Further Investigations of the Interaction of Trimethylsilyl Azide with Substituted Maleic Anhydrides. Synthesis of 4- and 5-Aryl Substituted 1,3-(3*H*)Oxazine-2,6-diones

*John H. MacMillan and Stephen S. Washburne**

Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122

Received August 4, 1975

The reactions of phenyl-, *o*-chlorophenyl-, *p*-chlorophenyl-, 3,4-dichlorophenyl-, *p*-fluoro- and *p*-anisylmaleic anhydrides with trimethylsilyl azide are described. In all cases mixtures of isomeric 4- and 5-aryl-2*H*-1,3-(3*H*)oxazine-2,6-diones are obtained after hydrolysis with the 4-isomer predominating. The yield of 5-isomer is greatest for *o*-chlorophenyl maleic anhydride, and substantial for other arylmaleic anhydrides, indicating increased importance of steric effects in these reactions, in contrast to previously reported syntheses of methyl and halo-substituted oxazinediones, where electronic factors appeared dominant.

The "oxauracil" or 2*H*-1,3-(3*H*)oxazine-2,6-dione ring **1a** has been the subject of intense recent synthetic study (1-3) due to the demonstrated activity of the parent **1a** (2,4), the 5-fluoro derivative **1b** (5) and *N*-ribosyl derivatives **1c** (6), and deoxyribosyl derivative **1d** (2) against various bacterial and tumor cell lines. We have previously reported (7) the synthesis of alkyl-, carboxyl-, and halo-substituted oxazinediones for antimalarial screening by reaction of trimethylsilyl azide with the corresponding maleic anhydride. Our continuing interest in the synthesis of substituted oxazinediones motivated us to develop a general synthetic procedure for aryl substituted oxazinediones. In the process we obtained further insight into the relative importance of steric and electronic factors in determining product distributions for these reactions.

Synthesis.

Our synthetic sequence involved initial condensation of commercially available substituted benzaldehydes with diethylmalonate (8a) followed by a Michael type addition of cyanide (8b). Subsequent hydrolysis of the intermediate cyano-esters yielded the corresponding aryl succinic acids **4** in good yield (8b). Selenium dioxide oxidation by the procedure of Hill (9) gave aryl substituted maleic anhydrides **5** in 60-70% yields. Refluxing of the anhydride with a *ca.* 2-4 fold molar excess of trimethylsilyl azide followed by hydrolysis gave isomeric mixtures of 4- and 5-aryloxazinediones **2a-q** in acceptable yields (see Table 1). These compounds were *N*-methylated in good yield by our previously described procedure (7a).

Discussion.

Of major synthetic and mechanistic significance is the observation by pmr and tlc analysis of substantial amounts of the 5-aryl isomers in the product mixtures. In most cases the 4- and 5-isomers could be readily separated by fractional crystallization from ethyl acetate or column chromatography on silica gel. With the exception of the poorly crystallizable 5-*o*-chlorophenyl derivative all 4- and 5-aryloxazinediones obtained were crystalline solids which showed the characteristic decarboxylative decomposition

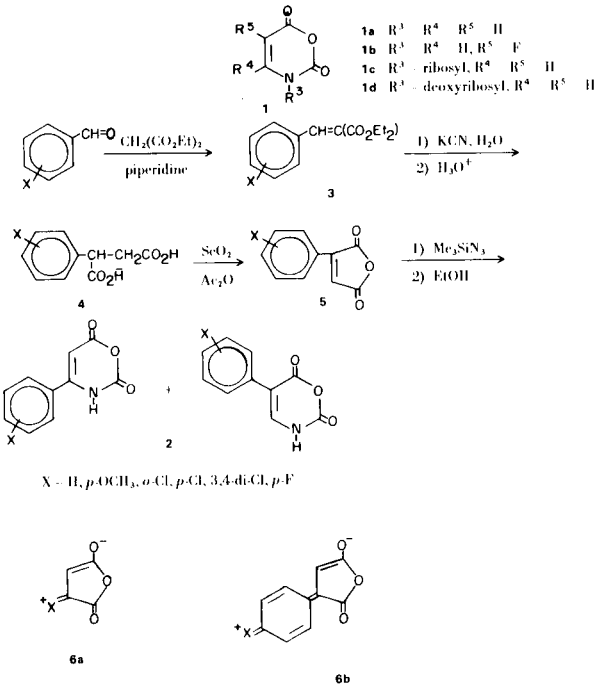


Table I

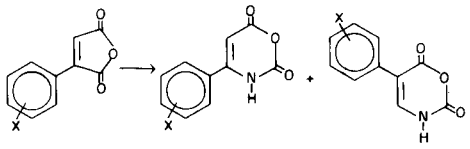
Aryl Substituted 2*H*-1,3-(3*H*)oxazine-2,6-diones, **1**

