The amine hydrochloride was removed by filtration and the clear supernatant liquid treated for 10 min. with dry hydrogen chloride gas by bubbling the gas continuously through the solution. A viscous oily semisolid separated which crystallized after standing under refrigeration for 48 hr. The crystals were collected by filtration, washed with anhydrous ether, and dried in a vacuum desiccator. All compounds were found to be hygroscopic. The results are summarized in Table I.

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New Compounds: Preparation and Hydrogenation of Azomethines Derived from 2,4-Dihydroxyphenyl Benzyl Ketones

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Reaction of 2,4-dihydroxyphenyl benzyl ketones with primary amines and subsequent catalytic hydrogenation with platinum catalyst has afforded a series of polyphenolic amines derived from resorcinol.

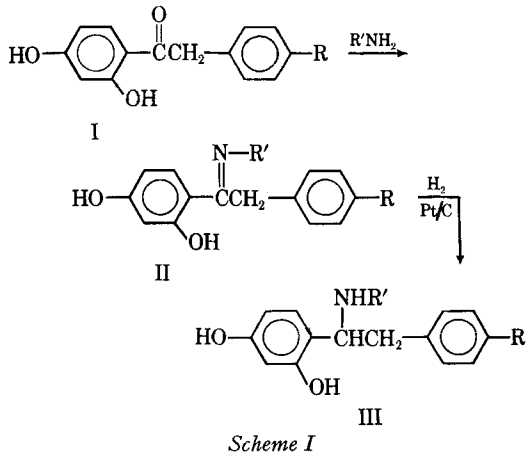
IT HAS BEEN alleged that quinine and mepacrine may exert their antimalarial activity by inhibition of the phosphorylation of glucose (1, 2). Because a number of polyphenolic compounds have been demonstrated to be inhibitors of oxidative phosphorylation (3–6), a number of polyphenolic amines derived from resorcinol have been synthesized in this laboratory as potential antimalarial agents.

The synthetic method is shown in Scheme I. Data on the compounds with structures II and III are presented in Tables I and II, respectively. All the compounds of structure III were isolated and characterized as the hydrochlorides.

Hydrogenation of the azomethines (Table I), where R′ = 2,4-dichlorobenzyl and 3,4-dichlorobenzyl, and subsequent treatment with hydrogen chloride gave a mixture of hydrochloride salts. 2,4-Dichlorobenzylamine hydrochloride was isolated from the former and 3,4-dichlorobenzylamine hydrochloride from the latter. Elemental analyses of the desired secondary amine salts indicated incomplete removal of the primary amine hydrochlorides (based on the calculation of the desired secondary amine salts).

EXPERIMENTAL[1]

The ketones (I), where R = H and R = Cl, were prepared by the method of Chapman and Stephen (7). The ketones (I), where R = OCH_3, was prepared as described by Klarmann (8).



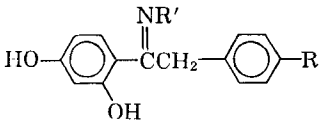
Scheme I

N - (2,4 - Dihydroxyphenyl - p - methoxybenzylmethylene)benzylamine—A solution of 10.3 Gm. (0.04 mole) of 2,4-dihydroxyphenyl-*p*-methoxybenzyl ketone and 4.3 Gm. (0.04 mole) of benzylamine in 350 ml. of dry toluene was refluxed for 24 hr. until the theoretical amount of water was collected in a Dean-Stark apparatus. The solution was concentrated *in vacuo* and the residue on recrystallization from toluene gave 14.0 Gm. (quantitative yield) of yellow crystalline product, m.p. 177–179°. An analytical sample was obtained after an additional recrystallization from toluene, m.p. 180–181°. (See Table I.)

