TABLE III
CHLOROFORM-INDUCED CARDIAC ARRHYTHMIAS AFTER TREATMENT WITH 4 COMMON, CLINICALLY USED ANTIARRHYTHMIC AGENTS

Drug	Number of mice	Equimolar dose (mg/kg)	Average rate (beats/min ± S.E.)	% protected	% toxic	% fatal
Quinidine·SO_4	40	118.47	129.05 ± 13.42	83.3	0.0	0.0
dl-Propranolol·HCl	40	77.47	185.61 ± 12.45	60.0	46.0	0.0
Procainamide·HCl	40	58.92	291.57 ± 17.11	13.3	0.0	0.0
Lidocaine·HCl	40	70.58	182.77 ± 14.78	56.7	86.7	0.0

structural requirements for substitution on N is unclear since good protection resulted from compounds having primary, secondary, and tertiary amine groups. In almost all cases, the primary amine derivatives caused greatly reduced toxicity when compared with the analogous substituted compounds (see **5**, **6**, **11**, **14**). In the comparison of the secondary amine analogs, an increase in the lipid solubility or hydrophobic character of the substituent increased both the antifibrillatory protection and the toxicity (see **3**, **4**). The substitution of more hydrophobic groups at any position on the saturated ring increased the antifibrillatory activity and also the toxicity (see **6**, **7**, and **9–17**). This may be due to an enhanced transport capability related to the relative partition characteristics of the molecule, as described by Levy,[5] rather than any specific receptor requirement.

From the results it is apparent that some of the 2-aminotetralins tested possess very good antifibrillatory protection properties compared with the commonly used antiarrhythmic agents and show little or no acute toxicity in effective doses. The relationship between toxicity and antiarrhythmic efficacy is very important. Although many agents possessing relatively potent antiarrhythmic activity have been developed, a great number of them have exhibited untoward toxic properties. Thus the absence of noticeable toxicity in dosage levels resulting in good antiarrhythmic activity in the screening experiments in highly desirable.[6]

Experimental Section

Adult male mice (Carworth strain CF 1) (22–28 g were weighed and injected ip with the test compound and placed in separate glass containers. The injections were given to groups of animals with 2-min intervals between individual animal treatments. After injection each animal was observed for toxic symptoms. Exactly 10 min after treatment each animal was transferred to a 250-ml beaker that held a cotton pad saturated with 20 ml of $CHCl_3$. The animal was removed immediately after respiratory arrest and the heart was quickly exposed by removing the anterior thoracic wall without touching the heart with the surgical instruments. The heart rate and fibrillatory movements were recorded with the aid of a stop watch and a binocular dissecting microscope. Any animal showing fibrillation or ventricular rates in excess of 200 beats/min was defined as unprotected. All animals exhibiting rates below 200 beats/min were reported as protected from fibrillation. In all cases where sufficient drug was available groups of 40 mice were used. Values for the percentage of animals protected were used to calculate an ED_{50} according to Litchfield and Wilcoxon.[7] All other statistical calculations were performed according to Steel and Torrie.[8]

(5) J. V. Levy, *Eur. J. Pharmacol.*, **2**, 250 (1968).
(6) M. M. Winbury, *Ann. N. Y. Acad. Sci.*, **64**, 564 (1956).
(7) J. T. Litchfield, Jr and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).
(8) R. G. D. Steel and J. H. "Torrie, Principles and Procedures of Statistics," McGraw-Hill, New York, N. Y., 1960.

Antimalarial and Other Biological Activities of Some 2′-Alkyl and 2′-Aryl Derivatives of Cinchona Alkaloids[1]

J. P. YARDLEY, R. E. BRIGHT, LEO RANE, R. W. A. REES, P. B. RUSSELL, AND HERCHEL SMITH

Research Division, Wyeth Laboratories, Inc., Radnor, Pennsylvania, and Malaria Screening Laboratory, University of Miami, Miami, Florida

Received June 17, 1970

We report an investigation undertaken primarily to compare with activities of 2′-alkyl and 2′-aryl derivatives of quinine, quinidine, and their 10,11-dihydrides against experimental malarias caused by *Plasmodium berghei and P. gallinaceum* in mice and chicks, respectively, in the framework of studying the effect of blocking the 2 position of the quinoline nucleus.[2–4] The substances were also examined for cardiac antiarrythmic and antibacterial activity.