	R_3	R_4	R_5	Method (a)	% Yield	m.p.	Elemental Analyses Calcd. C	H	N	Cl	Found C	H	N	Cl
2a	H	Ph	H	I	36 (b)	197-199° dec.	63.49	3.73	7.40		63.47	3.65	7.40	
2b	Me	Ph	H	II	47 (c)	120-122° dec.	65.02	4.46	6.89		65.15	4.50	6.85	
2c	H	*p*-Anisyl	H	I	58 (b)	198-200° dec.	60.27	4.14	6.39		60.10	4.08	6.32	
2d	Me	*p*-Anisyl	H	II	63 (c)	158-159° dec.	61.80	4.75	6.01		61.70	4.73	5.91	
2e	Me	H	*p*-Anisyl	II	55 (c)	159-161° dec.	61.80	4.75	6.01		61.74	4.68	5.91	
2f	H	*o*-Cl-Ph	H	I	30 (d)	168-170° dec.	53.71	2.70	6.26	15.85	53.51 (e)	2.59 (e)	6.52 (e)	16.03 (e)
2g	H	H	*o*-Cl-Ph	I	25 (d)	Oil	53.71	2.70	6.26	15.85	(e)	(e)	(e)	(e)
2h	H	*p*-Cl-Ph	H	I	26 (b)	207-209° dec.	53.71	2.70	6.26	15.85	53.89	2.78	6.20	15.74
2i	H	H	*p*-Cl-Ph	I	30 (c)	195-197° dec.	53.71	2.70	6.26	15.85	53.79	2.71	6.26	15.81
2j	Me	*p*-Cl-Ph	H	II	70 (c)	162-164° dec.	55.60	3.39	5.89	14.92	55.52	3.34	5.83	14.85
2k	H	3,4-di-Cl-Ph	H	I	30 (d)	199-201° dec.	46.54	1.95	5.42	27.48	46.40	2.05	5.39	27.42
2l	H	H	3,4-di-Cl-Ph	I	20 (d)	203-205° dec.	46.54	1.95	5.42	27.48	46.48	1.96	5.38	27.43
2m	Me	3,4-di-Cl-Ph	H	II	49 (c)	123-125° dec.	48.55	2.59	5.15	26.06	48.32	2.49	5.09	25.96
2n	Me	H	3,4-di-Cl-Ph	II	75 (c)	183-184° dec.	48.55	2.59	5.15	26.06	48.60	2.55	5.16	25.89
2o	H	*p*-F-Ph	H	I	38 (b)	196-198° dec.	57.98	2.92	6.76	9.17 (f)	58.05	2.91	6.70	9.20 (f)
2p	Me	*p*-F-Ph	H	II	85 (c)	108-110°	59.73	3.65	6.33	8.59 (f)	59.64	3.68	6.17	8.55 (f)
2q	Me	H	*p*-F-Ph	II	66 (c)	155-157° dec.	59.73	3.65	6.33	8.59 (f)	59.69	3.59	6.18	8.65 (f)

(a) I Trimethylsilyl azide/aryl maleic anhydride; II dimethyl sulfate/sodium bicarbonate/acetone. (b) Yield of crude product. (c) Yield of recrystallized product. (d) Yield from pmr analysis of crude product. (e) Mixture *ca.* 67% of 4-isomer, 33% of 5-isomer. (f) %F.

Table II

Isomer Distribution in the Reaction of Substituted Arylmaleic Anhydrides with Trimethylsilyl Azide (a)



X	% 4-Isomer	% 5-Isomer
H	90	10
p-F	80	20
p-Cl	70	30
p-OCH_3	70	30
3,4-Di-Cl	60	40
o-Cl	55	45

(a) Percentages from nmr analyses of crude reaction products.

at their melting points (10). Their pmr and ir spectra were similar to those previously reported (7a). In addition the 5-aryl derivatives showed characteristic blue fluorescence with long wavelength uv irradiation, which aided in tlc identification. The easy isolation of gram quantities of the 5-aryl isomers is a major advantage in the screening of this class of compound for antimalarial or antitumor activity, since in the uracil series materials with the substitution pattern of thymine (isosteric with 5-substituted oxazinediones) show greater biological activity than 6-substituted uracils (isosteric with 4-substituted oxazinediones). Since each isomer can easily be *N*-methylated, four new aryl oxazinediones can be prepared from each arylmaleic anhydride.

