriles was hydrolyzed and ring closed, as before, to a single dilactone XIII which was then methanolyzed to a mixture of two vulpinic acids (XIV and XV). Each pair of acids was separated by fractional crystallization and structures were assigned by their nuclear magnetic resonance spectra. The two aromatic protons in the ortho position adjacent to the furan ring were downfield from all the other aromatics (the pulvinic lactones had four such protons) and it was usually a simple matter to assign structures on this basis. Thus, in the case of the 3-chloro and 3′-chloro isomers the 3-chloro compound (XIV, X = 3-Cl; Y = H) showed a two-proton doublet at τ 8.10 due to the two protons at the 2′ and 6′ positions split by the protons at the 3′ and 5′ positions while the 3′-chloro compound (XV, X = 3-Cl; Y = H) showed a one-proton singlet at τ 8.15 due to the 2′ proton and a one-proton doublet at τ 8.05 due to the 6′ proton split by the 5′ proton.

The monohydroxyvulpinic acids (XIV and XV, X = 4-OH; Y = H) were prepared from the 4-methoxy dilactone (XIII, X = 4-MeO; Y = H) by a similar procedure to that described for the dihydroxy acid.

Structure–Activity Relationships. The antiinflammatory activity of each of the vulpinic acids was deter-

Scheme II

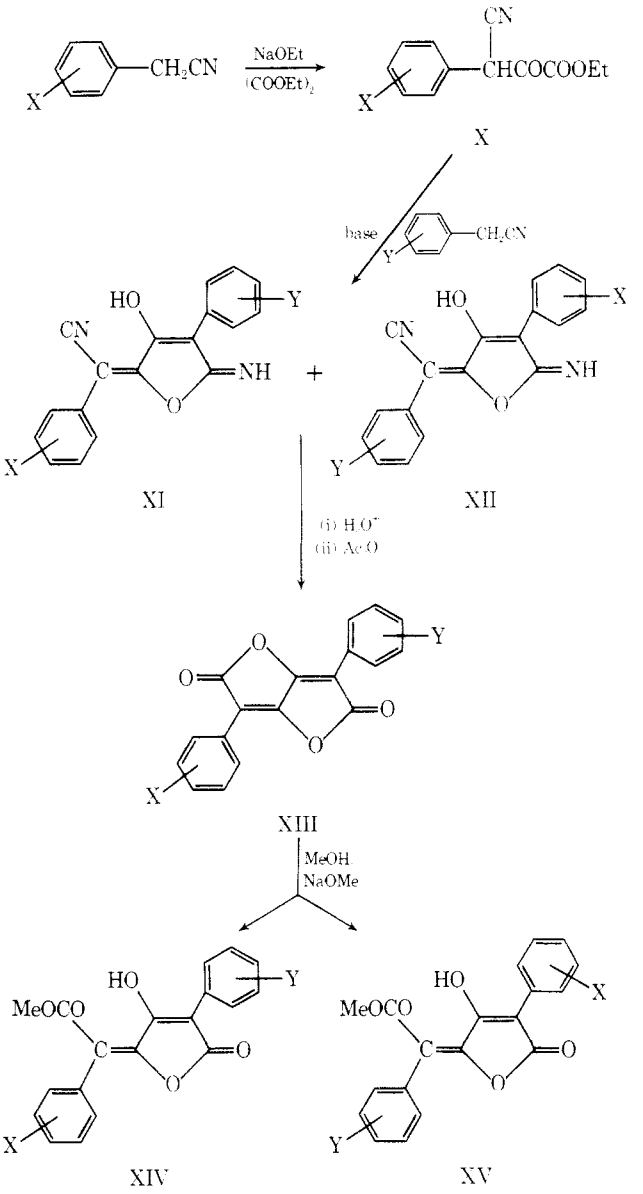
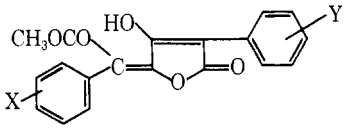


