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Aminoalkylphenols as Antimalarials. I. Simply Substituted α-Aminocresols[1]

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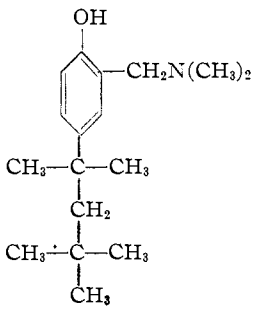
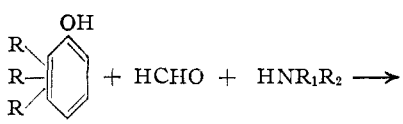
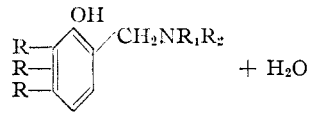
During an intensive program on antimalarials in this Laboratory, many types of compounds have been investigated in the search for a drug which might be a definite cure for malaria. One class of compounds which has appeared particularly promising is the substituted α-aminocresols. The first drug to be submitted for test in this series was α-dimethylamino-4-(1,1,3,3-tetramethylbutyl)-*o*-cresol.[1a]



Activity of Compound I 1 against trophozoite-induced chick malaria was established by Drs. R. J. Porter and L. T. Coggeshall, of the University of Michigan. This knowledge of antimalarial effectiveness by so unorthodox a compound indicated a lead which has resulted in the synthesis of several hundred compounds. More than one hundred of these constitute the subject of this first report.

Development of the first phase of this study has involved the testing of many compounds that are analogous or related to I 1.[1a] Several were obtained from an outside source,[2] but for the most part they were prepared in this Laboratory from various intermediate phenolic compounds by means of the Mannich reaction.[3,4] Phenols with at least one open position ortho or para to a phenolic hydroxyl were treated with formaldehyde and aliphatic amines to yield a wide variety of desired products. The following equation illustrates the general method used





R = hydrogen, alkyl, aryl, halo, alkoxy, aryloxy, etc.
R_1 = H or alkyl
R_2 = alkyl

As applied to phenolic compounds, the Mannich reaction may be carried out successfully with intermediates isolated from the treatment of formaldehyde with alkylamines. Dialkylaminomethanols,[5] dialkylamino alkyl ethers[6] and methylene-*bis*-dialkylamines[7] have all been employed in the preparation of α-dialkylamino-*o*-cresols. However, the authors generally chose simply to add the phenol to the mixture of dialkylamine, formaldehyde, and alcohol. Actually, this mixture has led to yields as great as were obtained from the use in a few experiments of pure dialkylaminomethyl alkyl ethers. Stock solutions containing four moles each of the dialkylamine and paraformaldehyde per liter of alcoholic solution have been kept for several months without apparent deterioration. For the sake of convenience in bringing together the reactants, the calculated volume of stock solution may simply be added to the phenol.

According to a recent report[8] no prior reference had been found in the literature to the interaction of a phenol with formaldehyde and diethylamine. Evidently, the claims of Bruson and his collaborators[9] had been overlooked. Because in this Laboratory diethylamine was found to enter into reaction so readily with formaldehyde and phenols, and especially because the diethylamino grouping is contained in several pharmaceutical agents, such as quinacrine, pamaquin, procaine, and trasentin, it was decided to employ this particular amine extensively in the outlined preparations.

Monoalkylamines have been used successfully with phenols in the Mannich reaction. With the exception of 2-aminoethanol,[10] a survey of the literature has failed to reveal any such previous use of primary aliphatic amines.

In general, paraformaldehyde and 37% formaldehyde have been found to be equally useful in this reaction.

The experiments of Décombe[11] afforded proof

(1) Presented at the 109th Meeting of the American Chemical Society, Atlantic City, N. J., April 8-12, 1946.

(1a) See Table I, Compound 1.

(2) Rohm and Haas Company, Philadelphia, Pa.

(3) Actually this reaction was applied to phenols [German Patent, *Frdl.*, **4**, 102 (1897)] several years before Mannich began his series of publications.

(4) F. F. Blicke, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, chapter 10.

(5) German Patent 90,908; *Frdl.*, **4**, 103 (1897).

(6) (a) McLeod and Robinson, *J. Chem. Soc.*, **119**, 1470 (1921); (b) Harradence and Lions, *C. A.*, **33**, 7799 (1939); (c) Tseou and Yang, *J. Org. Chem.*, **4**, 123 (1939); (d) Mason and Zief, THIS JOURNAL, **62**, 1450 (1940).

(7) (a) German Patent 90,907; *Frdl.*, **4**, 102 (1897); (b) Feldman and Wagner, *J. Org. Chem.*, **7**, 31 (1942).

(8) Grillot and Gormley, THIS JOURNAL, **67**, 1968 (1945).

(9) U. S. Patents, 2,031,557, 2,033,092, 2,045,517 and 2,220,834.

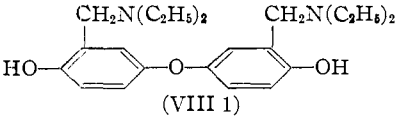
(10) U. S. Patent 2,114,122.

(11) Décombe, *Compt. rend.*, **196**, 866 (1933).