N-Methylated aryloxazinediones are of interest since they should be more resistant to hydrolysis under biological conditions than the N-H containing oxazinediones. Work in our laboratory (7b) as well as the work of Skoda *et al.*, (3) have demonstrated the proclivity of the oxazinedione ring to decompose under basic conditions. The replacement of the N-H by the N-CH_3 moiety renders the molecule inaccessible to hydrolysis by a mechanism involving ionization to anion and subsequent ring opening (7b).

In summary our procedure offers nearly unlimited utility for the preparation of aryloxazinediones from any functionalized benzaldehyde.

Orientation of Nitrogen Insertion into the Substituted Maleic Anhydrides.

The previously reported (7a) reactions of methyl- and halomaleic anhydrides with trimethylsilyl azide resulted in almost exclusive production of the more sterically crowded 3-silylated-4-substituted intermediate, with *ca.* 10% of the 5-isomer in the case of bromomaleic anhydride. These results were interpreted as involving electronic factors where the azide attacks the most electropositive carbonyl. A conjugative or hyperconjugative interaction such as **6a** would make the least hindered carbonyl electron deactivated toward nucleophilic attack resulting in azide attack at the carbonyl proximate to substituent, giving 4-substituted products. By contrast, Table II shows the isomer distribution for the reaction of arylmaleic anhydrides with trimethylsilyl azide. The 5-isomer is present in all cases, ranging from a low of 10% for the unsubstituted phenyl to a high of 45% with the *o*-chlorophenyl group. Obviously the greater steric bulk of the phenyl groups in contrast to methyl or halo substituents makes the neighboring carbonyl of the anhydride less accessible to nucleophilic attack of azide. Also it is quite possible that for steric reasons the phenyl groups in the anhydrides are not fully coplanar with the double bond of the anhydride, thus making a resonance interaction such as **6b** (favoring attack to give 4-substituted product) less efficient in deactivating the least hindered carbonyl. These effects are seen most clearly in the *o*-chlorophenyl case, where nearly equal amounts of 4- and 5-substituted oxazinedione are produced. However, the 4-substituted isomer **2f** still predominates, indicating that electronic interactions such as **6b** are operative, although probably to a lessened extent. It is hard to rationalize why arylmaleic anhydrides give more 5-substituted oxazinedione than does the parent phenylmaleic anhydride, particularly when one considers that the sigma constants of *p*-Cl and *p*-OCH_3 substituents are of opposite sign, and speculation on the mechanistic basis of our observation must await relative rate studies, which will be the subject of future communication.

EXPERIMENTAL

General Comments.

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 727 infrared spectrophotometer. Proton magnetic resonance spectra were obtained with Varian A-60A and XL-100-15 spectrometers using an internal tetramethylsilane standard. Elemental analyses were preformed by Galbraith Laboratories, Knoxville, Tennessee. Commercially available benzaldehydes were used in preparing arylsuccinic acids. Arylsuccinic acids were prepared (11) by the procedure of Allen and Johnson (8b). Arylmaleic anhydrides were prepared by the procedure of Hill (9). Trimethylsilyl azide was purchased from Petrarch Systems Inc., Levittown, Pa.

Synthesis of 4- and 5-Aryl-2*H*-1,3-(3*H*)oxazine-2,6-diones.

General Procedure.

The appropriately substituted arylmaleic anhydride was refluxed with a 2-4 fold molar excess of trimethylsilyl azide until approximately the stoichiometric amount of nitrogen had been evolved (generally 2-5 hours). In some instances several ml. of *p*-dioxane were added to aid solubility of the anhydride in the initial stages

of the reaction. For best results reactions should be run using glassware washed with dilute acid and distilled water followed by oven drying and flame drying under nitrogen. At the completion of the reaction the solution is cooled to 0° and a *ca.* 5-fold volume excess of benzene added. Addition of a stoichiometric amount of absolute ethanol caused quantitative precipitation of the aryloxazinedione isomers. The isomers could be separated by column chromatography on silica gel with ethyl acetate eluent or more conveniently by fractional crystallization from ethyl acetate. Generally the 4-isomer crystallized first from this solvent.

4-Phenyl-2*H*-1,3-(3*H*)oxazine-2,6-dione (**2a**).