Table II. Asymmetrically Substituted Vulpinic Acids

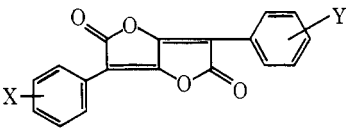


XIV

Compd no.	X substituent	Y substituent	% yield[a]	Recrystn solvent	Mp, °C	Formula	Analyses	Act. in rat arthritis test: Toxic dose, mg/kg	Act. in rat arthritis test: Min active dose, mg/kg
16	4-HO–	H–	30	EtOAc	235–236	$C_{19}H_{14}O_6$	C, H		50
17	H–	4-HO–	49	MeOH	240–242	$C_{19}H_{14}O_6 \cdot CH_3OH$	C, H	>100	25
18	4-Cl–	H–	24	AcOH	136–138	$C_{19}H_{13}ClO_5$	C, H, Cl	100*	25
19	H–	4-Cl–	35		161–162	$C_{19}H_{13}ClO_5$	C, H, Cl	>50	10
20	3-CF_3–	H–	35	$CHCl_3$	191–192	$C_{20}H_{13}F_3O_5$	C, H	100	5
21	H–	3-CF_3–	70	Toluene	234–235	$C_{20}H_{13}F_3O_5$	C, H	100	25
22	3-Cl–	H–	56	MeOAc	165–166	$C_{19}H_{13}ClO_5$	C, H, Cl	100*	2.5
23	H–	3-Cl–	97	MeOAc	240–242	$C_{19}H_{13}ClO_5$	C, H, Cl	>50	10
24	3,5-Cl_2–	H–	39	MeOH	193–195	$C_{19}H_{12}Cl_2O_5$	C, H, Cl	50	<10
25	H–	3,5-Cl_2–	62	MeOH	181–182	$C_{19}H_{12}Cl_2O_5$	C, H, Cl	>50	20

[a] Assuming an equal distribution of isomers in the preparation.

Table III. Furo[3,2-*b*]furans (Pulvinic Lactones)



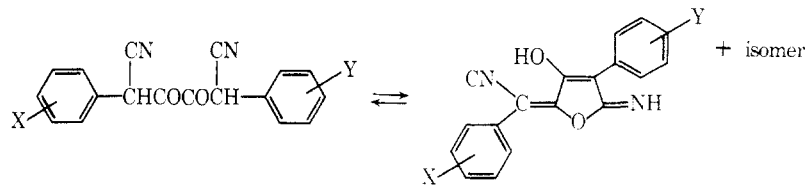
XIII

Compd no.	X substituent	Y substituent	% yield[e]	Recrystn solvent	Mp, °C	Formula	Analyses
28	4-Me–	4-Me–	60	Ac_2O	286–287	$C_{20}H_{14}O_4$	C, H
29	3-Me–	3-Me–	63	Ac_2O	232–234	$C_{20}H_{14}O_4$	C, H
30	2-Me–	2-Me–	75	Ac_2O	209–210	$C_{20}H_{14}O_4$	C, H
31	4-Ph–	4-Ph–	68	Ac_2O	306–308	$C_{30}H_{18}O_4$	C, H
32	4-Cyclohexyl–	4-Cyclohexyl–	84	$CHCl_3$	287–289	$C_{30}H_{30}O_4$	C, H
33	4-MeO–	4-MeO–	59	Ac_2O	278–280	$C_{20}H_{14}O_6$	H; C[a]
34	3-MeO–	3-MeO–	58	Ac_2O	231–232	$C_{20}H_{14}O_6$	C, H
35	3,4-$(MeO)_2$–	3,4-$(MeO)_2$–	53	Ac_2O	288–289[b]		
36	4-AcO–	4-AcO–	87[f]	Ac_2O	270–272[c]		
37	3-Cl–	3-Cl–	69	Ac_2O	280–282	$C_{18}H_8Cl_2O_4$	C, H
38	3-I–	3-I–	49	Ac_2O	301–302	$C_{18}H_8I_2O_4$	C, H, I
39	3-CF_3–	3-CF_3–	45	Ac_2O	204–205	$C_{20}H_8F_6O_4$	C, H, F
40	2-F–	2-F–	33	Ac_2O	198–201	$C_{18}H_8F_2O_4$	C, H
41	3,5-Cl_2–	3,5-Cl_2–	73	Ac_2O	298–299	$C_{18}H_6Cl_4O_4$	C, Cl; H[d]
42	4-AcO–	H–	43[g]	Dioxane	221–223	$C_{20}H_{12}O_6$	C, H
43	4-Cl–	H–	61	Ac_2O	222–223	$C_{18}H_9ClO_4$	C, H, Cl
44	3-CF_3–	H–	70	Ac_2O	168–169	$C_{19}H_9F_3O_4$	C, H
45	3-Cl–	H–	65	Ac_2O	210–211	$C_{18}H_9ClO_4$	C, H, Cl
46	3,5-Cl_2–	H–	60	Ac_2O	198–199	$C_{18}H_8Cl_2O_4$	C, H

