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References and Notes

(1) L. A. Mitscher, H. E. Gracey, G. W. Clark III, and T. Suzuki, *J. Med. Chem.*, 21, 485 (1978).
(2) D. Kaminsky and R. I. Meltzer, *J. Med. Chem.*, 11, 160 (1968).
(3) A. Sugino, C. L. Peebles, K. N. Kreuzer, and N. R. Cozzarelli, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 4767 (1977).
(4) M. Gellert, K. Mizuuchi, M. O'Dea, T. Itoh, and J. Tomizawa, *Proc. Natl. Acad. Sci., U.S.A.*, **74**, 4772 (1977).
(5) G. C. Crumplin and J. T. Smith, *Nature (London)*, **260**, 643 (1976).
(6) D. Pisetsky, I. Berkower, R. Wickner, and J. Hurwitz, *J. Mol. Biol.*, **71**, 557 (1972).
(7) Y. Sakakibara and J. Tomizawa, *Proc. Natl. Acad. Sci. U.S.A.*, **71**, 802 (1974).
(8) W. L. Staudenbauer, *Mol. Gen. Genet.*, **145**, 273 (1976).
(9) I. Itoh and J. Tomizawa, *Nature (London)*, **270**, 78 (1977).
(10) K. J. Marians, J. Ikeda, S. Schlagman, and J. Hurwitz, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 1965 (1977).
(11) P. K. Schneck, W. L. Staudenbauer, and P. H. Hofschneider, *Eur. J. Biochem.*, **38**, 130 (1973).
(12) K. Mizuuchi and H. Nash, *Proc. Natl. Acad. Sci. U.S.A.*, **73**, 3524 (1976).
(13) C. L. Smith, M. Kubo, and F. Imamoto, *Nature (London)*, **275**, 420 (1978).
(14) P. L. Chen and C. C. Cheng, *J. Med. Chem.*, **13**, 867 (1970).
(15) The method used was essentially that of E. C. Wagner and M. F. Fegley, in "Organic Syntheses", Collect. Vol. 3, Wiley, New York, 1955, p 488.
(16) B. R. Pai, S. Prabhakar, P. S. Santhanam, M. Seetha, and V. Sudarsanam, *Ind. J. Chem.*, **2**, 449 (1964).
(17) W. H. Perkin, Jr., and V. M. Trikojus, *J. Chem. Soc.*, **129**, 2925 (1926).
(18) S. Minami, T. Shono, and J. Matsumoto, *Chem. Pharm. Bull.*, **19**, 1482 (1971).
(19) H. Agui, T. Mitani, M. Nakashita, T. Nakagome, T. Komatsu, A. Izawa, and Y. Eda, Japanese Patent 97879 (1973); *Chem. Abstr.*, **80**, 82714 (1974).
(20) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, 1967, p 1158.

Dibenzotropone- and Dibenzosuberonecarboxylic Acids with Bronchodilator Activity[1]

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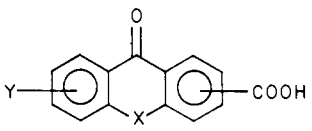
The syntheses of 44 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one derivatives bearing a carboxyl group at the 1, 2, 3, or 10 position and various substituents at the 7, 8, or 9 position are described. Some of the compounds showed significant bronchodilator activity in guinea pigs and protected the animals against a histamine challenge administered either by aerosol or intravenously. The most active compounds were 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one-2-carboxylic acids bearing a methyl or halogen substituent at the 9 position. These compounds were approximately as active as aminophylline by intraperitoneal administration.

Recent studies in these laboratories[2,3] have shown that a number of xanthonecarboxylic acids (**1a**) show useful



1a, X = O
b, X = CH=CH
c, X = CH_2CH_2

antiallergic activity. 7-(Methylsulfinyl)xanthone-2-carboxylic acid (tixanox, USAN) has been shown to be orally active against exercise-induced asthma in man.[4] Compounds **1a** show activity in the rat passive cutaneous anaphylaxis (PCA) assay.[5] We have synthesized a number of tricyclic carboxylic acids, including the dibenzotropone and dibenzosuberone derivatives **1b** and **1c**. Many of these compounds showed significant bronchodilator activity, potentially useful for the treatment of asthma and related diseases.

Chemistry. The compounds were synthesized by five basic routes, with a number of variations, shown in the accompanying schemes. The first reaction in Schemes I, a and b, and II is the same; the routes differ in the stage at which separation of the isomeric products was accomplished. The first reaction is the condensation, catalyzed by potassium acetate, of a substituted phenylacetic acid and trimellitic anhydride **2a**. The analogous condensation between phenylacetic acid and phthalic anhydride to give benzylidine phthalide (**3**, X = R = H) was first reported by Gabriel.[6] The reaction proceeds satisfactorily with trimellitic anhydride; however, approximately equal amounts of the two phthalides **3a** and **3b** are produced. Separation of these products was accomplished by fractional crystallization (Scheme Ia) or, when this was not possible, the mixture was reduced to the diphenylethanes **4a** and **4b**, which were then separated by crystallization (Scheme Ib). The products from condensation with *p*-methoxyphenylacetic acid were not separable either at the stage of the phthalides **3** or the reduction products **4**. In this case, partial reduction followed by base-catalyzed elimination gave the *trans*-stilbenes **7a** and **7b**, which were separable by crystallization (Scheme Ic) (phosphorus/hydroiodic acid reduction of the methoxyphthalides **3**, X = OCH_3, gave products of partial reduction and demethylation). The final reduction products **4** were cyclized to the corresponding 10,11-dihydrodibenzo[*a*,*d*]cycloheptenonecarboxylic acids **5**, using polyphosphoric acid in most cases. The relative orientation of the carboxyl groups in the reduction products **4** was determined from their NMR spectra. The meta dicarboxylic acids **4b** showed a 1-proton doublet ($J \approx 2$ Hz) at low field (ca. 8.40 ppm, dimethyl-d_6 sulfoxide) due to the 2 hydrogen, deshielded by two ortho carboxyl groups. The 1,4-diacids **4a**, on the other hand, showed a broad 3-proton singlet at ca. 7.82 ppm, due to the 2, 3, and 5 hydrogens, each of which is ortho to a carboxyl group.

In order to avoid the separations necessary for Scheme Ia–c, some specific routes to the desired tricyclic compounds were developed. The first (Scheme II) involved base-catalyzed condensation of phthalide-6-carboxylic acid (**8a**) or its methyl ester **8b** with a substituted benzaldehyde.