Phenylmaleic anhydride (9) (4.4 g., 25 mmoles) was refluxed with trimethylsilyl azide (4 ml., ~30 mmoles) and dioxane (5 ml.) for three hours. Standard workup gave 1.7 g. (36%) of isomeric oxazinediones m.p. 187-190° dec. Recrystallization from ethyl acetate gave the pure 4-isomer, m.p. 197-199° dec., (0.8 g., yellow-white microcrystals): ir (mull): 3210 (m), 3170 (m), 3100 (m), 1810 (s), 1710 (vs), 1630 (s), 1500 (s), 1280 (m), 1260 (m), 1120 (m), 1080 (m), 980 (s), 840 (m), 740 (m), 680 (m), cm^{-1}; pmr (DMSO-d_6): δ 11.0 (broad, 1, seen only in integration, N-*H*); 7.30 (m, 5, phenyl), 5.65 (s, 1, C_5-*H*) ppm.

4-(*p*-Anisyl)-2*H*-1,3-(3*H*)oxazine-2,6-dione (**2c**).

p-Anisylmaleic anhydride (9) (7 g., 34 mmoles) was refluxed with trimethylsilyl azide (10 ml., ~75 mmoles) and *p*-dioxane (12 ml.) for three hours. Standard workup gave 4.3 g. (58%) of isomeric oxazinedione, m.p. 165-175° dec. Crystallization from ethyl acetate gave 1.48 g. of **2c**, m.p. 199-201° dec.; ir (deuteriochloroform): 3350 (w), 3120 (w), 2910 (m), 1790 (vs), 1720 (d,s), 1630 (m), 1605 (m), 1560 (m), 1520 (m), 1280 (m), 1250 (m), 1210 (m), 1170 (d,m), 1080 (vs), 1030 (m), 980 (s) cm^{-1}; pmr (DMSO-d_6): δ 11.6 (s, broad, 1, N-*H*), 7.85 (d, 2, J = 9 Hz aromatic), 7.10 (d, 2, J = 9 Hz aromatics), 5.95 (s, 1, C_5-H), 3.90 (s, 3, OC*H*$_3$) ppm.

4-(*o*-Chlorophenyl)-2*H*-1,3-(3*H*)oxazine-2,6-dione (**2f**).

The isomeric 4- and 5-(*o*-chlorophenyl)oxazinediones failed to precipitate when worked up by the standard procedure, therefore the following workup procedure was adopted.

o-Chlorophenylmaleic anhydride (12) (1.7 g., 8 mmoles) was refluxed with 5 ml. (*ca.* 36 mmoles) of trimethylsilyl azide for 2.5 hours. The solution was cooled to 0° and hydrolyzed with 0.4 g. of absolute ethanol. The volatiles were removed under reduced pressure giving *ca.* 1.8 g. of crude brown semisolid. The semisolid was dissolved in 30 ml. of chloroform, extracted four times with 10 ml. saturated sodium bicarbonate portions, four times with 10 ml. distilled water portions, and dried over magnesium sulfate. Removal of the chloroform gave 1.0 g. (55%) of a pasty semisolid which pmr analysis indicated to consist of 55% of the 4-isomer and 45% of the 5-isomer. The semisolid was redissolved in 10 ml. of chloroform, cooled to 0° and hexane added dropwise to a point of permanent trubidity. Cooling resulted in precipitation of 200 mg. of pure 4-isomer, yellow-white crystals, m.p. 168-170° dec.; ir (deuteriochloroform): 3240 (m), 1800 (s), 1730 (vs,d), 1640 (s), 1590 (m), 1350 (m), 1310 (m), 1080 (m), 1050 (m), 1020 (m), 970 (s), 805 (m) cm^{-1}; pmr (deuteriochloroform): δ 9.22 (broad, 1, seen only in integration, N-*H*), 7.50 (m, 4, aromatics), 5.80 (s, 1, C_5-*H*) ppm.

5-(*o*-Chlorophenyl)-2*H*-1,3-(3*H*)oxazine-2,6-dione (**2g**).

The 5-isomer could be obtained as a viscous oil by fractional crystallization of the mother liquors from **2f** above (contaminated with *ca.* 10% of the 4-isomer); ir (deuteriochloroform): 3260 (m), 1800 (vs), 1730 (vs), 1640 (s), 1590 (m), 1280 (m), 1260 (m), 1240 (m), 1205 (m), 1150 (m), 1080 (m), 1020 (m), 970 (s) cm^{-1}; pmr (deuteriochloroform): δ 7.40 (m, 5, aromatics + C_4-*H*), 9.22 (broad, 1, seen only in integration, N-*H*) ppm.