[a] C: calcd, 68.6; found, 67.9. [b] Beaumont, *et al.*,[5] give mp 288°. [c] F. Kögl and H. Becker, *Justus Liebigs Ann. Chem.*, 465, 233 (1928), give mp 271°. [d] H: calcd, 1.4; found 2.0. [e] Based on amount of imino lactone (V or XI). [f] Based on 4,4′-dimethoxypulvinic lactone (XII, X = 4-OMe). [g] Based on 4-methoxypulvinic lactone (XIII, X = 4-MeO; Y = H).

mined by means of the adjuvant-induced arthritis test in rats, as described by Newbould.[2] Rats were divided into groups of three, and for each compound at least four groups were treated orally with a range of doses until a minimum active dose was determined which produced 30% inhibition of the swelling of the injected foot. For the active compounds a toxic dose, which caused death during the 14-day dosing period, was also found. In some instances death was observed to be due to hyperventilation, as with vulpinic acid itself, and those compounds are marked with an asterisk in the toxic dose column of Tables I and II. It should be emphasized that hyperventilation was difficult to observe in the rat because the animals were easily disturbed, which caused panting and obscured the symptoms. Only those instances where hyperventilation was clearly apparent and sustained for several minutes are indicated in Tables I and II. In most of the other groups death was due to the usual gastric damage seen with antiinflammatory agents. Since only small groups of animals were used for the determinations, the values for the active and toxic doses could only be taken as a guide. However, some trends were clearly apparent.