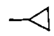
The 2′-alkyl and 2′-aryl derivatives were prepared from the alkaloid ar-*N*-oxides and appropriate Grignard or Li organometallic reagents (*cf.* ref 5). Satisfactory yields were obtained with simple primary alkyl Grignard reagents. *i*-BuMgBr and *sec*-RMgBr yielded predominantly the parent diamine along with a low yield of the corresponding 2′-alkyl derivative. The reaction failed with *t*-BuMgBr. However, 2′-*t*-Bu and 2′-cyclopropylquinidine were obtained from quinidine ar-*N*-oxide and the corresponding Li alkyl. The 10,11-dihydroquinidines and dihydroquinines were obtained by catalytic hydrogenation of the appropriate quinidine and quinine derivative I and II, respectively. Under the conditions used, no loss of halogen from the 2′-halophenyl derivatives was observed. Physical constants for the new compounds and other data are listed in Tables I–IV.

Antimalarial Activity.—Activity was measured against *P. berghei* in mice and *P. gallinaceum* in chicks by previously described methods.[6] The data in Table I show that 2′-alkyl substituents lower the maximum tolerated dose (MTD) thereby restricting testing to low dosage levels. Also, 2′-aryl substituents confer in-

(1) This paper is Contribution No. 688 from the Army Research Program on Malaria.

(2) M. M. Rapport, A. E. Senear, J. F. Mead, and J. B. Koepfli, *J. Amer. Chem. Soc.*, **68**, 2697 (1946).
(3) F. E. Kelsey, E. M. K. Geiling, F. K. Oldham, and E. M. Dearborn, *J. Pharmacol. Exp. Ther.*, **80**, 391 (1944); J. B. Mead, and J. B. Keopfli, *J. Biol. Chem.*, **154**, 507 (1944).
(4) (a) B. B. Brodie, J. E. Baer, and L. C. Craig, *ibid.*, **188**, 567 (1951). (b) J. F. Mead, M. M. Rapport, and J. B. Koepfli, *J. Amer. Chem. Soc.*, **68**, 2704 (1946).
(5) E. Kobayashi, *Yakugaku Zasshi*, **69**, 51 (1949).
(6) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

TABLE I
2′-SUBSTITUTED QUINIDINES

Compd[a]	R	Mp, °C	Recrystn solvent[b]	Yield, %	Formula	Analysis	Activity index[c]	*P. berghei*	*P. gallinaceum*
1	CH_3	160	A	75	$C_{21}H_{26}N_2O_2$	C, H,[d] N	I	320	120
							II	9.4	Cure[e]
							III	Ne[f]	60
1a		202–218	B		$C_{21}H_{26}N_2O_2 \cdot 2HCl \cdot {}^1/_4H_2O$	C, H, Cl,[g] N	IV	160	60
2	C_2H_5	138–140	C	39	$C_{22}H_{28}N_2O_2$	C, H, N	I	40	Ne
							II	Ne	Ne
							III		60
2a		171–175	D, E		$C_{22}H_{28}N_2O_2 \cdot 2HCl$		IV		Ne
3	C_3H_7	Amorph		33	$C_{23}H_{30}N_2O_2$		I	80	Nt[h]
							II	0	
3a		175	D, E		$C_{23}H_{30}N_2O_2 \cdot 2HCl \cdot H_2O$	C, H, Cl, N			
4	$C(CH_3)_3$	Amorph			$C_{24}H_{32}N_2O_2$[i,j]			Nt	Nt
4a		240	D, E	11	$C_{24}H_{32}N_2O_2 \cdot 2HCl$				
5	$(CH_2)_2CH(CH_3)_2$	Amorph		17	$C_{25}H_{34}N_2O_2$		I	320	Nt
							II	0	
5a		170–174	D, E		$C_{25}H_{34}N_2O_2 \cdot 2HCl \cdot {}^2/_3H_2O$	C, H, Cl, N			
6		59–72	F	14	$C_{23}H_{28}N_2O_2$[k]			Nt	Nt
6a		174	D, E		$C_{23}H_{28}N_2O_2 \cdot 2HCl$				
7	$(CH_2)_3N(CH_3)_2$	Amorph		19	$C_{25}H_{35}N_3O_2$[l]				
7a		Amorph			$C_{25}H_{35}N_3O_2 \cdot 3HCl$			Nt	Nt
8	C_6H_5	193–196	A, E	37	$C_{26}H_{28}N_2O_2$	C, H, N	I	640	Ne
							II	Cure	
							III	320	15
8a		Amorph			$C_{26}H_{28}N_2O_2 \cdot 2HCl$		IV	160	Ne
9	$4\text{-}ClC_6H_4$	118–122	E	23	$C_{26}H_{27}ClN_2O_2 \cdot {}^1/_2H_2O$	C, H, Cl, N	I	>640	>240
							II	Cure	Cure
							III	320	<60
9a		187–191	D, E		$C_{26}H_{27}ClN_2O_2 \cdot 2HCl$		IV	40	Ne
10	$4\text{-}CF_3C_6H_4$	Amorph		40	$C_{27}H_{27}F_3N_2O_2$		I	>640	>640
							II	Cure	14.7
							III	160	
10a		198–203	A, E		$C_{27}H_{27}F_3N_2O_2 \cdot 2HCl \cdot H_2O$	C, H, Cl, N	IV	20	<20