4-(*p*-Chlorophenyl)-2*H*-1,3-(3*H*)oxazine-2,6-dione (**2h**).

p-Chlorophenylmaleic anhydride (12) (3.5 g., 16.8 mmoles) was refluxed with 10 ml. of trimethylsilyl azide (~75 mmoles) and 5 ml. of *p*-dioxane for four hours. Standard workup gave 1.5 g. (37%) of isomeric oxazinedione m.p. 185-190° dec. Crystallization from ethyl acetate gave 810 mg. of pure 4-isomer m.p. 207-209° dec.; ir (mull): 3230 (w), 3160 (w), 3120 (w), 1790 (s), 1710 (s), 1630 (s), 1595 (m), 1560 (m), 1505 (m), 1370 (s), 1270 (m), 1250 (m), 1110 (m), 1090 (m), 1040 (m), 1010 (m), 970 (m), 840 (m), 820 (m), 810 (m), 750 (m), 710 (m) cm^{-1}; pmr (DMSO-d_6): δ 11.0 (s, broad, N-*H*), 7.2 (AB pattern, 4, aromatics), 5.6 (s, 1, C_5-*H*) ppm.

5-(*p*-Chlorophenyl)-2*H*-1,3-(3*H*)oxazine-2,6-dione (**2i**).

The pure 5-isomer could be isolated by careful fractional crystallization of the mother liquors from **2h** above. The yellow-white crystalline solid had m.p. 195-197° dec.; ir (mull): 3280 (m), 3160 (m), 1780 (s), 1710 (s), 1630 (s), 1260 (m), 1160 (m), 1080 (m), 990 (m), 970 (m), 930 (m), 810 (m), 740 (m) cm^{-1}; pmr (DMSO-d_6): δ 10.8 (broad, 1, seen only in integration, N-*H*), 7.65 (s, 1, C_4-H), 7.27 (AB pattern, 4, aromatics) ppm.

4-(3,4-Dichlorophenyl)-2*H*-1,3-(3*H*)oxazine-2,6-dione (**2k**).

3,4-Dichlorophenylmaleic anhydride (13) (7.7 g., 31.7 mmoles) was heated at reflux with trimethylsilyl azide (14 ml., 0.1 mole) and *p*-dioxane (3.5 ml.) for four hours. Standard workup gave 4.1 g. (50%) of isomeric mixture of oxazinediones m.p. 155-165° dec. Crystallization from ethyl acetate gave 1.01 g. of pure 4-isomer, m.p. 199-201° dec.; ir (mull): 3200 (m), 1790 (s), 1710 (s), 1630 (s), 1120 (m), 1100 (m), 1070 (m), 1010 (m), 960 (s), 870 (m), 840 (m), 740 (m), cm^{-1}; pmr (DMSO-d_6): δ 11.0 (broad, 1, N-*H*), 7.60 (s, 1, aromatic), 7.33 (s, 2, aromatic), 5.75 (s, 1, C_5-*H*) ppm.

5-(3,4-Dichlorophenyl)-2*H*-1,3-(3*H*)oxazine-2,6-dione (**2l**).

Careful fractional crystallization of the mother liquor from **2k** above gave 640 mg. of pure 5-isomer, m.p. 203-205° dec.; ir (mull): 3260 (w), 3180 (w), 1780 (s), 1720 (s), 1630 (s), 1340 (s), 1280 (m), 1240 (m), 1150 (m), 1120 (w), 1040 (w), 1010 (m), 990 (m), 980 (m), 950 (m), 920 (w), 870 (m), 820 (m), 740 (s), 660 (s) cm^{-1}; pmr (DMSO-d_6): δ 10.0 (broad, 1, N-*H*), 7.56 (s, 1, C_4-*H*), 7.40 (t, 1, J = 1 Hz, aromatic), 7.15 (d, 2, J = 1 Hz, aromatic) ppm.

p-Fluorophenylmaleic Anhydride (**7**).

This compound, previously unreported, was prepared by the method of Hill (9).

p-Fluorophenylsuccinic acid (14) (3.3 g., 15.6 mmoles) was refluxed with selenium dioxide (1.9 g., 17 mmoles) in acetic anhydride (40 ml.) for 24 hours. The precipitated selenium was removed by filtration through a sintered glass funnel and the filtrate concentrated under reduced pressure yielding a brown solid. The solid was washed with copious volumes of ether and hexane yielding 1.8 g. (60%) of tan crystalline solid, m.p. 112-114°; ir (deuteriochloroform): 3140 (w), 1860 (m), 1840 (m), 1810 (m), 1770 (vs), 1620 (m), 1600 (s), 1505 (s), 1415 (w), 1310 (w), 1300 (m), 1290 (w), 1225 (vs), 1160 (s), 1090 (m), 1050 (m), 1005 (w), 830 (s), 800 (m) cm^{-1}; pmr (DMSO-d_6): δ 8.1 (d of d, 2, H_o, J_{om} = 10 Hz, J_{oF} = 5 Hz), 7.55 (s, 1, Hα), 7.26 (t, 2, H_m, J_{om} = J_{mF} = 10 Hz) ppm.