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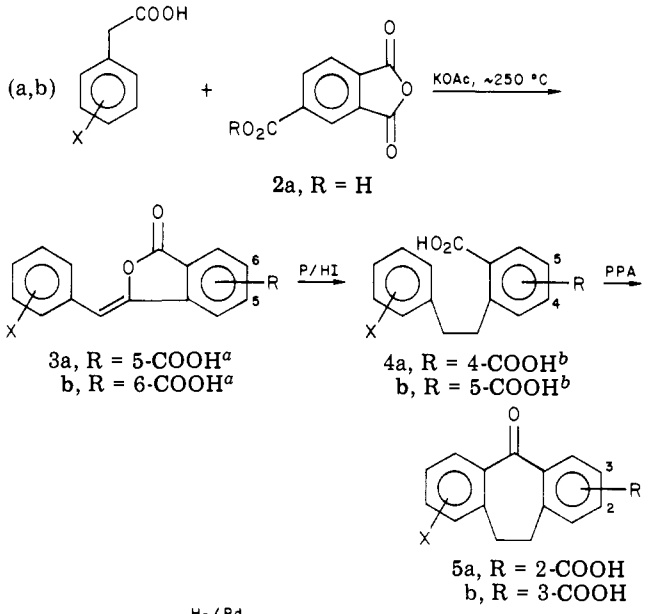
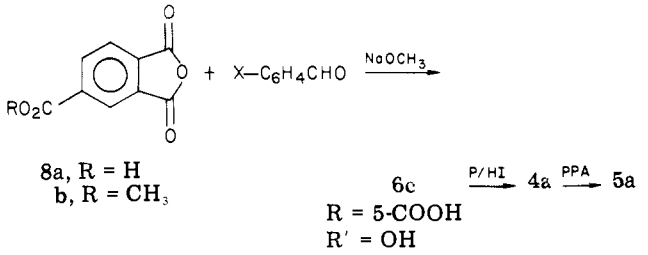
Scheme I



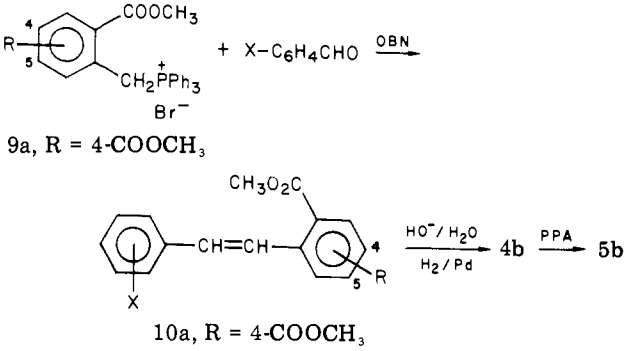
[a] Scheme Ia, separated by crystallization. [b] Scheme Ib, separated by crystallization. [c] Scheme Ic, separated by crystallization.

Scheme II

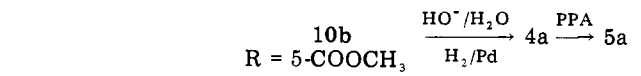


The analogous reaction between unsubstituted phthalide and benzaldehyde has been reported previously.[7] In the present case, the reaction proceeded satisfactorily to give the hydroxy products **6c**, which were reduced with phosphorus/hydroiodic acid to the substituted diacids **4a**. The condensation, however, proceeded in good yield only with benzaldehydes bearing an electron-withdrawing substituent. More general syntheses were then developed using the isomeric phosphonium salts **9a** and **9b** (Schemes III and IV). The double bond was introduced into the 10,11 position by bromination/dehydrobromination (Scheme V), and cyano and chloro substituents were in some cases introduced by displacement of the corresponding bromo substituent (Scheme VI). The tricyclic compounds synthesized by the above methods, with yields, melting points, and crystallization solvents, are shown in Table I. The diacids **4** are shown in Table III and the benzylidene phthalides **3** in Table IV.

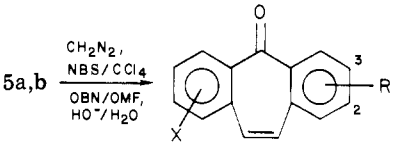
Scheme III



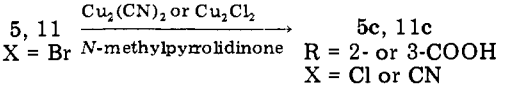
Scheme IV



Scheme V



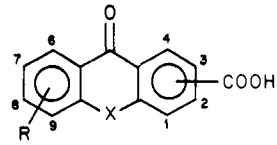
Scheme VI



Biological Results. The compounds were tested for their ability to reduce or abolish bronchoconstriction caused by aerosol administration of histamine to guinea pigs. Some of the compounds were also evaluated for their ability to directly relax guinea pig tracheal smooth muscle in vitro. The results are shown in Table I. In addition, a number of compounds were assayed for their ability to reduce or abolish the increase in pulmonary resistance caused by intravenous administration of histamine to guinea pigs. The results are shown in Table II. The methods are described under the Experimental Section.

Of the unsubstituted acids, only the 10,11-dihydro-2-carboxylic acid **12** and the unsaturated 3-carboxylic acid **47** showed good activity in the histamine aerosol assay. The remaining 2- and 3-carboxylic acids **29** and **33** and the 1- and 10-carboxylic acids **53–55** were inactive in vivo as bronchodilators, though **33** was active in the tracheal chain assay. The introduction of substituents into various positions of the 2- and 3-carboxylic acids resulted in marked changes in activity. There is no apparent correlation between physiochemical parameters of the substituent groups and biological activity of the compounds taken as a whole. However, for some subgroups of compounds, for example, 7-substituted 10,11-dihydro-3-carboxylic acids, it appears that medium-sized[13] substituents, such as OCH_3, Br, and $COCH_3$, are more consistent with high activity than are either large (*i*-Pr and *O*-*i*-Pr) or small (H, OH, CN, and Cl) substituents. Thus,