[a] a = hydrochloride, all antimalarial test results were obtained with HCl salts. [b] A = MeOH; B = Me_2CO; C = $CH_3(CH_2)_5CH_3$; D = *i*-PrOH; E = Et_2O; F = $CH_3(CH_2)_4CH_3$; G = CH_2Cl_2; H = aq $CH_3O(CH_2)_2OCH_3$. [c] I = Max tolerated dose, MTD in mg/kg (MTD = dose at which no toxic death occurred). II = Increase in mean survival time at MTD, in days; III = Minimum dose giving cure in mg/kg; IV = Minimum dose showing activity. [d] H: Calcd 7.74, found 7.25; [e] Cure is defined as a survival time of 60 days of the treated mouse over its control and of 30 days of the treated chick over its control. [f] Ne = not established. [g] Cl: Calcd 17.05, found 15.07. [h] Nt = not tested. [i] The molecular composition of difficult to analyze products was determined on an AEI MS-902 mass spectrometer at low resolution. The spectra were examined for M^+ and major fragmentation; only M^+ is reported. [j] *m/e*: Calcd 380, found 380. [k] *m/e*: Calcd 364, found 364; [l] *m/e*: Calcd 409, found 409.

TABLE II
2′-SUBSTITUTED 10,11-DIHYDROQUINIDINES

Compd	R[a]	Mp, °C	Recrystn solvent[b]	Formula	Analysis	Activity index[c]	*P. berghei*	*P. gallinaceum*
11	C_3H_7	168–171	E	$C_{23}H_{32}N_2O_2$	C, H, N	I	20	Nt[d]
11a		184–186	D, E	$C_{23}H_{32}N_2O_2 \cdot HCl$				
12	C_6H_5	260–270	A, E	$C_{26}H_{30}N_2O_2 \cdot 2H_2O$	C, H, N	I	>640	>120
						II	10.6	Cure[e]
						III		Ne[f]
12a		184–187	D, E	$C_{26}H_{30}N_2O_2 \cdot 2HCl$		IV	320	Ne
13	$4\text{-}ClC_6H_4$	163–174	E	$C_{26}H_{29}ClN_2O_2$	C, H, Cl, N	I	>640	>120
						II	Cure	Cure
						III	320	60
13a		185–189	D, E	$C_{26}H_{29}ClN_2O_2 \cdot 2HCl$		IV	40	30
14	$4\text{-}CF_3C_6H_4$	Amorph		$C_{27}H_{29}F_3N_2O_2$			Nt	Nt
14a		201–205	A, E	$C_{27}H_{29}F_3N_2O_2 \cdot 2HCl \cdot 1.5H_2O$	C, H,[g] Cl, N			

[a–f] See footnotes *a, b, c, h, e, f*, respectively, in Table I. [g] H: Calcd 5.43, found 4.91.

creased potency thereby enabling cures[7] to be observed. No significant differences in activity were detected between the quinine and quinidine derivatives and their corresponding dihydrides. In the 2′-aryl quinine series the minimal active dose decreased (*i.e.*, antimalarial potency increased) in the following order of 2′ substituents: C_6H_5 > *p*-FC_6H_4 > *p*-$CH_3OC_6H_4$ > *p*-ClC_6H_4 > *p*-$CF_3C_6H_4$. In our hands, 2-*p*-trifluoromethylphenylquinine, showing activity at 10 mg/kg, appears some 32 times as potent as quinine itself. Unfortunately, all of the 2′-arylquinines and quinidines

(7) See footnote *e* in Table I.

