

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 \pm S.E.) | % protected | % toxic | % fatal |
|----------------------------|----------------|------------------------|-------------------------------------|-------------|---------|---------|
| Quinidine·SO ₄ | 40 | 118.47 | 129.05 \pm 13.42 | 83.3 | 0.0 | 0.0 |
| <i>dl</i> -Propranolol·HCl | 40 | 77.47 | 185.61 \pm 12.45 | 60.0 | 46.0 | 0.0 |
| Procainamide·HCl | 40 | 58.92 | 291.57 \pm 17.11 | 13.3 | 0.0 | 0.0 |
| Lidocaine·HCl | 40 | 70.58 | 182.77 \pm 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 CHCl₃. 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 ED₅₀ according to Litchfield and Wilcoxon.⁷ All other statistical calculations were performed according to Steel and Torrie.⁸

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(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. "Torrice, 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 Alkaloids¹

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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 antiarrhythmic 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. Seneor, 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. Koepfli, *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 ₂ O 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 ₂ O ₂ ·2HCl· ¹ / ₄ H ₂ O | C, H, Cl, ^g N | IV | 160 | 60 |
| 2 | C ₂ H ₅ | 138-140 | C | 39 | C ₂₂ H ₂₈ N ₂ O ₂ | C, H, N | I | 40 | Ne |
| | | | | | | | II | Ne | Ne |
| | | | | | | | III | | 60 |
| 2a | | 171-175 | D, E | | C ₂₂ H ₂₈ N ₂ O ₂ ·2HCl | | IV | | Ne |
| 3 | C ₃ H ₇ | Amorph | | 33 | C ₂₃ H ₃₀ N ₂ O ₂ | | I | 80 | Nt ^h |
| | | | | | | | II | 0 | |
| 3a | | 175 | D, E | | C ₂₃ H ₃₀ N ₂ O ₂ ·2HCl·H ₂ O | C, H, Cl, N | | | |
| 4 | C(CH ₃) ₃ | Amorph | | | C ₂₄ H ₃₂ N ₂ O ₂ ^{i, j} | | | Nt | Nt |
| 4a | | 240 | D, E | 11 | C ₂₄ H ₃₂ N ₂ O ₂ ·2HCl | | | | |
| 5 | (CH ₂) ₂ CH(CH ₃) ₂ | Amorph | | 17 | C ₂₅ H ₃₄ N ₂ O ₂ | | I | 320 | Nt |
| | | | | | | | II | 0 | |
| 5a | | 170-174 | D, E | | C ₂₅ H ₃₄ N ₂ O ₂ ·2HCl· ² / ₃ H ₂ O | C, H, Cl, N | | | |
| 6 |  | 59-72 | F | 14 | C ₂₃ H ₂₈ N ₂ O ₂ ^k | | | Nt | Nt |
| 6a | | 174 | D, E | | C ₂₃ H ₂₈ N ₂ O ₂ ·2HCl | | | | |
| 7 | (CH ₂) ₃ N(CH ₃) ₂ | Amorph | | 19 | C ₂₅ H ₃₂ N ₃ O ₂ ^l | | | | |
| 7a | | Amorph | | | C ₂₅ H ₃₂ N ₃ O ₂ ·3HCl | | | Nt | Nt |
| 8 | C ₆ H ₅ | 193-196 | A, E | 37 | C ₂₆ H ₂₈ N ₂ O ₂ | C, H, N | I | 640 | Ne |
| | | | | | | | II | Cure | |
| | | | | | | | III | 320 | 15 |
| 8a | | Amorph | | | C ₂₆ H ₂₈ N ₂ O ₂ ·2HCl | | IV | 160 | Ne |
| 9 | 4-ClC ₆ H ₄ | 118-122 | E | 23 | C ₂₆ H ₂₇ ClN ₂ O ₂ · ¹ / ₂ H ₂ O | C, H, Cl, N | I | >640 | >240 |
| | | | | | | | II | Cure | Cure |
| | | | | | | | III | 320 | <60 |
| 9a | | 187-191 | D, E | | C ₂₆ H ₂₇ ClN ₂ O ₂ ·2HCl | | IV | 40 | Ne |
| 10 | 4-CF ₃ C ₆ H ₄ | Amorph | | 40 | C ₂₇ H ₂₇ F ₃ N ₂ O ₂ | | I | >640 | >640 |
| | | | | | | | II | Cure | 14.7 |
| | | | | | | | III | 160 | |
| 10a | | 198-203 | A, E | | C ₂₇ H ₂₇ F ₃ N ₂ O ₂ ·2HCl·H ₂ O | C, H, Cl, N | IV | 20 | <20 |