Table IV. Pulvinic Nitriles

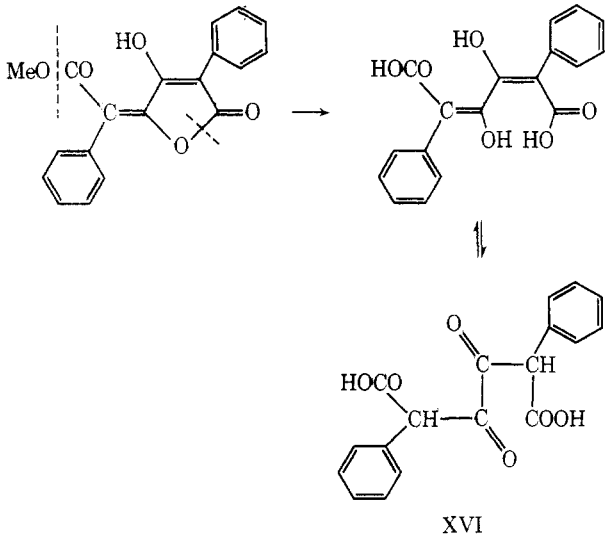


XI and XII

Compd no.	X substituent	Y substituent	% yield	Recrystn solvent	Mp, °C	Formula	Analyses
47	4-Me–	4-Me–	28	AcOH	285	$C_{20}H_{16}N_2O_2$	C, H, N
48	3-Me–	3-Me–	60	AcOH	264–265	$C_{20}H_{16}N_2O_2$	C, H, N
49	2-Me–	2-Me–	28	AcOH	256–257	$C_{20}H_{16}N_2O_2$	C, H, N
50	4-Ph–	4-Ph–	90	DMF	305–307	$C_{30}H_{20}N_2O_2 \cdot H_2O$	C, H, N
51	4-Cyclohexyl–	4-Cyclohexyl–	18	AcOH	283–284[a]		
52	4-MeO–	4-MeO–	45	AcOH	266–270[b]	$C_{20}H_{16}N_2O_4$	C, H, N
53	3-MeO–	3-MeO–	54	AcOH	213–214[c]		
54	3,4-$(MeO)_2$–	3,4-$(MeO)_2$–	10	AcOH	247–249[d]		
55	4-Cl–	4-Cl–	63	DMF	268–283[e]		
56	3-Cl–	3-Cl–	34	DMF–H_2O	284–285	$C_{18}H_{10}Cl_2N_2O_2$	C, H, N
57	3-I–	3-I–	34	DMF–H_2O	244–247	$C_{18}H_{10}I_2N_2O_2$	C, H, N, I
58	3-CF_3–	3-CF_3–	35	AcOH	238–240	$C_{20}H_{10}F_6N_2O_2 \cdot H_2O$	C, H, N, F
59	2-F–	2-F–	67	AcOH	245–246	$C_{18}H_{10}F_2N_2O_2 \cdot 0.25$ CH_3COOH	C, H, N
60	3,5-Cl_2–	3,5-Cl_2–	52	DMF	305–306	$C_{18}H_8Cl_4N_2O_2 \cdot DMF$	C, H, N, Cl
61	4-MeO–	H–	26	AcOH	268	$C_{19}H_{14}N_2O_3$	C, H, N
62	4-Cl–	H–	39	DMF	280–282	$C_{18}H_{11}ClN_2O_2$	C, H, N, Cl
63	3-CF_3–	H–	51	AcOH	249–251	$C_{19}H_{11}F_3N_2O_2$	C, H, N
64	3-Cl–	H–	50	AcOH	272–273	$C_{18}H_{11}ClN_2O_2$	C, H, N, Cl
65	3,5-Cl_2–	H–	58	DMF–H_2O	284–285	$C_{18}H_{10}Cl_2N_2O_2$	C, H, N
66	2-Cl–	H–	65	DMF–H_2O	274–275	$C_{18}H_{11}ClN_2O_2$	C, H, N

[a]No satisfactory analysis due to contamination by inorganic material. The derived furo[3,2-*b*]furan analyzed satisfactorily (32). [b]F. Kögl, *Justus Liebigs Ann. Chem.*, **465**, 243 (1928), gives mp 260°. [c]P. C. Beaumont, *et al.*,[5] give mp 213–214°. [d]P. C. Beaumont, *et al.*,[5] give mp 248–249°. [e]P. Karrer, *Helv. Chim. Acta*, **9**, 452 (1926), gives mp 273° dec.

It was thought originally that the antiinflammatory activity of vulpinic acid might be due to transport of phenylacetic acid residues to the receptor site, since it is well known that substituted phenylacetic acids are antiinflammatory agents.[9,10] If the ester and lactone bonds of vulpinic acid were to be hydrolyzed *in vivo* the product would be two phenylacetic residues joined by a diketone bridge (XVI). However, attempts to increase the activity by incorporating a more potent substituted phenylacetic acid such as 4-biphenylacetic acid (4) and 4-cyclohexylphenylacetic acid (5) failed. These compounds were less active than vulpinic acid itself. High activity was limited to compounds containing a halogeno substituent. A good separation between active and toxic doses was confined to those compounds with halogen in the meta positions of the rings (11, 20, 22). Although the para halogeno compounds were moderately active (10, 18, 19) they had a much poorer therapeutic ratio, while an ortho halogeno compound (14) was inactive. Two of the compounds (22 and 11) were selected for further evaluation. Although 22 was the most active of the series and it had a better therapeutic ratio it was finally abandoned because it provoked hyperventilation after oral dosing to dogs. Compound 11 did not provoke hyperventilation after oral dosing to rats, dogs, or monkeys although it did cause the usual gastric damage seen with antiinflammatory agents. Hyperventilation was caused by intravenous dosing in both rats and dogs, but at a relatively huge blood level (400 μg/ml compared with a therapeutic level of 30 μg/ml).



XVI

Experimental Section

General. Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Preparation of Symmetrically Substituted Imino Lactones (V, X = 3-Cl). Sodium pellets (7.4 g, 0.32 mol) were dissolved in 100 ml of absolute EtOH. Diethyl oxalate (23.1 g 0.158 mol) was added to the cooled solution followed by 49 g of *m*-chlorobenzyl

cyanide (0.32 mol). The mixture was stirred at 60–70° for 1 hr, cooled, diluted with 30 ml of H_2O, acidified to pH 5 with HOAc, diluted with 150 ml of H_2O, and filtered. The crude product was crystallized from DMF–H_2O: yield 19.7 g; 34%; mp 284–285°; ir bands at 3230 (NH) and 2220 cm^{-1} (CN) *Anal.* ($C_{18}H_{10}Cl_2N_2O_2$) C, H, N.