Table III

2′-Substituted Quinines

Compd	R[a]	Mp, °C	Recrystn solvent[b]	Yield, %	Formula	Analysis	Activity index[c]	*P. berghei*	*P. gallinaceum*
15	C_6H_5[d]	151	B, E	44	$C_{26}H_{28}N_2O_2$		I	>640	>120
							II	9.6	Cure[e]
							III		60
15a		215	B, G		$C_{26}H_{28}N_2O_2 \cdot 2HCl$		IV	320	30
16	FC_6H_4	130	E	45	$C_{26}H_{27}FN_2O_2$		I	640	120
							II	Cure	Cure
							III	640	120
16a		215	A, E		$C_{26}H_{27}FN_2O_2 \cdot 2HCl$	C, H, F, Cl,[f] N	IV	160	30
17	4-$CH_3OC_6H_4$				$C_{27}H_{30}N_2O_3$		I	>640	>120
							II	Cure	Cure
							III	160	30
17a		215	H	35	$C_{27}H_{30}N_2O_3 \cdot 2HCl$	C, H, Cl, N	IV	80	<30
18	4-ClC_6H_4				$C_{26}H_{27}ClN_2O_2$		I	>640	120
							II	Cure	Cure
							III	80	60
18a		215	A, E	48	$C_{26}H_{27}ClN_2O_2 \cdot 2HCl$	C, H, Cl,[g] N	IV	80	30
19	4-$CF_3C_6H_4$				$C_{27}H_{27}F_3N_2O_2$		I	>640	>120
							II	Cure	10.6
							III	20	
19a		210–218	A, E	32	$C_{27}H_{27}F_3N_2O_2 \cdot 2HCl$	C, H,[h] F,[i] Cl, N	IV	10	Ne[j]

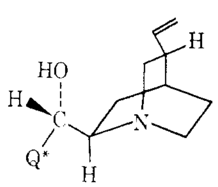
[a–c] See footnotes *a–c*, respectively, in Table I. [d] Kobayshi, *Yakugaku Zasshi*, **71**, 260 (1951), reported mp 145–147°. [e] See footnote *e* in Table I. [f] Cl: Calcd 14.4, found 13.8. [g] Cl: Calcd 20.94, found 20.20. [h] H: Calcd 5.58, found 5.07. [i] F: Calcd 10.18, found 9.55. [j] See footnote *f* in Table I.

Table IV

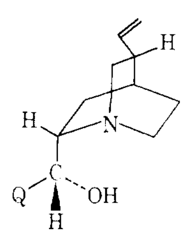
2′-Substituted 10,11-Dihydroquinines

Compd[a]	R	Mp, °C	Recrystn solvent[b]	Yield, %	Formula	Activity index[c]	*P. berghei*	*P. gallinaceum*
20	4-$CF_3C_6H_4$				$C_{27}H_{29}F_3N_2O_2$[d]	I	>320	>120
						III	Cure[e]	10.8
						III	80	
20a		Amorph	M, E	50	$C_{27}H_{29}F_3N_2O_2 \cdot HCl$	IV	10	120

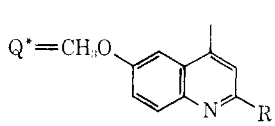
[a–c] See footnotes *a–c* in Table I. [d] *m/e*: Calcd 470, found 470. [e] See footnote *e* in Table I.



I



II



showed severe phototoxicity[8] in a laboratory animal test.[9] Quinine itself is inactive in this test while displaying slight photoactivity in an *in vitro* screening procedure.[10] The phototoxicity of 6,8-dichloro-2-phenyl-α-phenyl-α-2-piperidyl-4-quinolinemethanol, the potent antimalarial arylquinoline closely related to series I and II, has produced severe complications in man,[11] and it may be that, in animals, the phototoxicity of these compounds is directly related to their antimalarial potencies.

(8) Private communication by Dr. D. P. Jacobus and Col. William E. Rothe, Walter Reed Army Medical Center, Washington, D. C.

(9) W. E. Rothe, and D. P. Jacobus, *J. Med. Chem.*, **11**, 366 (1968).