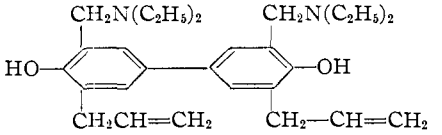
of nuclear substitution rather than ether formation by the entering aminomethyl group. The studies of others[12] determined whether or not the entry is ortho or para to the phenolic hydroxyl by catalytic hydrogenolysis of the α-aminocresols to the corresponding amino-free cresols, which were identified by comparison with structurally known cresols. In assigning structural formulas to the compounds in this paper, the data of Caldwell and Thompson[12a] have been advantageously used, with the assumption having been made that the identity of the starting amine exerts no influence upon the position taken by the entering group. Further, it was found that alkyl, phenyl or halo α-dialkylamino-*o*-cresols are insoluble in 5% caustic soda at room temperature, whereas the isomeric and analogous *p*-cresols are soluble. This observation has been valuable in confirming the structures of several compounds. Steric considerations, together with the fact that hydrogenolysis of 5-methyl-α-1-piperidyl-*o*-cresol yielded 2,5-dimethylphenol,[12a] were the guides in the tentative assignment of structural formulas to the following compounds: II 21, 23, 26, 33, 34; III 8, 28; VII 2. Only the analogy of quinolinols to naphthols[12a] determined the assignment of structures to VI 3, 4 and 5.[13]

The activity in avian malaria of certain (2,5-dimethyl-1-pyrryl)-quinolines has been known,[14] and so it was of interest to introduce the pyrryl grouping into the α-amino-*o*-cresol nucleus. The essential intermediate 4-(2,5-dimethyl-1-pyrryl)-phenol was prepared in good yield by treatment of *p*-aminophenol with acetonylacetone.

Intermediate 4,4′-oxybiphenol was obtained from diazotized 4,4′-diaminophenyl ether in 40% yield by improvement of an old procedure[15] and employed in the synthesis of VIII 1. Later, because of further interest in allyl compounds as a result of the activity of VII 8, the diallyl ether of 4,4′-oxybiphenol was rearranged to 3,3′-diallyl-4,4′-oxybiphenol. Application of a similar rearrangement produced the intermediate 2-allyl-4-*t*-butylphenol in satisfactory yield.

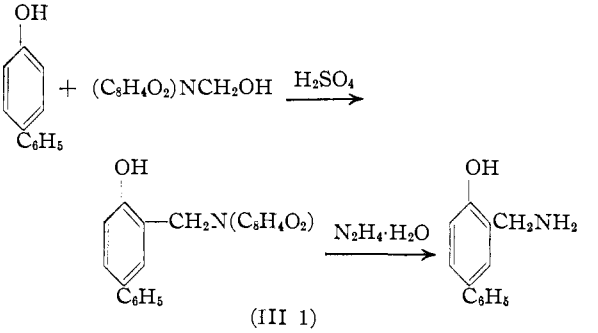


(VIII 1)



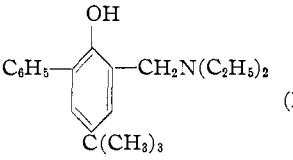
(VII 8)

In order to prepare a quantity of desired α-amino-4-phenyl-*o*-cresol (III 1), 4-phenylphenol was condensed with phthalimidomethanol and the resulting product hydrolyzed with hydrazine hydrate



(III 1)

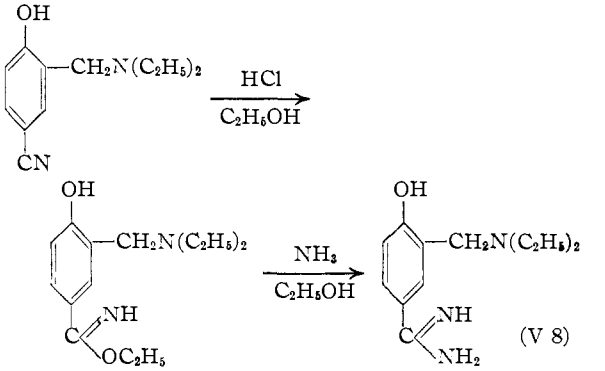
After the establishment of the interesting antimalarial activity of III 20, it was important to learn the effect of O-substitution on the activity



(III 20)

of this and certain related compounds. Three different O-acylated derivatives (III 21, VII 15 and 16) were prepared by heating the hydrochlorides of α-diethylamino-*o*-cresols with an excess of acyl anhydride. 2-Bromo-4-*t*-butyl-6-phenylanisole, which was obtained in good yield from the bromination of 4-*t*-butyl-6-phenylanisole, was converted by treatment of its Grignard reagent with diethylaminomethyl ethyl ether[6d] to O-methyl-4-*t*-butyl-6-phenyl-α-diethylamino-*o*-cresol (III 22).

The known effectiveness of amidines against human malaria[16] suggested a substitution of the guanyl radical in an α-amino-*o*-cresol nucleus. The synthesis was accomplished by conversion of 4-cyano-α-diethylamino-*o*-cresol (V 7) to the corresponding benziminoethyl ether. Treatment of the ether with alcoholic ammonia produced the desired 4-guanyl derivative (V 8).