Table I. Physical and Biological Data



compd	position of COOH	R	X	mp, °C	% yield[b]	anal.[c]	meth of synth	% protection,[d] histamine aerosol	tracheal chain X aminophylline
12	2	H	$(CH_2)_2$	203-204[e]	42	C, H	Ia	62.5	inact[g]
13	2	7-CH_3	$(CH_2)_2$	235[h]	72	C, H	IV	62.5	
14	2	7-OCH_3	$(CH_2)_2$	196-198[i]	48	C, H	Ic	50	
15	2	7-Br	$(CH_2)_2$	252-254[j]	61	C, H	Ia	50	7[k]
16	2	7-Cl	$(CH_2)_2$	255-256[j]	75	C, H	VI	0	
17	2	7-*i*-Pr	$(CH_2)_2$	178-182[e]	47	C,[l] H	Ia	62.5	10[m]
18	2	7-*O*-*i*-Pr	$(CH_2)_2$	174-177[j]	78	C, H	*n*	50	
19	2	7-$COCH_3$	$(CH_2)_2$	201-203[p]	*n*	C, H	*n*	25	
20	2	8-CH_3	$(CH_2)_2$	196-197[h]	72	C, H	IV	12.5	
21	2	8-OCH_3	$(CH_2)_2$	220-222[h]	74	C, H	IV	37.5	
22	2	8-Br	$(CH_2)_2$	213-215[j]	30	C, H	Ib	25	
23	2	9-CH_3	$(CH_2)_2$	232-234[q]	70	C, H	IV	87.5	
24	2	9-Cl	$(CH_2)_2$	258-260[j]	55	C, H	VI	75	
25	2	9-Br	$(CH_2)_2$	260-262[j]	63	C, H	Ib	75[r]	
26	2	9-*i*-Pr	$(CH_2)_2$	230-231[s]	61	C, H	II	25	
27	2	9-F	$(CH_2)_2$	243-245[j]	48	C,[l] H	II	75	
28	2	7,9-Cl_2	$(CH_2)_2$	254-255[j]	32[t]	C, H	II	50	
29	2	H	CH=CH	261-262[j]	60[u]	C, H	V	0	
30	2	9-Br	CH=CH	358 dec[j]	71[u]	C, H	V	25	
31	2	9-F	CH=CH	340 dec[j]	57[u]	C, H	V	25	
32	2	7,9-Cl_2	CH=CH	338-340[j]	71[u]	C, H	V	0	
33	3	H	$(CH_2)_2$	218-219[j]	40	C, H	Ib	0	7[v]
34	3	7-CN	$(CH_2)_2$	293-296[j]	64	C, H, N	VI	0	5[v]
35	3	7-Cl	$(CH_2)_2$	265-266[j]	55	C,[l] H	VI	25	25[w]
36	3	7-$COCH_3$	$(CH_2)_2$	243-245[j]	*n*	C, H	*n*	62.5	<1[v]
37	3	7-*O*-*i*-Pr	$(CH_2)_2$	213-216[j]	*n*	C, H	*n*	0[x]	0.5[v]
38	3	7-*i*-Pr	$(CH_2)_2$	206-208[e]	64	C, H	Ia	25	5[k]
39	3	7-OCH_3	$(CH_2)_2$	196-198[p]	58	C, H	Ic	50	
40	3	7-Br	$(CH_2)_2$	282-283[j]	79	C,[l] H	Ib	62.5	~10[y]
41	3	8-CN	$(CH_2)_2$	286-287[j]	63	C, H	VI	12.5	
42	3	8-Cl	$(CH_2)_2$	239-240[j]	78	C, H	VI	25	
43	3	8-Br	$(CH_2)_2$	238-239[j]	79	C, H	Ia	0	
44	3	9-Br	$(CH_2)_2$	263-264[j]	72	C, H	Ia	0	
45	3	7,9-$(CH_3)_2$	$(CH_2)_2$	273-275[j]	68	C, H	III	37.5	
46	3	7-OH	$(CH_2)_2$	232-234[h]	78	C, H	*n*	12.5	
47	3	H	CH=CH	262-270[s]	61[u]	C, H	VI	62.5	
48	3	7-Br	CH=CH	374-377[j]	73[u]	C, H	V	12.5	
49	3	7-$COCH_3$	CH=CH	340-345[j]	*n*	C, H	*n*	37.5	
50	3	7-COOH	CH=CH	>400[j]	*n*	C, H	*n*	25	
51	3	7-*O*-*i*-Pr	CH=CH	233-234[j]	75[u]	C, H	V	62.5	
52	3	7-Cl	CH=CH	224-226[j]	64[u]	C, H	II	0	
53	1	H	$(CH_2)_2$	189-190[q]	32	C, H	II	0	
54	1	H	CH=CH	286-287[j]	71[u]	C, H	VI	12.5	
55	10	H	CH=C				*z*	0	
aminophylline (100 mg/kg, ip)								75	
aminophylline (75 mg/kg, ip)								50	
aminophylline (50 mg/kg, ip)								25	

[a] Uncorrected. [b] Yield of last step, recrystallized. [c] Microanalysis plus or minus 0.4% unless indicated. [d] 100 × (number of animals protected)/(total number of animals), at 100 mg/kg, ip. The mean collapse time plus or minus SD for 66 randomly tested guinea pigs exposed to 0.04% aqueous histamine aerosol was 129.4 ± 47.4 s. Chi square analysis with Yates correction using 66 control animals indicates that protection of two or more drug-treated animals for the 5-min exposure time is significant with $p < 0.01$. [e] Aqueous HOAc. [f] 125 mg/kg, ip. [g] 4-Aminophylline measurements at 5 μg/mL; test compound at 0.5 and 5 μg/mL. [h] Aqueous EtOH. [i] EtOH. [j] Aqueous DMF. [k] 3-Aminophylline measurements at 5 μg/mL; test compound at 0.5 and 5 μg/mL. [l] 17: calcd, 77.53; found, 77.97. 27: calcd, 71.11; found, 71.91. 35: calcd, 67.02; found, 66.51. 40: calcd, 58.01; found, 58.49. [m] Aminophylline at 1.25, 2.5, and 5 μg/mL; test compound at 0.125, 0.25, and 0.5 μg/mL. [n] See Experimental Section. [p] HOAc. [q] MeOH. [r] 90 mg/kg, ip. [s] C_6H_6–EtOH. [t] Cyclization was performed using phosphorus pentoxide in nitrobenzene; see ref 8. [u] Overall yield from the corresponding 10,11-dihydrocarboxylic acid. [v] 2-Aminophylline measurements at 5 μg/mL; test compound at 0.05 and 0.5 μg/mL. [w] 7-Aminophylline measurements at 2.5–10 μg/mL; test compound at 0.005–5 μg/mL. [x] 50 mg/kg, ip. [y] 4-Aminophylline measurements at 5 μg/mL; test compound at 0.05 and 0.5 μg/mL. [z] See ref 9.