^a a = hydrochloride, all antimalarial test results were obtained with HCl salts. ^b A = MeOH; B = Me₂CO; C = CH₃(CH₂)₅CH₃; D = *i*-PrOH; E = Et₂O; F = CH₃(CH₂)₄CH₃; G = CH₂Cl₂; H = aq CH₃O(CH₂)₂OCH₃. ^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 ₃ H ₇ | 168-171 | E | C ₂₃ H ₃₂ N ₂ O ₂ | C, H, N | I | 20 | Nt ^d |
| 11a | | 184-186 | D, E | C ₂₃ H ₃₂ N ₂ O ₂ ·HCl | | | | |
| 12 | C ₆ H ₅ | 260-270 | A, E | C ₂₆ H ₃₀ N ₂ O ₂ ·2H ₂ O | C, H, N | I | >640 | >120 |
| | | | | | | II | 10.6 | Cure ^e |
| | | | | | | III | | Ne ^f |
| 12a | | 184-187 | D, E | C ₂₆ H ₃₀ N ₂ O ₂ ·2HCl | | IV | 320 | Ne |
| 13 | 4-ClC ₆ H ₄ | 163-174 | E | C ₂₆ H ₂₉ ClN ₂ O ₂ | C, H, Cl, N | I | >640 | >120 |
| | | | | | | II | Cure | Cure |
| | | | | | | III | 320 | 60 |
| 13a | | 185-189 | D, E | C ₂₆ H ₂₉ ClN ₂ O ₂ ·2HCl | | IV | 40 | 30 |
| 14 | 4-CF ₃ C ₆ H ₄ | Amorph | | C ₂₇ H ₂₉ F ₃ N ₂ O ₂ | | | Nt | Nt |
| 14a | | 201-205 | A, E | C ₂₇ H ₂₉ F ₃ N ₂ O ₂ ·2HCl 1.5H ₂ O | 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 cures⁷ 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.*, anti-

(7) See footnote e in Table I.

malarial potency increased) in the following order of 2' substituents: C₆H₅ > *p*-FC₆H₄ > *p*-CH₃OC₆H₄ > *p*-ClC₆H₄ > *p*-CF₃C₆H₄. 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

TABLE III
 2'-SUBSTITUTED QUININES

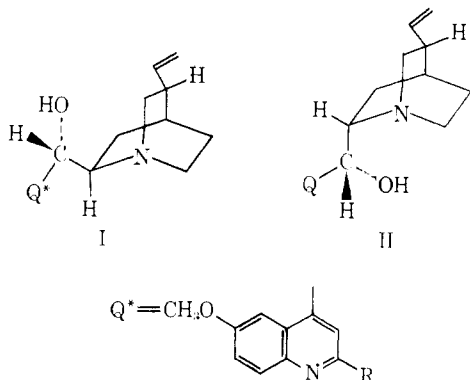
| Compd | R ^a | Mp, °C | Recrystn solvent ^b | Yield, % | Formula | Analysis | Activity index ^c | <i>P. berghei</i> | <i>P. gallinaceum</i> |
|-------|--|---------|-------------------------------|----------|--|--|-----------------------------|-------------------|-----------------------|
| 15 | C ₆ H ₅ ^d | 151 | B, E | 44 | C ₂₆ H ₂₈ N ₂ O ₂ | | I | >640 | >120 |
| | | | | | | | II | 9.6 | Cure ^e |
| | | | | | | | III | | 60 |
| 15a | | 215 | B, G | | C ₂₆ H ₂₈ N ₂ O ₂ ·2HCl | | IV | 320 | 30 |
| 16 | FC ₆ H ₄ | 130 | E | 45 | C ₂₆ H ₂₇ FN ₂ O ₂ | | I | 640 | 120 |
| | | | | | | | II | Cure | Cure |
| | | | | | | | III | 640 | 120 |
| 16a | | 215 | A, E | | C ₂₆ H ₂₇ FN ₂ O ₂ ·2HCl | C, H, F, Cl, ^f N | IV | 160 | 30 |
| 17 | 4-CH ₃ OC ₆ H ₄ | | | | C ₂₇ H ₃₀ N ₂ O ₃ | | I | >640 | >120 |
| | | | | | | | II | Cure | Cure |
| | | | | | | | III | 160 | 30 |
| 17a | | 215 | H | 35 | C ₂₇ H ₃₀ N ₂ O ₃ ·2HCl | C, H, Cl, N | IV | 80 | <30 |
| 18 | 4-ClC ₆ H ₄ | | | | C ₂₆ H ₂₇ ClN ₂ O ₂ | | I | >640 | 120 |
| | | | | | | | II | Cure | Cure |
| | | | | | | | III | 80 | 60 |
| 18a | | 215 | A, E | 48 | C ₂₆ H ₂₇ ClN ₂ O ₂ ·2HCl | C, H, Cl, ^g N | IV | 80 | 30 |
| 19 | 4-CF ₃ C ₆ H ₄ | | | | C ₂₇ H ₂₇ F ₃ N ₂ O ₂ | | I | >640 | >120 |
| | | | | | | | II | Cure | 10.6 |
| | | | | | | | III | 20 | |
| 19a | | 210-218 | A, E | 32 | C ₂₇ H ₂₇ F ₃ N ₂ O ₂ ·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 j in Table I.