Preparation of Symmetrically Substituted Pulvinic Lactones (VII, X = 3-Cl). The above imino lactone (19.7 g, 55 mmol) was refluxed with 250 ml of AcOH, 125 ml of H_2O, and 105 ml of concentrated H_2SO_4 for 0.5 hr. The mixture was cooled; the precipitate of crude 3,3′-dichloropulvinic acid (16 g) was filtered off, washed with water, dried, and boiled with 160 ml of Ac_2O for 0.5 hr. After cooling the product was filtered off, washed with a little AcOH, and dried: 13.7 g; 69%; mp 280–282°. *Anal.* ($C_{18}H_8Cl_2O_4$) C, H.

Preparation of Symmetrically Substituted Vulpinic Acids (IX, X = 3-Cl). The above dilactone (13.7 g, 38 mmol) was stirred with 130 ml of methanol and 5 ml of 18 *N* NaOH (90 mmol). After 5 min the resulting clear solution was diluted with water and acidified with concentrated HCl. The precipitate of crude product was filtered off and recrystallized from toluene: 12.9 g; 86%; mp 178–180°. *Anal.* ($C_{19}H_{12}Cl_2O_5$) C, H, Cl.

Preparation of Vulpinic Acids by Direct Conversion from Imino Lactones (IX, X = 4-Cl). 4,4′-Dichloroimino lactone (V, X = 4-Cl, 10 g, 28 mmol) was refluxed with 60 ml of MeOH and 20 ml of concentrated H_2SO_4 for 17 hr. After cooling, the crude product was filtered off, washed with MeOH, and recrystallized from BuOH: 3.7 g; 34%; mp 183–185°. *Anal.* ($C_{19}H_{12}Cl_2O_5$) C, H, Cl. Karrer[8] gives mp 214–216° but we have found 183–185° for material prepared by both this route and the dilactone route described above.

4,4′-Dihydroxypulvinic Acid (VI, X = 4-OH). Dimethoxypulvinic lactone (VII, X = 4-OMe, 9 g, 26 mmol) was refluxed with 110 ml of constant boiling HI and 450 ml of AcOH for 2 hr. The mixture was evaporated *in vacuo* and the residue was dissolved in 300 ml of Et_2O. The ethereal solution was extracted with 3 × 100 ml of saturated $Na_2S_2O_3$, washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to a glass. The glass was crystallized from water to give the product: 3.0 g; 34%; mp 330–332° dec.

4,4′-Diacetoxypulvinic lactone (VII, X = 4-OAc) was prepared from 1.5 g of 4,4′-dihydroxypulvinic acid by the procedure described above for VII (X = 3-Cl): 1.55 g; 87%; mp 270–272° (see Table III).

4,4′-Dihydroxyvulpinic Acid (IX, X = 4-OH). 4,4′-Diacetoxypulvinic lactone (1.05 g, 2.59 mmol) was stirred with 15 ml of MeOH and 0.5 ml of 18 *N* NaOH (9 mmol) for 15 min. The resulting clear solution was diluted with 15 ml of water and acidified with concentrated HCl. The product was filtered off, washed with MeOH, and dried: 0.85 g; 90%; mp 360–362°. *Anal.* ($C_{19}H_{14}O_7 \cdot 0.5H_2O$) C, H.