a fit of the molecule to a receptor site, rather than, for example, rate of transport, may be the critical step in determining the activity of these compounds in the aerosol test. The histamine aerosol activity of the unsaturated 7-substituted 2-carboxylic acids showed no obvious correlations with either molar refractivity or lipophilicity (π value[13]). 10,11-Dihydro-2-carboxylic acids bearing a halogen or a methyl group in the 9 position were among the most active compounds in the aerosol assay; the compound bearing the larger isopropyl group was considerably less active. The compounds which were tested in the intravenous histamine challenge assay (Table II)

Table II. Intravenous Histamine Challenge Assay

no.	dose, mg/kg, iv	no. of animals	mean % inhibn of histamine response (range)
12	12.5	1	0
	25	3	11 (0-34)
14	12.5	3	13 (0-29)
	25	2	68 (56-80)
16	6.25	2	0
	12.5	1	24
	25	1	*a*
20	12.5	2	0
	25	2	*a*
21	25	2	20 (0-40)
23	3.175	1	0
	6.25	1	0
	12.5	3	0
	25	2	0
24	12.5	2	76 (60-91)
	25	1	*a*
25	6.25	2	0
	12.5	2	46 (41-50)
	25	1	77
28	12.5	2	53 (31-75)
	25	2	*a*
31	12.5	4	22 (0-88)
	25	7	43 (0-75)
40	12.5	1	0
	25	2	61 (39-83)

[a] Animal(s) showed signs of severe airway constriction after dosing at this level. No histamine was given to animals showing these signs.

showed only moderate activity which did not correlate well with the histamine aerosol data (cf. **23–25**).

A number of compounds were shown to possess significant activity in directly relaxing tracheal smooth muscle (see Table I). Such studies indicate that the agents are true bronchodilator substances. It is unlikely that they act as histamine antagonists at specific receptor sites.

The most active compounds in the histamine aerosol assay, **23–25**, show bronchodilating activity in vivo comparable to that of aminophylline. The appearance of such activity in tricyclic arylcarboxylic acids has not previously been reported. In vitro, several compounds, e.g., **17**, **37**, and **40**, are many times as active as aminophylline. One reasonable explanation of the differences between in vivo and in vitro results is the occurrence, in vivo, of nonspecific binding of these agents to plasma proteins. Acidic compounds, especially carboxylic acids, bind tenaciously and may therefore show much greater activity in vitro than in vivo. Compounds **24** and **26** were also tested by oral administration at 200 and 90 mg/kg, respectively, but did not show significant activity.

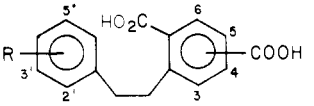
Experimental Section

Melting points are uncorrected. NMR spectra were obtained at 100 MHz in Me_2SO-d_6.

Condensation of Phenylacetic Acids and Trimellitic Anhydride. Benzene-1,2,4-tricarboxylic anhydride (19.2 g, 0.01 mol), 4-isopropylphenylacetic acid (16.2 g, 0.09 mol), and KOAc (0.15 g, 0.0015 mol) were mixed together and heated to 255–265 °C, using an air bath, for 9 h. A thermometer was immersed in the molten mixture, which was stirred mechanically. The mixture was cooled, the reaction flask was broken, and the pulverized product was extracted in a Soxhlet apparatus with EtOH (700 mL). The solution was cooled; filtration then afforded **(4-isopropylbenzylidene)phthalide-5-carboxylic acid (79)**: yield 4.7 g (17%); mp 285–290 °C dec. Anal. ($C_{19}H_{16}O_4$) C, H. The filtrate was heated, diluted with water, and then cooled to afford impure **(4-isopropylbenzylidene)phthalide-6-carboxylic acid (80)**. Two recrystallizations from aqueous EtOH gave pure **80**: yield 9.2 g (34%); mp 259–262 °C. Anal. ($C_{19}H_{16}O_4$) C, H. The other benzylidenephthalides were prepared similarly (see Table IV).

Phosphorus/Hydroiodic Acid Reduction. The enol lactone **79** (2.3 g, 0.0075 mol), 57% aqueous HI (7 mL), HOAc (10 mL), and red phosphorus (1.0 g) were refluxed for 5 days. The solution was diluted with water and filtered. The residue was shaken with MeOH, and the solution was filtered and diluted with water to

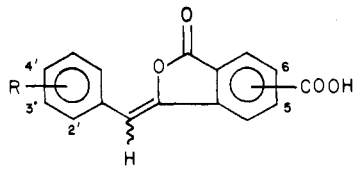
Table III. 1,2-Diphenylethanedicarboxylic Acids



no.	position of COOH	R	mp,[a] °C	% yield[b]	anal.[c]	method of synth
56	4	H	290 dec[d]	45	C, H	Ia
57	4	4'-CH_3	272–273[d]	83[e]	C, H	IV
58	4	4'-OCH_3	264–265[d]	90	C, H	Ic
59	4	4'-Br	294–296[h]	79	C, H	Ia
60	4	4'-Pr^i	260–264[d]	61	C, H	Ia
61	4	3'-CH_3	270–271[h]	84[e]	C, H	IV
62	4	3'-OCH_3	254–255[i]	90[e]	C, H	IV
63	4	3'-Br	240–245[d]	31[f]	C,[j] H	Ib
64	4	2'-CH_3	282–284[h]	80[e]	C, H	IV
65	4	2'-Br	284–286[h]	34[f]	C,[k] H	Ib
66	4	2'-Pr^i	265–266[h]	72[l]	C, H	II
67	4	2'-F	256–258[h]	28[m]	C, H	II
68	4	2',4'-Cl_2	270–272[h]	80[l]	C, H	II
69	5	H	202–206[n]	51	C, H	Ia
70	5	4'-Pr^i	211–213[n]	91	C, H	Ia
71	5	4'-OCH_3	230–231[h]	82	C, H	Ic
72	5	2'-Br	230–231[h]	33	C, H	Ia
73	5	4'-Br	279–282[d]	35[f]	C, H	Ib
74	5	2,4-$(CH_3)_2$	226–230[h]	60[e]	C, H	III
75	5	3'-Br	192–194[d]	91	C, H	Ia
76		2'-COOH	173–175[h]	30[p]	C, H	II

[a] Uncorrected. [b] From immediate precursor, recrystallized. [c] ±0.4% of theory unless otherwise indicated. [d] Aqueous dimethylformamide. [e] Overall yield from the appropriate phosphonium salt. [f] Isolated yield after fractional crystallization of reduction product of the appropriate benzylidene phthalide mixture. [g] MeOH. [h] Aqueous EtOH. [i] EtOH. [j] C: calcd, 55.01; found, 54.52. [k] C: calcd, 69.54; found 69.04. [l] Overall yield from 6-carboxyphthalide. [m] Overall yield from 6-carbomethoxyphthalide. [n] EtOAc–hexane. [o] 1,2-Bis(2-carboxyphenyl)ethane. [p] Overall yield from phthalide; see Experimental Section.