(10) I. G. Fels, *ibid.*, **11**, 887 (1968).

(11) T. N. Pullman, L. Eichelberger, A. S. Alving, R. Jones, Jr., B. Craige, Jr., and C. M. Wherton, *J. Clin. Invest.*, **27**, 12 (1948).

Table V

Activity of Standard Compounds against *P. berghei* in Mice and *P. gallinaceum* in Chicks

Standard compd	Activity index[a]	*P. berghei*	*P. gallinaceum*
Quinidine	I	>640	>320
	II	11.7	Not active
	IV	320	
Dihydroquinidine	I	>640	Ne
	II	11.7	Not active
	IV	640	
Quinine	I	>320	>160
	II	13.2	3.2
	IV	320	160
Dihydroquinine	I	>640	>120
	II	6.5	3.2
	IV	640	Ne[b]

[a] See footnote *c* in Table I, the compounds were tested as the free base. [b] See footnote *f* in Table I.

Antiarrythmic and Antibacterial Activity.—The 2′-alkylquinidines **1, 2, 6,** and **7,** largely retained quinidine-like activity in a test recording the effective refractive period of the isolated guinea pig atria,[12] the first showing a potency equal to or greater than that of quinidine.

All of the new substances reported here were also screened against strains of bacteria noted in Table VI. In the quinidine series antibacterial activity ran closely

(12) G .S. Dawes, *Brit. J. Pharmacol.*, **1**, 90 (1946).

TABLE VI

ANTIBACTERIAL ACTIVITY OF 2′-ALKYL AND 2′-ARYL DERIVATIVES OF CINCHONA ALKALOIDS

Test Organism[a]	1a[b]	2a	6	7a	8a	9a	10a	14a	15a	16a	17a	18a	19a
Bacillus subtilis 6633	Na	250[c]	125	Na	15.6	7.81	7.81	1.95	15.6	7.81	3.90	15.6	7.81
Staphylococcus aureus 6538P	Na	Na	250	Na	62.5	15.6	7.81	3.90	62.5	31.3	15.6	62.5	15.6
S. aureus Smith	Na	Na	250	Na	62.5	15.6	7.81	3.90	62.5	31.3	15.6	62.5	15.6
S. aureus CHP	Na	Na	250	Na	62.5	7.81	7.81	1.95	62.5	15.6	15.6	15.6	7.81
S. aureus 53-180	Na	Na	250	Na	62.5	15.6	Na	1.95	62.5	15.6	15.6	62.5	15.6
Mycobacterium smegmatis 10143	Na	Na	Na	Na	Na	Na	7.81	Na	Na	Na	Na	Na	Na
Neisseria catarrhalis 8193	Na	Na	250	Na	31.3	15.6	Na	1.95	31.3	15.6	7.81	31.3	7.81
Pseudomonas aeruginosa 10145	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na
Escherichia coli 6880	Na	Na	250	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na
E. intermedia 65-1	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na
Salmonella paratyphi 11737	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na
Enterobacter aerogenes 884	Na	Na	250	Na	Na	62.5	62.5	62.5	31.3	31.3	15.6	62.5	62.5
Klebsiella pneumoniae 10031	Na	Na	250	Na	62.5	7.81	15.6	7.81	31.3	31.3	15.6	62.5	62.5
Bordetella bronchiseptica 4617	Na	Na	250	Na	250	125	31.3	62.5	62.5	62.5	62.5	Na	62.5
Proteus vulgaris 6896	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na
Herellea sp. 9955	Na	Na	250	Na	Na	Na	Na	Na	250	250	250	Na	Na

[a] The antibacterial activity was tested by the Agar Serial Dilution Technique. [b] For numbering of compound see Tables I–IV; [c] Minimal inhibitory concentration in μg/ml.

parallel to the observed antimalarial activity, the 2′-alkyl derivatives showing little or no activity, and the 2′-aryl derivatives being moderately to highly active, with 2′-*p*-trifluoromethylphenyl member again the most potent of the series.