 TABLE IV
 2'-SUBSTITUTED 10,11-DIHYDROQUININES

| Compd ^a | R | Mp, °C | Recrystn solvent ^b | Yield, % | Formula | Activity index ^c | <i>P. berghei</i> | <i>P. gallinaceum</i> |
|--------------------|---|--------|-------------------------------|----------|---|-----------------------------|-------------------|-----------------------|
| 20 | 4-CF ₃ C ₆ H ₄ | | | | C ₂₇ H ₂₉ F ₃ N ₂ O ₂ ^d | I | >320 | >120 |
| | | | | | | III | Cure ^e | 10.8 |
| 20a | | Amorph | M, E | 50 | C ₂₇ H ₂₉ F ₃ N ₂ O ₂ ·HCl | IV | 80 | 120 |

^{a-c} See footnotes a-c in Table I. ^d m/e: Calcd 470, found 470. ^e See footnote e in Table I.



showed severe phototoxicity⁸ 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 | <i>P. berghei</i> | <i>P. gallinaceum</i> |
|------------------|-----------------------------|-------------------|-----------------------|
| 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.

Antiarrhythmic 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 |
|---|-----------------|------------------|-----|----|------|------|------|------|------|------|------|------|------|
| <i>Bacillus subtilis</i> 6633 | Na | 250 ^c | 125 | Na | 15.6 | 7.81 | 7.81 | 1.95 | 15.6 | 7.81 | 3.90 | 15.6 | 7.81 |
| <i>Staphylococcus aureus</i> 6538P | Na | Na | 250 | Na | 62.5 | 15.6 | 7.81 | 3.90 | 62.5 | 31.3 | 15.6 | 62.5 | 15.6 |
| <i>S. aureus</i> Smith | Na | Na | 250 | Na | 62.5 | 15.6 | 7.81 | 3.90 | 62.5 | 31.3 | 15.6 | 62.5 | 15.6 |
| <i>S. aureus</i> CHP | Na | Na | 250 | Na | 62.5 | 7.81 | 7.81 | 1.95 | 62.5 | 15.6 | 15.6 | 15.6 | 7.81 |
| <i>S. aureus</i> 53-180 | Na | Na | 250 | Na | 62.5 | 15.6 | Na | 1.95 | 62.5 | 15.6 | 15.6 | 62.5 | 15.6 |
| <i>Mycobacterium smegmatis</i> 10143 | Na | Na | Na | Na | Na | Na | 7.81 | Na | Na | Na | Na | Na | Na |
| <i>Neisseria catarrhalis</i> 8193 | Na | Na | 250 | Na | 31.3 | 15.6 | Na | 1.95 | 31.3 | 15.6 | 7.81 | 31.3 | 7.81 |
| <i>Pseudomonas aeruginosa</i> 10145 | Na | Na | Na | Na | Na | Na | Na | Na | Na | Na | Na | Na | Na |
| <i>Escherichia coli</i> 6880 | Na | Na | 250 | Na | Na | Na | Na | Na | Na | Na | Na | Na | Na |
| <i>E. intermedia</i> 65-1 | Na | Na | Na | Na | Na | Na | Na | Na | Na | Na | Na | Na | Na |
| <i>Salmonella paratyphi</i> 11737 | Na | Na | Na | Na | Na | Na | Na | Na | Na | Na | Na | Na | Na |
| <i>Enterobacter aerogenes</i> 884 | Na | Na | 250 | Na | Na | 62.5 | 62.5 | 62.5 | 31.3 | 31.3 | 15.6 | 62.5 | 62.5 |
| <i>Klebsiella pneumoniae</i> 10031 | Na | Na | 250 | Na | 62.5 | 7.81 | 15.6 | 7.81 | 31.3 | 31.3 | 15.6 | 62.5 | 62.5 |
| <i>Bordetella bronchiseptica</i> 4617 | Na | Na | 250 | Na | 250 | 125 | 31.3 | 62.5 | 62.5 | 62.5 | 62.5 | Na | 62.5 |
| <i>Proteus vulgaris</i> 6896 | Na | Na | Na | Na | Na | Na | Na | Na | Na | Na | Na | Na | Na |
| <i>Herellea sp.</i> 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 $\mu\text{g/ml}$.

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 $\text{DMSO}-d_6$ 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).

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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 $0-5^\circ$ 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 $\cdot 2\text{HCl}$ (2.6 g, 5 mmoles) was dissolved in MeOH (100 ml) and added to pre-reduced 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).

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