Table IV. Benzylidene Phthalides



no.	position of COOH	R	react temp, °C	mp, °C[a]	% yield[b]	anal.[b]
77	5	H	280	326–330[d]	13	C, H
78	6	H	280	304–307[d]	11	C, H
79	5	4'-Pr[i]	270	285–290[e] dec	17	C, H
80	6	4'-Pr[i]	270	259–262[f]	34	C, H
81	5	4'-Br	270	g	25	g
82	6	4'-Br	270	g	18	g
83	6	2'-Br	280	284–290[d]	20	C, H

[a] Uncorrected. [b] Recrystallized. [c] ±0.4% of theory unless otherwise stated. [d] Aqueous DMF. [e] EtOH. [f] Aqueous EtOH. [g] Not obtained analytically pure.

produce 2-(4-isopropylphenethyl)benzene-1,4-dicarboxylic acid (**60**): yield 1.4 g (61%); mp 260–264 °C. Anal. ($C_{19}H_{20}O_4$) C, H. The other benzylidenephthalides, either after separation or as the ca. 1:1 mixtures obtained from the condensation, were reduced similarly. Physical data, yields, etc. are shown in Table III.

Polyphosphoric Acid Cyclizations. The diacid **60** (1.7 g, 0.06 mol) was dissolved in sulfolane (5 mL) and PPA (15 mL) was added. The mixture was stirred at 170 °C for 90 min and then poured into water (50 mL), and the crude product was filtered and recrystallized from aqueous HOAc (charcoal) to afford **7-isopropyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one-2-carboxylic acid (17)**: yield 0.87 g (47%); mp 178–182 °C. Anal. ($C_{19}H_{18}O_3$) C, H.

Similar cyclization conditions were used for the other diacids. Methoxyl-substituted compounds, however, required lower temperatures (90–120 °C). The dichloro dicarboxylic acid **68** was unaffected by PPA but was cyclized using P_2O_5–nitrobenzene.[8]

4-Methoxy-*trans*-stilbene-2',4'- and -2',5'-dicarboxylic Acids (7b and 7a). Benzene-1,2,4-tricarboxylic anhydride and *p*-methoxyphenylacetic acid were condensed as described above. The crude product was recrystallized from aqueous DMF to give a 53% yield of an ca. 1:1 mixture (as indicated by NMR) of benzylidine phthalides **3a** and **3b**, X = 4-OCH_3. A solution of 35 g of this mixture in DMF (300 mL) containing 10% Pd/C (3.5 g) was hydrogenated in a Parr shaker (60 psi, 3.5 h). The solution was filtered and evaporated, and the residue was recrystallized from aqueous HOAc to give 22 g of a mixture of **6a** and **6b**. This material was dissolved in Me_2SO (90 mL) at 60 °C, and KOBu[t] (30 g, 3 equiv) was added. After 15 min, the solution was poured into water, acidified with HOAc, and filtered. The residue (15.8 g) was crystallized from aqueous dioxane. The first crop (6.5 g) was recrystallized from dioxane to give **7b**: yield 2.4 g (11%); mp 245–248 °C. Anal. ($C_{17}H_{14}O_5$) C, H. The initial mother liquors were evaporated, and the residue was recrystallized two times from dioxane–hexane to give **7a**: yield 4.3 g (20%); mp 265–270 °C. Anal. ($C_{17}H_{14}O_5$) C, H. Additional quantities of **7a** and **7b** were obtained by further crystallizations of mother liquor materials.

2-(4'-Methoxyphenethyl)benzene-1,4- and -1,5-dicarboxylic Acids (58 and 71). The stilbenedicarboxylic acid **7b** (2.4 g) was hydrogenated in HOAc (20 mL) over 10% Pd/C (0.3 g) for 1.5 h at atmospheric pressure. The solution was filtered and evaporated, and the residue was recrystallized from aqueous DMF to give **71**: yield 1.2 g (80%); mp 230–231 °C. Anal. ($C_{17}H_{16}O_5$) C, H. Similarly, hydrogenation of **7a** yielded **58** (90%), mp 264–265 °C (EtOH). Anal. ($C_{17}H_{16}O_5$) C, H.

Base-Catalyzed Condensation of Substituted Benzaldehydes with 6-Carboxyphthalide.[6] Sodium (2.9 g, 0.125 mol) was dissolved in MeOH (500 mL) and *o*-isopropylbenzaldehyde (8.5 g, 0.058 mol) and 6-carboxyphthalide (10.1 g, 0.058 mol) were added. The solution was refluxed for 48 h, then most of the solvent was removed under vacuum, and the residue was poured into water and extracted with Et_2O to remove neutral compounds. The aqueous solution was acidified (dilute HCl) and extracted with EtOAc. The extract was washed, dried, and evaporated. The residue (11.7 g) was refluxed for 48 h in HOAc (60 mL), 57% aqueous HI (36 mL, 0.35 mol), and red phosphorus (6 g, 0.19 mol). The cooled solution was poured into water, and the solid was filtered off and shaken with EtOH. The ethanolic solution was filtered and evaporated, and the residue was recrystallized three times from aqueous EtOH to afford **2-(2-isopropylphenethyl)benzene-1,4-dicarboxylic acid (66)**: yield 1.2 g (7% overall); mp 265–266 °C. Anal. ($C_{19}H_{20}O_4$) C, H. The use of 2,4-dichlorobenzaldehyde in the above procedure gave the dichlorodicarboxylic acid **68** (36%), mp 270–272 °C (aqueous EtOH). Anal. ($C_{16}H_{12}Cl_2O_4$) C, H. Similarly, condensation of *o*-carbomethoxybenzaldehyde and phthalide, followed by reduction, gave **1,2-bis(2-carboxyphenyl)ethane (7b)** (30%), mp 173–175 °C (aqueous EtOH). Anal. ($C_{17}H_{14}O_4$) C, H. *o*-Fluorobenzaldehyde was condensed with 6-carbomethoxyphthalide rather than with the free acid, using 1 equiv of sodium, and the crude product was reduced as described above to afford **2-(2-fluorophenethyl)-benzene-1,4-dicarboxylic acid (67)**: yield 28%; mp 256–258 °C (aqueous EtOH). Anal. ($C_{16}H_{13}FO_4$) C, H.