Experimental Section

Melting points were taken on a Kofler block under microscopic magnification or in capillary tubes using the Thomas-Hoover apparatus and are uncorrected. Pmr spectra of all compounds were measured with a Varian Associates A-60 spectrometer on 10–15% solution in $CDCl_3$ or DMSO-d_6 and confirmed the suggested structures. Compounds were examined for purity by tlc on silica gel plates irrigated with the lower phase of the equilibrated system $CHCl_3$–MeOH–NH_4OH (9:1:5), visualization was carried out with Dragendorff reagent.[13] Quinine and quinidine ar-*N*-oxides were prepared by Ishikawa's method.[14]

Materials.—Commercially available Grignard reagents were used whenever possible, MeMgI, EtMgBr, PhMgBr were obtained from Arapahoe Chemical Company, Boulder, Colo. Others were prepared *in situ* from their respective halides and magnesium.

2′-Methylquinidine.—Quinidine ar-*N*-oxide (2.0 g, 5.9 mmoles) in 40 ml of anhyd C_6H_6 was added dropwise to a stirred 3 *M* sol of MeMgI in Et_2O (25 ml, 75 mmoles) over a period of 15 min. The mixture was refluxed under N_2 for 30 min then cooled to $-10°$ and treated with ice water followed by excess 2 *N* HCl. The aq phase was sepd washed with Et_2O and strongly basified with ice-cold KOH soln $CHCl_3$ (250 ml) was added and the mixture stirred vigorously for a few minutes and then filtered through Celite. After washing the filter aid with $CHCl_3$ the extracts were combined washed with brine and dried (K_2CO_3). Evapn of the $CHCl_3$ gave 2.1 g of residue, readily crystallizing on trituration with MeOH to give 1.5 g of product, (as the MeOH solvate), mp 150°. The analytical sample (from MeOH), mp 160°, lost MeOH of solvation after drying for 5 hr at 80° *in vacuo*.

(13) H. Schriftman, *J. Amer. Pharm. Ass., Sci. Ed.*, **48**, 111 (1959).

(14) M. Ishikawa, T. Kagawa, C. Kaneko, T. Miyasaka, and T. Tsuchiya Shika, *Zairyo Kenkyusho Hokoku*, **2**, 181 (1961); *Chem. Abstr.*, **58**, 4609 (1963).

2′-Cyclopropylquinidine.—To a soln of cyclopropyllithium in Et_2O (250 ml), prepared from Li (4.4 g, 646 mmoles) and cyclopropyl bromide (36.7 g, 331 mmoles)[15] was added while stirring at 0–5° under N_2 a soln of quinidine ar-*N*-oxide (10.0 g, 29.5 mmoles) in C_6H_6 (200 ml). When addition was complete stirring was continued while allowing the reaction to warm to room temp over a period of 1 hr. The mixture was then chilled in an ice bath and 2 *N* HCl was added. The layers were sepd and the aq phase washed with a small quantity of Et_2O. It was then basified with cold 50% NaOH soln, and extd with 5 portions of $CHCl_3$. The exts ($CHCl_3$) were combined, dried, and taken to dryness. The oily residue was chromatographed on a column of Florisil, fractions eluted with 1 and 2% MeOH in $CHCl_3$ crystd from hexane to give 1.5 g of product.

2′-(*p*-Chlorophenyl)dihydroquinidine.—2′-(*p*-Chlorophenyl)-quinidine·2HCl (2.6 g, 5 mmoles) was dissolved in MeOH (100 ml) and added to prereduced 5% Pd–C (0.89 g) in 25 ml of MeOH and hydrogenated at atmospheric pressure for 45 min until 5 mmoles of H_2 had been taken up. The catalyst was then filtered off and the filtrate taken to dryness. The residue was dissolved in H_2O and basified by the addition of NaOH soln. The aq phase was then extracted with $CHCl_3$, the combined extracts were dried and concd *in vacuo*. The residue gave 1.02 g of cryst product (from Et_2O).

Acknowledgments.—The authors wish to thank Dr. D. P. Jacobus, and Col. William E. Rothe, Walter Reed Army Medical Center, Washington, D. C. for the testing of phototoxicity, Dr. T. Baum of Wyeth Laboratories for the antiarrythmic testing, Dr. G. Warren and associates for the antibacterial screening, Mrs. J. T. Rees of these laboratories for recording and interpretation of various mass spectra, Dr. C. Hetzel, Mr. B. Hofmann, and associates for pmr spectra and elemental analysis. Dr. Rane acknowledges the support of a U. S. Army Research and Development Command Contract No. D.A.-49-193-M.D.-2218.

(15) O. Seyferth and O. Cohen, *J. Organomet. Chem.*, **1**, 15 (1963).