(V 8)

(12) (a) Caldwell and Thompson, THIS JOURNAL, **61**, 2354 (1939); (b) Cornforth, Cornforth and Robinson, *J. Chem. Soc.*, 168 (1943).

(13) Further reports on structure studies will appear in a later communication.

(14) Private communication. Chemical data: Gilman, Stuckwisch and Nobis, THIS JOURNAL, **68**, 326 (1946).

(15) Haussermann and Bauer, *Ber.*, **30**, 738 (1897).

(16) Glyn-Hughes, Lowrie and Yorke, *Ann. Trop. Med. Parasit.*, **32**, 103 (1938).

Experimental

Procedure I.—An equimolecular mixture[17] of the appropriate amine and paraformaldehyde was warmed with sufficient alcohol to form a clear solution. This solution was cooled and added to an alcoholic solution or suspension of an equimolecular amount of the appropriate phenolic compound. The resulting mixture was usually allowed to stand for about an hour before it was heated at refluxing temperature for two hours. The volume of the mixture was reduced by evaporation or distillation, and the residue was extracted with ether. The ethereal extracts were washed, first with 5–10% sodium hydroxide solution and afterward with water, and finally dried over anhydrous potassium carbonate. (In certain cases solid free base was obtained by evaporation of the ether solution and recrystallized from the solvent given in the table). The hydrochloride was prepared by treating the dried ethereal solution with excess alcoholic hydrogen chloride. The solvent was ordinarily decanted from the precipitated salt which was triturated with fresh ether or other solvents until crystallization occurred.

Although in some experiments positive results appeared to depend upon the proper addition of the phenolic solution to the cooled amine—formaldehyde mixture, generally equally satisfactory results were effected by a simultaneous mixing of all the reactants.

Procedure II.—The preparative method followed for certain compounds was the same as Procedure I, except that the alkaline wash was eliminated. When aqueous formaldehyde was not used, the water wash and drying were omitted as well. Also, where a compound is listed in the tables as a free base, it was isolated from the reaction mixture as such without the ether extraction.

Procedure III.—An equimolecular mixture[17] of formaldehyde, appropriate amine and phenol in alcohol was refluxed for from two to four hours. The solution was diluted with water. The precipitated product was dissolved in ether and extracted with dilute hydrochloric acid. The acid extract was then separated, treated with an excess of ammonia and extracted with ether. The ethereal extract was washed with water, dried over potassium carbonate and evaporated to an oily residue, which was converted by means of concentrated hydrochloric acid or alcoholic hydrogen chloride to the hydrochloride.

Procedure IV.—The reaction was carried out as indicated in Procedure I, but the product was isolated by complete removal of the solvent and distillation of the free base under reduced pressure. To avoid polymerization, the pressure should usually not be greater than 10 mm. When desired, the hydrochloride was precipitated in the customary manner by treatment of an ethereal solution of the base with alcoholic hydrogen chloride.

Procedure V.—A mixture of equimolecular amounts of dimethylamine hydrochloride, paraformaldehyde and the suitable phenol in alcoholic solution was refluxed for two hours. The volatile materials were removed by distillation and the residue poured into several times its volume of ether. Successive triturations and decantations using fresh volumes of ether and acetone were carried out until a crystalline product formed.

Procedure VI.—The *bis*-(diethylamino)-bi-*o*-cresol dihydrochloride was dissolved in several times its weight of acetic or propionic anhydride and heated to 130°. Several drops of concentrated sulfuric acid were added and the solution cooled. The diester dihydrochloride was precipitated with ether.

4-(2,5-Dimethyl-1-pyrryl)-phenol.—A mixture of 57 g. (0.5 mole) of acetonylacetone, 54.5 g. (0.5 mole) of *p*-aminophenol, 100 cc. of absolute alcohol and 1 cc. of acetic acid was refluxed for twenty hours and then poured into 600 cc. of water. The oily precipitate solidified upon cooling; m. p. 90–95°. The crude product was dissolved in dilute potassium hydroxide solution and reprecipitated by passing in a stream of carbon dioxide; m. p. 102–104°. Reprecipitation from an alkaline solution with acetic acid did not change the melting point, but recrystallization from ligroin yielded 76.6 g. (82%) of a white product which melted at 104–106°. This intermediate was used as such without analysis for the preparation of V 5 because of its discoloration upon exposure to light and air.

4,4'-Oxybiphenol.—To a 12-liter flask containing a solution of 50 cc. of concentrated hydrochloric acid and 115 cc. of concentrated sulfuric acid in five liters of water at 40–50°, there was added 60 g. (0.3 mole) of 4,4'-diaminophenyl ether, and the mixture was stirred until a clear solution resulted (one to two hours). By application of ice externally and internally, the mixture was cooled to 0–5°, and then a solution of 41.4 g. of sodium nitrite in 100 cc. of water was added with stirring and cooling during a period of thirty minutes. After standing overnight the mixture was boiled until a sample gave no red color with alkaline β-naphthol (two to three hours). Considerable tar had formed, so the liquid was filtered hot through Supercel and poured into 12-liter flask containing 2 kg. of sodium chloride, which was dissolved with stirring. Then the solution was cooled to room temperature and the precipitated solid collected. The wet filter cake was dissolved in 300 cc. of ether and filtered through Supercel. Evaporation of the ether gave 25 g. of product; m. p. 154–158°. After dissolving this material in dilute potassium hydroxide and reprecipitating with dilute hydrochloric acid, 24 g. (40% yield) of 4,4'-oxybiphenol was obtained; m. p. 165–167°.[18] The product is slightly soluble in benzene and toluene, and is very soluble in ethanol, acetone and ether. It may be recrystallized from large volumes of water.