Wittig Reaction Syntheses (Schemes III and IV). (a) 2,4- and 2,5-Dicarbomethoxybenzyltriphenylphosphonium Bromides (9a and 9b). Dimethyl 4-methylbenzene-1,3-dicarboxylate (7.0 g, 0.034 mol) and *N*-bromosuccinimide (NBS; 5.69 g, 0.032 mol) were refluxed in CCl_4 (250 mL), irradiating with a 100-W incandescent lamp, for 1.5 h. The cooled solution was evaporated to an oil. Acetonitrile (50 mL) was added, the solution was reevaporated, and the process was repeated so as to remove traces of CCl_4. The residue was dissolved in acetonitrile (100 mL), PPh_3 (8.82 g, 0.034 mol) was added, and the solution was refluxed for 3 h. The solution was cooled and diluted with Et_2O (300 mL). The white product was filtered off and dried under vacuum to afford 13.6 g (73%), mp 245 °C dec. Anal. ($C_{29}H_{26}BrO_4P$) C, H. The 2,5-dicarbomethoxy salt **9b** was prepared similarly from dimethyl 2-methylbenzene-1,4-dicarboxylate in 69% yield, mp 235–245 °C. Anal. ($C_{29}H_{26}BrO_4P$) C, H.

(b) Wittig Reaction. 4-(2,4-Dimethylphenethyl)benzene-1,3-dicarboxylic Acid (74). 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN; 2.5 g, 0.02 mol) was added to a mixture of **9a** (4.9 g, 0.009 mol) and 2,4-dimethylbenzaldehyde (1.75 g, 0.013 mol) in acetonitrile (40 mL). The solution was refluxed briefly, cooled, poured into water, and then extracted with ethyl acetate. The extract was washed (dilute HCl, water), dried, and evaporated. The residue was refluxed for 16 h in MeOH (5 mL) and water (60 mL) containing KOH (5 g). The solution was cooled and extracted three times with CH_2Cl_2 to remove Ph_3PO and then acidified (dilute HCl), and the precipitate was filtered off and dried. This material was dissolved in EtOH (150 mL) and hydrogenated for 40 min at atmospheric pressure over 5% Pd/C (0.3 g). The solution was filtered and evaporated, and the residue was crystallized from aqueous EtOH to afford acid **74**: yield 1.57 g (60%); mp 256–260 °C. Anal. ($C_{18}H_{14}O_4$) C, H. This material was cyclized as described previously. Wittig reaction, using the salt **9b**, and reduction of the product thereof were performed similarly.

Introduction of the 10,11 Double Bond. 7-Bromo-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one-3-carboxylic Acid (48). A suspension of 7-bromo-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one-3-carboxylic acid (**40**; 1.0 g, 0.003 mol) in EtOAc (50 mL) was treated with excess ethereal diazomethane. After 1 h, the acid had dissolved. The solution was evaporated to give the methyl ester of **40**, which was dissolved in CCl_4 (300 mL) containing NBS (0.505 g, 0.0028 mol); the mixture was refluxed and irradiated (100-W incandescent lamp) for 3 h. The solution was cooled, filtered, and evaporated to an oil, which was dissolved in DMF (15 mL). DBN (0.8 g, 0.0065 mol) was added and the mixture was warmed to 80 °C for 10 min. Water and EtOAc were added, and the organic layer was washed (dilute HCl, water), dried, and evaporated. The residue was refluxed for 6 h in MeOH (30 mL) and water (20 mL) containing KOH (1 g), then poured into water, and acidified (dilute HCl). The product was filtered and recrystallized from aqueous DMF to afford 0.71 g (73% overall), mp 374–377 °C. Anal. ($C_{16}H_9BrO_3$) C, H. The same procedure was used to convert other 10,11-dihydrocarboxylic acids into the

corresponding unsaturated compounds. Yields, melting points, etc. are shown in Table I.

Conversion of Bromo into Chloro or Cyano Substituents. 7-Chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-one-2-carboxylic Acid (39). Compound **40** (5.0 g, 0.015 mol) was refluxed for 8 h in *N*-methylpyrrolidinone (50 mL) containing cuprous chloride (2.0 g, 0.018 mol). The cooled solution was poured into water and the solid filtered. This material was stirred at 90 °C in 50 mL of acidified ferric chloride solution ($FeCl_3$, $6H_2O$, 220 g; concentrated HCl, 150 mL; water, 300 mL) to oxidize insoluble cuprous salts. The solution was filtered, and the product was washed, dried, and recrystallized from aqueous DMF (charcoal) to afford **35**: yield 2.4 g (55%); mp 265–266 °C. Anal. ($C_{16}H_{11}ClO_3$) C, H. Other chloro acids were made similarly (see Table I). Use of cuprous cyanide under the same conditions gave the corresponding cyano-substituted compounds.

7-Hydroxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-one-3-carboxylic Acid (46). Concentrated HCl (1.1 mL) was added to pyridine (1 mL), and the mixture was heated in a 220 °C oil bath until the boiling stopped. The methoxycarboxylic acid **39** (0.5 g) was then added, and the mixture was heated to 210–215 °C for 70 min. The solution was cooled and water was added. The solid was filtered off and recrystallized from aqueous EtOH to afford **46**: yield 0.37 g (78%); mp 232–234 °C. Anal. ($C_{16}H_{12}O_4$) C, H.