4-(*p*-Fluorophenyl-2*H*-1,3-(3*H*)oxazine-2,6-dione (**2o**).

p-Fluorophenylmaleic anhydride (**7**) (1.7 g., 8.9 mmoles) was refluxed with trimethylsilyl azide (5 ml., ~36 mmoles) and several drops of *p*-dioxane for two hours. Standard workup gave 850 mg. (47%) of isomeric oxazinediones, m.p. 170-180° dec. Crystallization from ethyl acetate gave 535 mg. of pure 4-isomer, m.p. 196-198° dec.; ir (mull): 3210 (m), 3170 (m), 1780 (s), 1725 (s), 1705 (s), 1625 (s), 1580 (m), 1300 (m), 1220 (m), 1160 (m), 1080 (m), 1030 (w), 975 (m), 840 (m), 820 (m), 760 (m) cm^{-1}; pmr (acetone-d_6): δ 10.0 (broad, 1, seen only in integration, N-*H*), 7.84 (d of d, H_o, 2, J_{om} = 10 Hz, J_{oF} = 5 Hz), 7.28 (t, 2, H_m, J_{om} = J_{mF} = 10 Hz), 5.84 (s, 1, C_5-*H*) ppm.

N-Methylated Products.

These compounds were synthesized by our previously described procedure (**7a**). Standard workup involves removal of sodium bicarbonate by filtration, concentration of the filtrate and trituration of the residue with hot ethyl acetate. Cooling affords the *N*-methylated products.

3-Methyl-4-phenyl-2*H*-1,3-(3*H*)oxazine-2,6-dione (**2b**).

Compound **2a** (0.8 g., 4 mmoles) was refluxed with dimethylsulfate (1.9 g., 9 mmoles) and sodium bicarbonate (0.6 g., 7 mmoles) for 23 hours in acetone (15 ml.). Standard workup gave 0.4 g. (47%) of **2b**, m.p. 120-122° dec.; ir (deuteriochloroform): 3120 (w), 3070 (w), 2970 (w), 1790 (s), 1720 (s), 1630 (s), 1600 (m), 1440 (m), 1410 (s), 1320 (s), 1210 (m), 1090 (m), 1010 (m), 960 (m), 805 (m) cm^{-1}; pmr (DMSO-d_6): δ 7.3 (s, 5, aromatics), 5.28 (s, 1, C_5-*H*), 3.10 (s, 3, N-CH_3) ppm.

3-Methyl-4-*p*-anisyl-2*H*-1,3-(3*H*)oxazine-2,6-dione (**2d**).

Compound **2c** (1.0 g., 4.6 mmoles) was refluxed with dimethylsulfate (1.8 g., 14 mmoles) and sodium bicarbonate (1.0 g., 12 mmoles) in acetone (20 ml.) for 24 hours. Standard workup gave 670 mg. (63%) of **2d**, m.p. 158-159° dec.; ir (deuteriochloroform): 3030 (w), 2990 (w), 2950 (w), 2930 (w), 1780 (vs), 1720 (vs), 1620 (s), 1610 (s), 1570 (m), 1520 (s), 1435 (s), 1320 (s), 1300 (s), 1250 (s), 1210 (m), 1170 (s), 1090 (m), 1070 (m), 1020 (m), 1005 (m), 970 (m), 830 (s) cm^{-1}; pmr (DMSO-d_6): δ 7.45 (d, 2, J = 9 Hz, aromatics), 7.05 (d, 2, J = 9 Hz, aromatics), 5.55 (s, 1, C_5-*H*), 3.80 (s, 3, OCH_3), 3.10 (s, 3, N-CH_3) ppm.

3-Methyl-5-*p*-anisyl-2*H*-1,3-(3*H*)oxazine-2,6-dione (**2e**).