3,3'-Diallyl-4,4'-oxybiphenol.—A mixture of 20.2 g. (0.1 mole) of 4,4'-oxybiphenol, 27.8 g. (0.2 mole) of potassium carbonate and 150 cc. of acetone was heated under reflux and 24.2 g. (0.2 mole) of allyl bromide was added dropwise to the mixture during a period of thirty minutes. Refluxing was continued for two hours, after which water was added and the mixture was extracted with ether. The ethereal extract was washed first with dilute potassium hydroxide solution and then with water and finally dried over potassium carbonate. After removal of the ether by evaporation, a crystalline residue of 3,3'-diallyl-4,4'-oxybiphenol weighing 22 g. remained; m. p. 78–80°.

The crude allyl ether was placed in a 50-cc. Claisen flask and heated to 250° *in vacuo* (20 mm.). Then the liquid was distilled under reduced pressure. The product was a thick liquid which was collected at 195–200° (1.5 mm.); yield 16 g. (52%).

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.05; H, 6.51.

2-Allyl-4-*t*-butylphenol.—The foregoing general procedure was followed in this preparation. The rearrangement was carried out by refluxing the ether for five minutes after the temperature of the liquid had reached a maximum of 268°. Distillation *in vacuo* gave a colorless liquid which boiled at 127–129° (8 mm.). The over-all yield was 79%.

Anal. Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.06; H, 9.32.

4-Phenyl-α-amino-*o*-cresol (III 1).—A mixture of 17 g. (0.1 mole) of 4-phenylphenol, 18 g. (0.1 mole) of phthalimidomethanol,[19] 200 cc. of benzene and six drops of concentrated sulfuric acid was refluxed for two hours during which time the water was removed by means of a take-off attachment. The solution was then evaporated to dryness and the residue, dissolved in 100 cc. of alcohol, was heated to reflux with 10 cc. of 85% hydrazine hydrate solution. After twenty minutes, the mixture suddenly solidified. Two hundred cc. of 3 *N* hydrochloric acid was added and the mixture boiled for an hour. It was then cooled and filtered. Excess ammonia was added to the filtrate to pre-

(17) The molecular proportions of formaldehyde and amine to phenol used in these preparations depended upon the number of alkylaminomethyl groups desired in the final product. For example, two moles of both were used for each mole of intermediate biphenol in the preparation of VII 1.

(18) Haussermann and Bauer [*Ber.*, **30**, 738 (1897)] gave 160–161° and indicated a low yield.

(19) Sachs, *ibid.*, **31**, 3232 (1898).

TABLE I

4-(1,1,3,3-TETRAMETHYLBUTYL)-α-AMINO-*o*-CRESOLS

No.	SN	Q equiv. B4	Substituents	Procedure	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	5018	0.3[a]	α-Dimethylamino[b,c]										
2	7867	.03i	α-Dimethylamino[b,d]										
3	7494	.05i	α-Di-*n*-amylamino[e]	I	143[g]	81	$C_{25}H_{45}NO\cdot HBr$					3.07	3.09
4	6798	.02	α-1-Piperidyl[c]	II	70[h]	95							
5	7137	.03i	α-4-Morpholinyl	III	200[i]	52	$C_{19}H_{31}NO_2\cdot HCl$	66.71	66.93	9.43	9.28		
6	7821	.08	α-Ethyl-2-hydroxyethylamino	II	151[j]	93	$C_{19}H_{33}NO_2\cdot HCl$	66.35	66.49	9.97	9.92		
7	6803	.03	α-Di-2-hydroxyethylamino	II	81[k]	24	$C_{19}H_{33}NO_3$					4.32	4.31
8	6797	.02i	α-Dibenzylamino	II	118[h]	70	$C_{29}H_{37}NO$	83.80	83.94	8.98	8.64		
9	6804	.20	6-Methyl-α-dimethylamino[b]										
10	7491	.11	6-Chloro-α-diethylamino[b,f]										

[a] Q 0.67i by J1 test. [b] Sample from Rohm and Haas Co. [c] Described in U. S. Patent 2,033,092. [d] Methochloride. [e] Intermediate phenol from Rohm and Haas Co. [f] Phosphate. [g] From chloroform–ligroin. [h] From ethanol. [i] From iso-propanol. [j] From ethanol–acetone. [k] From ligroin.