7-Isopropoxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-one-3-carboxylic Acid (37). The hydroxycarboxylic acid **46** (1.5 g, 0.0056 mol) was converted to the methyl ester by treatment with diazomethane as described above. The ester, without purification, was stirred in DMF (20 mL) containing isopropyl bromide (4 g, 0.033 mol) and anhydrous K_2CO_3 (2 g, 0.0135 mol) for 16 h. The mixture was warmed briefly to 60 °C, then poured into water, and extracted with ethyl acetate. The extract was washed, dried, and evaporated, and the residue was refluxed for 2 h in MeOH (20 mL) and water (10 mL) containing NaOH (2 g). The mixture was cooled, acidified (dilute HCl), and extracted with EtOAc. The dried extract was evaporated and the residue was recrystallized from aqueous DMF to afford **37**: yield 1.0 g (60%); mp 213–216 °C. Anal. ($C_{19}H_{18}O_4$) C, H.

7-Acetyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-one-2- and -3-carboxylic Acids (19 and 36). 7-Cyano-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-one-3-carboxylic acid (**34**; 13.2 g, 0.048 mol) was stirred at room temperature in a mixture of $CHCl_3$ (250 mL), $SOCl_2$ (5 mL, 0.07 mol), and DMF (1.0 mL) until a clear solution was obtained (ca. 3 h). The solvents were removed under vacuum and the residue was recrystallized from acetonitrile to afford the acid chloride, yield 9.7 g (69%). This material was dissolved in $CHCl_3$ (400 mL) at 0 °C and to the solution was added, with stirring, an ethereal solution of diazomethane (from 15 g of nitrosomethylurea). After 2 h, the solution was evaporated to dryness and the product, 3-cyano-7-(diazoacetyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-one, was recrystallized from acetonitrile, yield 5.0 g (51%). This material was dissolved in $CHCl_3$ (600 mL), the solution was cooled to 0 °C, and 57% aqueous HI (10 mL) was added with vigorous stirring. After 30 min, water was added, and the organic solution was washed (water, aqueous sodium thiosulfate), dried, and evaporated. The residue was recrystallized from EtOAc–hexane to afford 3-acetyl-7-cyano-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-one, yield 2.3 g (50%). This material was refluxed for 24 h in EtOH (50 mL) and water (150 mL) containing NaOH (3.45 g). The solution was cooled and acidified (dilute HCl) and the product was recrystallized from aqueous DMF to afford **36**: yield 1.95 g (73%, 14% overall); mp 243–245 °C. Anal. ($C_{18}H_{12}O_4$) C, H.

The first three steps of the above procedure, using the 8-bromocarboxylic acid **43** as starting material, afforded 3-acetyl-8-bromo-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-one which, when reacted with cuprous cyanide as described above, gave the 8-cyano compound (25% overall). Base hydrolysis as described above afforded **19**: yield 85%; mp 201–203 °C (aqueous HOAc). Anal. ($C_{18}H_{14}O_3$) C, H.

Biological Assays. Inhibition of Histamine Aerosol Induced Bronchoconstriction in the Unanesthetized Guinea Pig. Bronchoconstriction leading to anoxic convulsions and unconsciousness can be induced in guinea pigs by exposure to a histamine aerosol. Compounds possessing antihistaminic or bronchodilator activity inhibit such responses. Guinea pigs were placed in 1-L glass jars and exposed to an aerosol of 0.04% histamine (diphosphate) delivered from a DeVilbiss no. 40 nebulizer until they collapsed (loss of righting) or, if protected, were removed after 5-min exposure. In evaluating each compound, one group of eight animals served as a control group, and it was ascertained that all animals within the group collapsed before compound evaluation was made. Additional animals, in groups of eight each, were then exposed to the aerosol 15 min after intraperitoneal and 30 min after oral administration of the compound under study. Incidence of collapse was recorded and indicated as percent protection in terms of animals surviving the 5-min aerosol exposure. This method closely resembles that of Siegmund et al.[10a]

Intravenous Histamine Challenge Assay. A procedure modeled after those described by Dessy et al.[11] and Rosenthale et al.[12] was used. Female guinea pigs weighing 400–500 g were anesthetized with urethan (1 g/kg, ip) and both the trachea and a jugular vein were cannulated. The tracheal cannula (plastic tube) was attached to a Harvard ventilator, which delivered 5.5 mL of air at a frequency of 38 strokes per minute; a side arm of the cannula was connected to a pressure transducer to measure changes in pulmonary resistance (a combination of increased airway resistance and decreased lung compliance caused by histamine). The jugular cannula (a 22-gauge needle) permitted injection of the compounds. Recording was done via a Harvard Biograph. A histamine phosphate (10 μg/kg in buffered saline) challenge was given to determine the animal's sensitivity to histamine. Serial histamine challenges, as with those given using test agents, elicited reproducible responses when given to non-drug-treated animals. Five minutes after the first histamine challenge, the test material was given, followed by a second histamine challenge 5 min after giving the test material. All of the test agents were given as the sodium salt in water, and each guinea pig received a single dose of the test agent. The percent inhibition of the histamine response, calculated by comparing the maximum pulmonary resistance obtained with histamine after giving the test material with that obtained prior to giving the test material, was determined. Biological results are shown in Table II.

Relaxation of Guinea Pig Tracheal Smooth Muscle in Vitro. Some of the agents under study were evaluated for direct bronchodilator effects by determining if they relax the smooth muscle of the pulmonary tract in vitro.[10b] For each study, a guinea pig was sacrificed, and the trachea was dissected and placed in Krebs–Henseleit solution. It was cut transversely between the cartilages into a series of rings, which were tied into a chain. The smooth-muscle strips were oriented longitudinally. The chain was mounted into a 20-mL isolated organ chamber in Krebs–Henseleit solution at 37 °C and aerated with 5% CO_2, 95% O_2. The tone of the muscle preparation was measured with a force-displacement transducer coupled to an appropriate amplifier and recorder. Muscles were placed under a resting lever load of 0.2 to 0.5 g. They generally increased in tone initially. After stabilization in tone, compounds under study were evaluated for their ability to directly relax this muscle. In each instance, comparisons were made with a standard, viz., aminophylline (15-min exposure throughout), to obtain an estimate of potency using a simple three- or four-point assay,[14] using a plot of concentration against degree of relaxation. Each agent was assayed in a single muscle preparation. Compounds **17** and **35** were reassayed using a six-point assay analysis. Repeated analyses were not conducted to obtain fiducial limits. The test compounds were administered as the sodium salts in aqueous solution at concentrations up to 5 μg/mL.