An isomeric 1:1 mixture of **2c** and the corresponding 5-isomer (1.83 g., 8.36 mmoles) was refluxed with dimethylsulfate (4.0 g., 32 mmoles) and sodium bicarbonate (2.0 g., 24 mmoles) in acetone (35 ml.) for 24 hours. Standard workup resulted in preferential crystallization of **2e**, 470 mg., m.p. 159-161° dec. Further product was obtained by column chromatography (silica gel, 1:1 chloroform/ethyl acetate resulting in a total yield of 545 mg. (~55%); ir (deuteriochloroform): 3020 (w), 2990 (w), 2910 (w), 2850 (w), 1790 (s), 1730 (s), 1640 (s), 1610 (m), 1515 (m), 1330 (s), 1290 (m), 1250 (s), 1230 (m), 1180 (m), 1150 (m), 1080 (s), 1030 (m), 1010 (m), 975 (m), 820 (s) cm^{-1}; pmr (DMSO-d_6): δ 8.0 (s, 1, C_4-*H*), 7.50 (d, 2, J = 9 Hz, aromatics), 6.95 (d, 2, J = 9 Hz, aromatics), 3.80 (s, 3, OCH_3), 3.40 (s, 3, N-CH_3) ppm.

3-Methyl-4-(*p*-Chlorophenyl)-2*H*-1,3-(3*H*)oxazine-2,6-dione (**2j**).

Compound **2h** (760 mg., 3.4 mmoles) was refluxed with dimethylsulfate (700 mg., 5.6 mmoles) and sodium bicarbonate (340 mg., 4 mmoles) in acetone (20 ml.) for 42 hours. Standard workup gave 565 mg. of **2j** (70%), m.p. 163-165° dec.; ir (deuteriochloroform): 3120 (w), 1790 (vs), 1730 (vs), 1625 (s), 1595 (m), 1495 (s), 1430 (s), 1405 (s), 1320 (s), 1210 (m), 1180 (m), 1080 (s), 1060 (m), 1020 (m), 1005 (s), 960 (m), 820 (s), 805 (s) cm^{-1}; pmr (deuteriochloroform): δ 7.40 (AB pattern, 4, aromatics), 5.56 (s, 1, C_5-*H*), 3.33 (s, 3, N-CH_3) ppm.

3-Methyl-4-(3,4-dichlorophenyl)-2*H*-1,3-(3*H*)oxazine-2,6-dione (**2m**).

Compound **2k** (1.0 g., 3.9 mmoles) was refluxed with dimethylsulfate (1.4 g., 11 mmoles), and sodium bicarbonate (1.0 g., 12 mmoles) in acetone (15 ml.) for 48 hours. Standard workup gave 525 mg. (49%) of **2m**, m.p. 123-125° dec.; ir (deuteriochloroform): 3120 (w), 1790 (s), 1730 (vs), 1630 (m), 1590 (w), 1440 (m), 1400 (m), 1320 (m), 1300 (w), 1250 (s), 1220 (m), 1140 (m), 1090 (m), 1070 (m), 1040 (s), 980 (m), 820 (m) cm^{-1}; pmr (acetone-d_6): δ 7.8 (d, 1, J = 2 Hz, H_o), 7.72 (d, 1, J = 9 Hz, H_m) 7.54 (d of d, 1, J_1 = 9 Hz, J_2 = 2 Hz, H_o), 5.80 (s, 1, C_5-*H*), 3.20 (s, 3, N-CH_3) ppm.

3-Methyl-5-(3,4-dichlorophenyl)-2*H*-1,3-(3*H*)oxazine-2,6-dione (**2n**).

An isomeric mixture of *ca.* 60% of **2l** and 40% of **2k** (3.0 g., 16.3 mmoles) was refluxed with dimethyl sulfate (3.0 g., 23.8 mmoles) and sodium bicarbonate (2.5 g., 29.8 mmoles) in acetone (60 ml.) for eight hours. Standard workup resulted in preferential crystallization of **2n**, 1.41 g. (~75%), m.p. 183-184° dec.; ir (deuteriochloroform): 2990 (w), 1790 (s), 1730 (s), 1640 (s), 1600 (w), 1560 (w), 1450 (s), 1320 (m), 1180 (m), 1120 (m), 1090 (s), 1020 (m), 970 (m) cm^{-1}; pmr (acetone-d_6): δ 8.1 (s, 1, C_4-H), 7.8 (d of d, 1, J_1 = 8 Hz, J_2 = 2 Hz, H_o), 7.55 (m, 2, H_o + H_m), 3.44 (s, 3, N-CH_3) ppm.

3-Methyl-4-(*p*-fluorophenyl)-2*H*-1,3-(3*H*)oxazine-2,6-dione (**2p**).