TABLE II

ALKYL AND HALO α-AMINO-*o*-CRESOLS

No.	SN	Q. equiv. B4	Q. equiv. J1	Substituents	Procedure	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
				α-Dimethylamino-								
1	7502	0.03i		None[b]								
2	7498	.03i	0.05i	6-Methyl[b]								
3	7497	.1		4-*t*-Butyl[b,c]								
				α-Diethylamino-								
4	4769		0.2i	None[d]	IV	135[u]	32	$C_{11}H_{17}NO\cdot HCl$	61.24	61.17	8.41	8.47
5	6802	.05t		6-Methyl[e]	IV	161[v]	36	$C_{12}H_{19}NO\cdot HCl$	62.73	63.01	8.78	8.34
6	6805	.04		4-Methyl[f]	IV		71	$C_{12}H_{19}NO$				
			0.05i		...	157[v]	..	$C_{12}H_{19}NO\cdot HCl$[n]	62.73	62.68	8.78	8.95
7	7496	.4		4-*t*-Butyl	III	36[w]	38	$C_{16}H_{25}NO$	76.54	76.55	10.71	10.20
8	7741	.07i		4-*t*-Butyl-6-hydroxy	II	142[w]	96	$C_{16}H_{25}NO_2$	71.67	71.88	10.03	9.80
9	7503	.18t		4-2′-Methylcyclohexyl[g]	I	148[x]	46	$C_{18}H_{29}NO\cdot HCl$	69.31	69.53	9.70	9.41
10	8459	.1		6-*n*-Heptyl[h,i]	II	126[v]	46	$C_{18}H_{33}NO_2\cdot HCl$[o]	65.13	65.26	10.33	10.25
11	8458	.04i		4-*n*-Octyl[h,i]	II	86[y]	39	$C_{19}H_{33}NO\cdot HCl$	69.64	69.45	10.45	10.36
12	7500	.10		4-*n*-Dodecyl[b]								
13	7493	.06		4-Chloro	I	158[z]	56	$C_{11}H_{16}ClNO\cdot HCl$	52.78	52.93	6.85	6.89
14	7488	.06		4-Bromo[h]	II	165[aa]	..	$C_{11}H_{16}BrNO\cdot HCl$[p]				
15	7296	.05i		6-Bromo	I	175[bb]	10	$C_{11}H_{18}BrNO\cdot HCl$	44.82	45.08	5.82	5.68
16	13700	.05i		4-Methyl-6-bromo[h]	I	170[bb]	65	$C_{12}H_{18}BrNO\cdot HCl$	46.69	46.89	6.20	6.29
17	8456	.4t		4-Bromo-6-methyl[h]	I	175[cc]	38	$C_{12}H_{18}BrNO\cdot HCl$	46.69	46.66	6.20	6.45
18	9000	.06		4-Cyclohexyl-6-bromo[h]	II	92[w]	63	$C_{17}H_{26}BrNO$	60.00	60.21	7.69	7.58
19	8294		1.0	4-Chloro-6,1′-methallyl[h]	III	130[z]	44	$C_{15}H_{22}ClNO\cdot HCl$[q]				
20	7492	.1		4-*t*-Amyl-6-chloro[h]	I	148[dd]	83	$C_{16}H_{26}ClNO\cdot HCl$	59.99	60.23	8.50	8.50
21	8497	.08		4-Chloro-5-methyl	III	192[z]	51	$C_{12}H_{18}ClNO\cdot HCl$[r]				
22	8370	.06		3-Methyl-4-chloro-6-*n*-hexyl	II	132[v]	81	$C_{18}H_{32}ClNO_2\cdot HCl$[o]	59.01	59.13	9.08	9.26
23	7304	.2t		4,5-Dimethyl	I	190[u]	83	$C_{13}H_{21}NO\cdot HCl$	64.05	64.16	9.10	9.10
24	10989	.25		3,5-Dimethyl	II	156[bb]	77	$C_{13}H_{21}NO\cdot HCl$	64.05	64.31	9.10	9.07
25	7303	.10	0.4t	3,5,6-Trimethyl[k]	I	175[u]	94	$C_{14}H_{23}NO\cdot HCl$	65.22	65.14	9.38	9.05
26	10505	.05i		4-*t*-Butyl-5-methyl[l]	I	177[w]	12	$C_{16}H_{27}NO\cdot HCl$	67.22	67.05	9.87	9.63
27	9576	.3	1.0	4-*t*-Butyl-6-methyl[h]	I	150[bb]	45	$C_{16}H_{27}NO\cdot HCl$	67.22	67.46	9.87	9.89
28	7819	.2		4-*t*-Butyl-6-allyl	III	139[y]	48	$C_{18}H_{29}NO\cdot HCl$[s]				
29	8051	.17		4-*t*-Amyl-6-allyl[h]	III	151[z]	41	$C_{19}H_{31}NO\cdot HCl$[t]				
30	8383	.18		4-Cyclohexyl-6-allyl[h]	II	142[w]	59	$C_{20}H_{31}NO\cdot HCl$	71.08	71.37	9.55	9.52
31	8393	2.0[a]		4-*t*-Butyl-6-cyclohexyl[h]	II	192[w]	56	$C_{21}H_{33}NO\cdot HCl$	71.26	71.58	10.25	10.00
32	6799	0.04i		4-Chloro-α-1-piperidyl[m]	II	57[w]	82	$C_{12}H_{16}ClNO$	63.85	63.94	7.15	7.10
33	7298	.08i		4-Chloro-5-methyl-α-1-piperidyl[j]	III	85[w]	62	$C_{13}H_{18}ClNO$	65.14	64.91	7.57	7.55
34	6796	.05i		4-Chloro-5-methyl-α-4-morpholinyl[j]	III	215[aa]	31	$C_{12}H_{16}ClNO_2\cdot HCl$	51.80	52.00	6.16	5.81