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References and Notes

(1) Contribution no. 505 from the Syntex Institute of Organic Chemistry.
(2) Pfister, J. R.; Ferraresi, R. W.; Harrison, I. T.; Roszkowski, A. P.; Van Horn, A.; Fried, J. H. *J. Med. Chem.* **1972**, *15*, 1032.
(3) Pfister, J. R.; Ferraresi, R. W.; Harrison, I. T.; Rooks II, W. H.; Fried, J. H. *J. Med. Chem.* **1978**, *21*, 669.
(4) Sprenkle, A. C.; Van Arsdel, P. R.; Bierman, C. W. *J. Allergy Clin. Immunol.* **1975**, *55*, 118.
(5) Mota, I. *Immunology* **1964**, *7*, 681.
(6) Gabriel, S. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 2433.
(7) Zimmer, H.; Barry, R. D. *J. Org. Chem.* **1962**, *27*, 1602.
(8) Cook, J. W. *J. Chem. Soc.* **1932**, 1472.
(9) Tochtermann, W.; Walter, U.; Mannschreck, A. *Tetrahedron Lett.* **1964**, 2981.
(10) (a) Siegmund, O. H.; Granger, H. R.; Lands, A. M. *J. Pharmacol. Exp. Ther.* **1947**, *90*, 254; (b) Castillo, J. C.; de Beer, E. K. *ibid.* **1947**, *90*, 104.
(11) Dessy, F.; Maleux, M. R.; Cognioul, A. *Arch. Int. Pharmacodyn.* **1973**, *206*, 368.
(12) Rosenthale, M. E.; Dervinis, A.; Kassarich, J. *J. Pharmacol. Exp. Ther.* **1971**, *178*, 541.
(13) Substituent size is inferred from the molar refractivity. Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207.
(14) Using the method described in "Pharmacological Experiments on Isolated Preparations", Livingstone: Edinburgh and London, 1968; pp 14–20.

Synthesis of 4-Alkyl and 4-(β-Alkylvinyl) Derivatives of Primaquine as Potential Antimalarials

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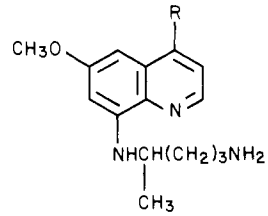
4-(β-Alkylvinyl)-6-methoxy-8-nitroquinolines (**6**) were prepared from 6-methoxy-8-nitroquinoline-4-carboxaldehyde (**5**) via a Wittig reaction. Stannous chloride reduction of **6** gave 4-(β-alkylvinyl)-8-amino-6-methoxyquinolines (**8**), whereas catalytic reduction of **6** using Raney nickel catalyst gave 4-alkyl-8-amino-6-methoxyquinolines (**7**). Alkylation of **7** and **8** with 4-iodo-1-phthalimidopentane, followed by removal of the phthaloyl-protecting group with hydrazine, gave 4-alkyl and 4-(β-alkylvinyl) derivatives of primiquine, respectively. These compounds were evaluated for antimalarial activity against *P. berghei* and *P. berghei yoelii* in mice and against *P. cynomolgi* in rhesus monkeys. Several of the compounds were active in the *P. bergheii yoelii* screen. None of the compounds showed significant activity in the other two screens.

In a recent study,[1] we reported that 8-[(4′-amino-1′-methylbutyl)amino]-4-ethyl-6-methoxyquinoline (**1a**, 4-

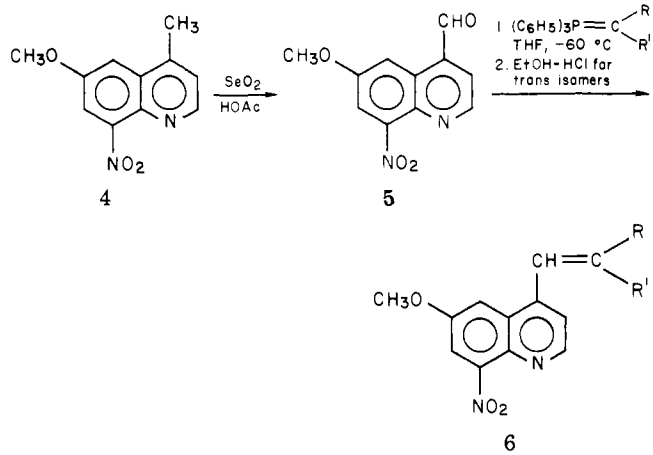


1a, R = C_2H_5
b, R = $CH{=}CH_2$
c, R = H

ethylprimaquine) and 8-[(4′-amino-1′-methylbutyl)-amino]-6-methoxy-4-vinylquinoline (**1b**, 4-vinylprimaquine) showed antimalarial activity against *Plasmodia cynomolgi* in rhesus monkeys comparable to that of primaquine (**1c**) but were less toxic. As a continuation of this study, we have synthesized several new 4-(alkylvinyl)- and 4-alkyl-8-[(4′-amino-1′-methylbutyl)amino]-6-methoxyquinolines (**2** and **3**, respectively) for antimalarial evaluation. In this paper, we describe the synthetic procedures used to prepare **2** and **3** and report antimalarial test data for these compounds.

Chemistry. We envisioned that the 4-(alkylvinyl)-6-methoxy-8-nitroquinoline (**6**) could serve as an intermediate for the syntheses of both **2** and **3**. Thus, we developed a synthetic scheme for the preparation of these intermediates (see Scheme I). By modification of the literature procedure,[2] we were able to effect the selenium dioxide oxidation of 6-methoxy-4-methyl-8-nitroquinoline (**4**) to the corresponding 4-carboxaldehyde **5** in 80% yield. Condensation of **5** with the appropriate alkylidenetriphenylphosphorane in tetrahydrofuran at −60 °C gave the

Scheme I



olefin **6**. The use of higher temperatures resulted in lower yields. In addition, the quinoline aldehyde **5** was extremely sensitive to strong bases. Thus, it was essential to use conditions that avoided even trace amounts of excess strong base.

In the course of this study it was also discovered that the stereochemistry of the disubstituted olefins could be influenced to a certain degree by the workup conditions. If the Wittig reaction mixture was treated with ethanolic hydrogen chloride, followed by basification and isolation of product, essentially pure *trans*-olefins were obtained. However, if no acid was used in the isolation procedure, the product was predominantly *cis*-olefins. This finding afforded an additional variable to our syntheses of the 4-(alkylvinyl) compounds **2**. Since reports in the literature[3] indicated that the use of Me_2SO as solvent in the Wittig

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