Compound **2o** (1.2 g., 5.8 mmoles) was refluxed with dimethylsulfate (1.1 g., 8.7 mmoles) and sodium bicarbonate (1.2 g., 14 mmoles) in acetone (30 ml.) for 18 hours. Standard workup gave a yellow semisolid which was taken up in the minimum of ethyl acetate (~5 ml.). Addition of *n*-hexane to the solution to a point of permanent turbidity and cooling resulted in precipitation of 1.09 g. (85%) of **2p**, white crystals, m.p. 108-110°; ir (deuteriochloroform): 3120 (w), 1785 (s), 1720 (s), 1625 (s), 1605 (m), 1510 (s), 1430 (s), 1380 (s), 1240 (s), 1220 (m), 1205 (m), 1155 (s), 1090 (m), 1065 (m), 1010 (m), 1005 (m), 960 (m), 830 (s), 805 (s) cm^{-1}; pmr (deuteriochloroform): δ 7.38 (4, AB pattern, aromatics), 5.68 (s, 1, C_5-*H*), 3.28 (s, 3, N-CH_3) ppm.

3-Methyl-5-(*p*-fluorophenyl)-2*H*-1,3-(3*H*)oxazine-2,6-dione (**2q**).

An isomeric mixture of **2o** and the corresponding 5-isomer (~1:1 molar ratio, 3.3 g., 16 mmoles) was refluxed with dimethylsulfate (3.0 g., 24 mmoles) and sodium bicarbonate (2.7 g., 32 mmoles) for 18 hours in acetone (75 ml.). Standard workup resulted in preferential crystallization of **2q**, yellow-white microcrystals (1.02 g., ~66%), m.p. 155-157° dec.; ir (deuteriochloroform): 3110 (w), 1790 (s), 1730 (s), 1640 (s), 1605 (m), 1520 (s), 1430 (d,m), 1360 (m), 1330 (s), 1300 (m), 1230 (s), 1160 (s), 1080 (s), 1005 (m), 980 (s), 830 (s) cm^{-1}; pmr (DMSO-d_6): δ 8.05 (s, 1, C_4-*H*), 7.55 (d of d with long range splitting, 2, H_o, J_{om} = 9 Hz, J_{oF} = 5.5 Hz), 7.10 (t, with long range splitting, H_m, J_{om} = J_{mF} = 9 Hz), 3.40 (s, 3, N-CH_3) ppm.

REFERENCES

This research was supported by Contract No. DAMD 17-74-C-4100 from the U.S. Army Medical Research and Development Command. This is Contribution No. 1381 to the Army Research Program on Malaria.

(1) S. S. Washburne, W. R. Peterson and D. A. Berman, *J. Org. Chem.*, **37**, 1738 (1972).

(2) M. Bobek and A. Bloch, *Tetrahedron Letters*, 3493 (1973).

(3) J. Škoda, I. Votruba, and J. Farkaš, *Collect, Czech. Chem. Commun.*, **39**, 1500 (1974).

(4) J. Škoda, Z. Flegelova, and J. Farkaš, *Biochem. Biophys. Res. Commun.*, **50**, 80 (1973).

(5) M. Bobek and A. Bloch, Abstracts, 168th National Meeting of the American Chemical Society, Atlantic City, N.J., Sept. 1974, Med. #65.

(6) T. H. Chwang and C. Heidelberger, *Tetrahedron Letters*, 95 (1974).

(7a) J. D. Warren, J. H. MacMillan and S. S. Washburne, *J. Org. Chem.*, **40**, 743 (1975); (b) S. S. Washburne and K. K. Park, in the press.

(8a) C. F. H. Allen and F. W. Spangler, *Org. Syn. Coll. Vol.*, **3**, 377 (1955); (b) C. F. H. Allen and H. B. Johnson, *Org. Syn. Coll. Vol.*, **4**, 804 (1963).

(9) R. K. Hill, *J. Org. Chem.*, **26**, 4745 (1961).

(10) H. R. Kricheldorf, *Makromol. Chem.*, **173**, 13 (1973).

(11) We wish to thank Mr. Mark Lenhart and Miss Alice Maragliano for assistance with the synthesis of aryl succinic acids.

(12) M. Artico and V. Nacci, *Farmaco Ed. Sci.*, **20**, 523 (1965), *Chem. Abstr.*, **63**, 8247e (1965).

(13) C. Farbwerke, German Patent 870,106; *Chem. Abstr.*, **50**, 16864c (1956).

(14) U. Tadeusz and J. Lange, *Rocz. Chem.*, **33**, 197 (1959); *Chem. Abstr.*, **53**, 10749d (1959).