[a] Q 1.0 by D1 tests. [b] Sample from Rohm and Haas Co. [c] Hydrochloride. [d] Base distilled at 100–110° (3 mm.). Grillot and Gormley [THIS JOURNAL, **67**, 1968 (1945)] found 63–67° (1–2 mm.). [e] Base distilled at 107–108° (3 mm.). Grillot and Gormley [*ibid.*] found 93–97° (1–2 mm.). [f] B. p. ,122° (4 mm.). [g] Intermediate phenol from Monsanto Chemical Co., St. Louis. [h] Intermediate phenol from Dow Chemical Co. [i] Microanalysis by Arlington Laboratories. [j] Intermediate phenol from Monsanto Chemicals, Ltd. [k] Intermediate phenol from Shell Development Co. [l] Intermediate phenol from The Koppers Co. [m] Yang describes this compound prepared by essentially the same procedure (m. p. 55°) in *J. Org. Chem.*, **10**, 67 (1945), but assigns the structure of 4-chloro-α-1-piperidyl-*m*-cresol. [n] Prepared by treatment of an ethereal solution of the base with alcoholic hydrochloric acid. [o] Includes $1H_2O$. [p] *Anal.* for N: Calcd. 4.75. Found 4.91. [q] *Anal.* for N: Calcd. 4.64. Found 4.70. [r] *Anal.* for N: Calcd. 5.30. Found 5.21. [s] *Anal.* for N: Calcd. 4.49. Found 4.57. [t] *Anal.* for N: Calcd. 4.30. Found 4.23. [u] From acetone–ethanol. [v] From acetone. [w] From ethanol. [x] From acetone–ethyl acetate. [y] From ethyl acetate. [z] From isopropanol–ether. [aa] From isopropanol. [bb] From ethanol–ether. [cc] From methanol–acetone. [dd] From acetone–ether.