Preparation of Asymmetrically Substituted Imino Lactones (XI and XII, X = 3-Cl; Y = H) (Table IV). Diethyl oxalate (465 g, 3.18 mol) was stirred with 172 g of NaOMe (3.185 mol) in 3 l. of dioxane (dried over molecular sieve type 4A) for 1 hr. *m*-Chlorobenzyl cyanide (475 g, 3.135 mol) was added and stirred for a further hour. The resulting solution of the sodium enolate of X (X = 3-Cl) was added to 376 g of benzyl cyanide (3.213 mol) which had been stirred with 690 g of NaOMe (12.8 mol) in 3 l. of dry dioxane for 2 hr. The resulting mixture was stirred for 20 hr, then poured into 100 l. of water, and acidified to pH 1 with concentrated HCl. The precipitate of crude product was filtered off, washed with EtOH, and dried: 510 g; 50.4%; mp 272–273°. This mixture of imino lactones was converted to 300 g (58.4%) of 3-chloropulvinic lactone (XIII, X = 3-Cl; Y = H) and then to 326 g (98.9%) of a mixture of vulpinic acids (XIV and XV, X = 3-Cl; Y = H) by exactly the same procedures as those described above for the symmetrical compounds.

Separation of Isomeric Vulpinic Acids (XIV and XV, X = 3-Cl; Y = H). The mixture of the two vulpinic acids (326 g) was dissolved in 3.3 l. of boiling MeOAc, cooled, and filtered. The residue (211 g) was recrystallized from 750 ml of MeOAc to give pure 3′-chlorovulpinic acid (XV, X = 3-Cl; Y = H): 160 g; 97%; mp 240–242°. *Anal.* ($C_{19}H_{13}ClO_5$) C, H, Cl. The filtrate from the original crystallization was evaporated *in vacuo* to 1 l. and cooled. The resulting precipitate (112 g) was recrystallized from 600 ml of MeOAc to give pure 3-chlorovulpinic acid (XIV, X = 3-Cl; Y = H): 63 g; mp 165–166°. *Anal.* ($C_{19}H_{13}ClO_5$) C, H, Cl. A further 28 g of 3-chlorovulpinic acid was recovered from the two mother liquors to give a total yield of 56%. The percentage yields calculated in this separation are based upon an equal distribution of isomers in the mixture. The differences in the nmr spectra of the two compounds are discussed in the text.

Acknowledgments. We are indebted to Drs. G. E. Davies, D. P. Evans, and B. B. Newbould for biological evaluations, Mr. C. Howarth for microanalyses, Mr. D. Greatbanks for nmr data, and Miss S. J. Alcock for the toxicological data.

References

(1) D. M. O'Mant, *J. Chem. Soc.*, 1501 (1968).
(2) B. B. Newbould, *Brit. J. Pharmacol. Chemother.*, **21**, 127 (1963).
(3) U. Soderberg, *Acta Physiol. Scand.*, **27**, 97 (1952).
(4) J. Volhard, *Justus Liebigs Ann. Chem.*, **282**, 1 (1894).
(5) P. C. Beaumont, R. L. Edwards, and G. C. Elsworthy, *J. Chem. Soc.*, 2968 (1968).
(6) F. Kögl and H. Becker, *Justus Liebigs Ann. Chem.*, **465**, 211 (1928).
(7) B. Akermark, *Acta Chem. Scand.*, **15**, 1695 (1961).
(8) P. Karrer, K. A. Gehrckens, and W. Heuss, *Helv. Chim. Acta*, **9**, 446 (1926).
(9) I. M. Chalmers, *Ann. Rheum. Dis.*, **31**, 110 (1972).
(10) R. C. Nickander, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **30**, 2059 (1971).

Notes

Hydroaromatic Analogs of 2-Nitro-1,3-indandiones

Derek R. Buckle,* Neil J. Morgan, and Harry Smith

Beecham Research Laboratories, Brockham Park, Betchworth, Surrey, England. *Received July 9, 1974*

During a search for new antiallergic drugs we have previously reported potent activity, as measured by the rat passive cutaneous anaphylaxis or PCA test, in a series of 2-nitroindandiones **1**.[1] We now report our continuation of this work which has led to a study of analogous systems in which the aromatic or "support" ring has undergone varying degrees of saturation. Two series, the tetrahydroaromatic system **2** and the perhydroaromatic system **3**, both of which are novel, were synthesized and screened for biological activity. A dramatic reduction in activity in the rat PCA test relative to the aromatic indandione analogs was shown by compounds containing these systems.

In the indandiones **1** the aromatic ring necessarily confers planarity on the overall system with the effect of giving the molecule a plane of symmetry. This symmetry is more obvious when the preferred nitronic acid tautomer of