N - (2,4 - Dihydroxyphenyl - p - chlorobenzylmethyl)veratrylamine Hydrochloride—A solution of *N*-(2,4-dihydroxyphenyl-*p*-chlorobenzylmethylene)veratrylamine (4.1 Gm., 0.01 mole) in 150 ml. of acetone was hydrogenated at a pressure of 30 p.s.i. and room temperature, using 1.0 Gm. of 5% platinum-on-charcoal as the catalyst. After 90 min. the theoretical uptake of hydrogen was observed and the catalyst and solvent removed. The waxy residue was dissolved in 50 ml. of anhydrous

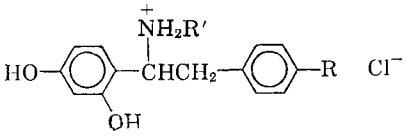
Received June 7, 1967, from the Midwest Research Institute, Kansas City, MO 64110
Accepted for publication August 8, 1967.
The authors express their appreciation to Mrs. Margaret L. Rounds, Mr. John R. Gravatt, and Mr. Leland R. Lewis for the analytical and instrumental measurements.
This investigation was supported by contract DA-47-193-MD-2953, U. S. Army Medical Research and Development Command, Office of the Surgeon General, Washington, D. C.
This paper is contribution No. 236 for the Army Research program on malaria.
[1] All melting points (corrected) were taken on a Thomas-Hoover melting point apparatus.

TABLE I—AZOMETHINES



R	R′	M.p., °C.	Yield, %	Recrystn. Solvents	Anal., % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	Benzyl	165–167	45	Methanol	79.47	6.03	4.41	79.20	6.34	4.26
Cl	Benzyl	209–210	85	Methanol	71.69	5.16	3.98	71.86	5.29	4.11
OCH_3	Benzyl	180–181	100	Toluene	76.06	6.09	4.03	75.89	6.08	4.01
Cl	Piperonyl	178–180	93	Toluene	66.75	4.58	3.54	66.95	4.68	3.64
Cl	Veratryl	102 dec.	80	Benzene	67.07	5.38	3.40	67.32	5.70	3.24
OCH_3	Piperonyl	169–170.5	89	Ethanol	70.58	5.41	3.58	70.51	5.41	3.51
OCH_3	Veratryl	147–149	80	Benzene	70.75	6.18	3.44	70.76	6.36	3.45
OCH_3	2,4-Dichlorobenzyl	197–198	64	Methanol	63.47	4.60	3.36	63.58	4.56	3.47
OCH_3	3,4-Dichlorobenzyl	179–180	90	Xylene	63.47	4.60	3.36	63.80	4.59	3.29

TABLE II—SECONDARY AMINE SALTS



R	R′	M.p., °C.	Yield, %	Recrystn. Solvents	Anal., % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	Benzyl[a]	170–172	66	Propanol–hexane	70.88	6.23	3.94	71.13	6.50	3.77
OCH_3	Benzyl	180–181	100	Ethanol	68.48	6.27	3.63	68.32	6.36	3.50
Cl	Piperonyl[b]	181–183	74	Propanol–ether	60.84	4.87	3.23	61.13	5.17	3.49[d]
Cl	Veratryl[c]	185–187	67	Isopropyl alcohol	61.34	5.60	3.11	61.70	5.83	3.22
OCH_3	Piperonyl	229–231	42	Ethanol	64.26	5.63	3.26	64.03	5.43	3.10
OCH_3	Veratryl	174–175.5	69	Ethanol	64.64	6.33	3.14	64.76	6.27	3.28
Cl	Benzyl	178–180	38	Propanol ether	63.17	5.55	3.51	62.92	5.46	3.38[e]

[a] Compounds (R′ = benzyl) were hydrogenated in methanol. [b] Compounds (R′ = piperonyl) were hydrogenated in methanol–acetonitrile (1:4). [c] Compounds (R′ = veratryl) were hydrogenated in acetone. [d] Calcd. for Cl: 16.33. Found: Cl, 16.28. [e] Analyzed for 0.5 mole water.

methanol and saturated in the cold with dry hydrogen chloride which gave 3.0 Gm. (67% yield) of hydrochloride salt, m.p. 184–186°. Recrystallization from isopropyl alcohol gave an analytical sample, m.p. 185–187°. (See Table II.)

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