TABLE III

ARYL α-AMINO-*o*-CRESOLS

No.	SN	Q. equiv. B4	Q. equiv. J1	Substituents	Procedure	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	9578		1.0	4-Phenyl-α-amino[a]		235[k]		$C_{13}H_{13}ClNO.HCl$	66.24	65.88	5.97	5.90
2	5017	0.2	0.5	4-Phenyl-α-dimethylamino[b]								
		D1 0.12										
		D2 0.25										
3	7301	.12i		4-Phenyl-α-diethylamino	I	165[l]	46	$C_{17}H_{21}NO\cdot HCl$	69.97	70.23	7.60	7.37
4	7487	.03i		4-Phenyl-α-ethyl-2-hydroxyethyl-amino	III	149[m]	18	$C_{17}H_{21}NO_2\cdot HCl$	66.34	66.30	7.21	7.25
5	7142	.02		4-Phenyl-α-1-piperidyl	III	90[n]	62	$C_{18}H_{21}NO$	80.87	80.71	7.92	7.61
6	7143	.03i		4-Phenyl-α-4-morpholinyl	III	91[n]	50	$C_{17}H_{19}NO_2$	75.82	75.66	7.11	7.06
7	7740	.05i	0.2t	4-Phenyl-6-hydroxy-α-diethylamino	II	108[m]	64	$C_{17}H_{21}NO_2$	75.24	75.36	7.80	7.95
8	7820	.4	0.4t	5-Phenyl-α-diethylamino[c]	I	78[o]	76	$C_{17}H_{21}NO$	79.96	79.77	8.29	8.26
9	6895	.35	1.0	6-Phenyl-α-diethylamino[d]								
10	9283	.2		6-Phenyl-α-ethylamino[c]	I	186[l]	..	$C_{16}H_{17}NO\cdot HCl$	68.30	68.38	6.88	6.87
11	8268	.1		6-Phenyl-α-2-hydroxyethylamino[e]								
		D1 0.06										
		D2 0.25										
12	8298	.13		6-Phenyl-α-*n*-decylamino[c]	I	134[p]	50[f]	$C_{23}H_{33}NO\cdot HCl$	73.47	73.53	9.11	9.03
13			0.17	4-Phenyl-6-chloro-α-diethylamino[c]	I	141[p]	31	$C_{17}H_{20}ClN\cdot OHCl$[g]	62.58	62.46	6.49	6.30
14	7489	.01i		4-Phenyl-6-chloro-α-1-piperidyl[c]	II	80[n]	92	$C_{18}H_{20}ClNO$	71.63	71.41	6.68	6.68
15	7294	.05i		4-Phenyl-6-bromo-α-diethylamino[c]	I	141[n]	89	$C_{17}H_{20}BrNO\cdot HCl$	55.07	54.91	5.71	5.71
16	7297	.18	1.0	4-Chloro-6-phenyl-α-diethylamino	I	128[m]	43	$C_{17}H_{20}ClNO\cdot HCl$	62.58	62.57	6.49	6.16
		D1 0.5										
		D2 1.0										
17	14111	.3		4-Bromo-6-phenyl-α-diethylamino[c]	I	146[m]	70	$C_{17}H_{20}BrNO\cdot HCl$[h]				
18	7490	.2		2-Chloro-3-phenyl-α-diethylamino[c]	I	65[n]	54	$C_{17}H_{20}ClNO$[i]	70.45	70.20	6.96	6.84
19	7282	1.5	2.0	4-*t*-Butyl-6-phenyl-α-dimethylamino[c]	I	207[m]	85	$C_{19}H_{25}NO\cdot HCl$	71.34	71.36	8.19	8.00
20	7744	2.0	1.0i	4-*t*-Butyl-6-phenyl-α-diethylamino[c]	I	173[p]	83	$C_{21}H_{29}NO\cdot HCl$	72.50	72.54	8.69	8.71
		D1 2.0										
21	9636	1.5		O-Acetyl-4-*t*-butyl-6-phenyl-α-di-ethylamino[a]		201[q]	67	$C_{28}H_{31}NO_2\cdot HCl$	70.84	70.92	8.27	8.23
22	10122	0.16t		O-Methyl-4-*t*-butyl-6-phenyl-α-di-ethylamino[a]		142[r]	50	$C_{22}H_{31}NO\cdot HCl$	73.00	73.03	8.91	9.07
23	9557	2.5		4-*t*-Butyl-6-phenyl-α-ethylamino[c]	II	216[m]	42	$C_{19}H_{25}NO\cdot HCl$	71.34	71.36	8.19	8.36
24	9202	1.0		4-*t*-Butyl-6-phenyl-α-2-hydroxyethyl-amino[c]	II	158[s]	45	$C_{19}H_{29}NO_4\cdot HCl$[j]	61.36	61.70	8.19	7.82
25	8368	1.6	2.0	4-*t*-Amyl-6-phenyl-α-diethylamino[c]	II	168[p]	80	$C_{22}H_{31}NO\cdot HCl$	73.00	72.94	8.91	8.70
		D1 1.0										
26	8303	0.6	0.2	4-(1,1,3,3-Tetramethylbutyl)-6-phenyl-α-diethylamino[c]	II	178[s]	88	$C_{25}H_{37}NO\cdot HCl$	74.31	74.31	9.48	9.39
		D1 1.0										
27	8289	0.55		4-Phenyl-6-1-methallyl-α-diethyl-amino	I	151[q]	50	$C_{21}H_{27}NO\cdot HCl$	72.91	72.92	8.16	8.39
28	8500	0.08		4-*t*-Butyl-5-phenyl-α-diethylamino[c]	II	190[p]	83	$C_{21}H_{29}NO\cdot HCl$	72.50	72.22	8.69	8.66

[a] For Preparation see the Experimental Part. [b] Sample obtained from Rohm and Haas Company. [c] Intermediate phenol from Dow Chemical Company. [d] Preparation and proof of structure will appear in a later publication; tested as the hydrochloride. [e] Described in U. S. Patent 2,114,122. [f] By Procedure V the percentage yield was 47. [g] *Anal.* for N: Calcd. 4.29. Found 4.14. [h] *Anal.* for N: Calcd. 3.78. Found 3.72. [i] *Anal.* for N: Calcd. 4.83. Found 4.90. [j] Includes $2H_2O$. [k] From ethanol–ligroin. [l] From ethanol–acetone. [m] From isopropanol. [n] From ethanol. [o] From dilute ethanol. [p] From acetone. [q] From ethyl acetate. [r] From toluene. [s] From ethanol–ether.

cipitate 6 g. of solid base; m. p. 157–158°. The crude product was dissolved in potassium hydroxide solution and the mixture was filtered through Supercel. A stream of carbon dioxide through the solution reprecipitated 5.8 g. (29% yield) of light tan colored base; m. p. 157–158°.

The hydrochloride was prepared by dissolving the base in alcoholic hydrogen chloride. By evaporating the solution to a low volume, a yellow crystalline precipitate formed; m. p. 228–233°. After treatment with Norite in alcoholic solution and recrystallization twice from alcohol–ligroin, the white product melted at 235°.

O-Acetyl-4-*t*-butyl-6-phenyl-α-diethylamino-*o*-cresol (III 21).—A mixture of 20 g. (0.057 mole) of α-diethylamino-4-*t*-butyl-6-phenyl-*o*-cresol hydrochloride (III 20) and 70 g. of acetic anhydride was warmed until complete solution was effected. After a drop of concentrated sulfuric acid had been added, the solution was allowed to stand for about five minutes before the excess acetic anhydride was removed under reduced pressure. The crude crystalline hydrochloride was collected and washed with ether.

O-Methyl-4-*t*-butyl-6-phenyl-α-diethylamino-*o*-cresol (III 22).—From 144 g. (0.637 mole) of 4-*t*-butyl-*o*-phenylphenol, an essentially quantitative yield of 4-*t*-butyl-*o*-phenylanisole [b. p. 143–145 (3 mm.)] was obtained by methylation with dimethyl sulfate.

Anal. Calcd. for $C_{17}H_{20}O$: C, 84.96; H, 8.39. Found: C, 85.06; H, 8.43.

To a stirred solution of 144 g. (0.6 mole) of 4-*t*-butyl-*o*-phenylanisole in 100 cc. of glacial acetic acid, 96 g. (0.6 mole) of bromine in 100 cc. of glacial acetic acid was added over a period of an hour. At the end of the addition, the temperature of the solution was 40°. After standing for half an hour, the solution was poured into two liters of water. The resulting mixture was extracted with ether and the ether layer washed with two different portions of water. After removal of the solvent, the residue was distilled at 154–160° (2 mm.) to yield 159 g. (83%) of product. Upon redistillation, 130 g. was collected at 147–148° (2 mm.), yielding 68% of an oil considered to be 2-bromo-4-*t*-butyl-6-phenylanisole.

A Grignard reagent was made from 76.3 g. (0.24 mole) of 2-bromo-4-*t*-butyl-6-phenylanisole, 5.8 g. of magnesium turnings and 250 cc. of dry ether. Initiation of the reaction was very difficult despite the use of customary pro-

TABLE IV

BENZYL-TYPE α-DIETHYLAMINO-*o*-CRESOLS

No.	SN	Q equiv. B4	Substituents	Procedure	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	7499	0.13[a]	4-Benzyl[c]	II	160[e]	10	$C_{18}H_{23}NO\cdot HCl$					4.58	4.68
2	7300	.06[b]	6-Benzyl[c]	II	149[e]	48	$C_{18}H_{23}NO\cdot HCl$					4.58	4.58
3	14309	.06	4,6-Dibenzyl[c]	II	152[f]	..	$C_{25}H_{29}NO\cdot HCl$					3.54	3.54
4	7742	.21	4-Benzyl-6-methyl[d]	I	109[f]	50	$C_{19}H_{25}NO\cdot HCl$	71.34	71.12	8.19	8.18		
5	7295	.12t	4-Phenylhydroxymethyl	I	106[g]	59	$C_{18}H_{23}NO_2$					4.90	4.84
6	8049	.05i	4-(1-Methyl-1-phenylethyl)	I	150[h]	42	$C_{20}H_{27}NO\cdot HCl$					4.20	4.24
7	8996	.1t	4-(1-Methyl-1-phenylethyl)-6-hydroxy[c]	II	97[i]	35	$C_{20}H_{27}NO_2$	76.63	76.67	8.68	8.73		

[a] Q0.06 by D1 test. [b] Q0.09 by D1 test. [c] Intermediate phenol from Dow Chemical Company. [d] Analyses by Arlington Laboratories [e] From isopropanol. [f] From ethyl acetate. [g] From ethanol. [h] From ethanol–ethyl acetate. [i] From ligroin.

TABLE V

MISCELLANEOUS 4-SUBSTITUTED α-DIETHYLAMINO-*o*-CRESOLS

No.	SN	Q. equiv. B4	Q. equiv. J1	Substituents	Procedure	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	7363	0.08i	0.4t	Methoxy[a]	IV		52	$C_{19}H_{19}NO_2$					6.69	6.77
2	7364	.06i	0.4	Ethoxy[b,c]	IV		66	$C_{13}H_{21}NO_2$					6.27	6.13
3	8371	.08		Benzyloxy	I	133[f]	37	$C_{18}H_{23}NO_2\cdot HCl$	67.17	67.13	7.51	7.51		
4	8048	.04	1.0i	Phenoxy[c]	III	130[g]	39	$C_{17}H_{21}NO_2\cdot HCl$					4.55	4.54
5		.05i		2,5-Dimethyl-1-pyrryl[d]	III	164[h]	25	$C_{17}H_{24}N_2O$	74.96	75.14	8.88	8.83		
6	8309	0.15		4′-Morpholinyl[c]	II	176[h]	..	$C_{15}H_{24}N_2O_2\cdot HCl$					9.31	9.31
7	7738	0.05		Cyano	II	208[h,i]	37	$C_{12}H_{16}N_2O\cdot HCl$					11.66	11.61
8	7637	.05i		Guanyl[e]		215[h]	68	$C_{12}H_{19}N_3O\cdot 2HCl$	48.98	49.30	7.20	7.10		

[a] Colorless liquid; b. p. 133–135° (3 mm.). [b] Slightly greenish colored liquid; b. p. 144–147° (3 mm.). [c] Intermediate phenol from Dow Chemical Company. [d] See Experimental Part for preparation of the intermediate phenol. [e] For preparation see experimental part. [f] From methyl ethyl ketone. [g] From isopropanol–ether. [h] From ethanol. [i] Light yellow-colored crystals.

cedures. Finally, after all the halide had been added, the mixture was heated at refluxing temperature and stirred for a total of twenty hours, at the end of which time nearly all the magnesium had dissolved.

To the Grignard reagent was added drop by drop with stirring 34 g. (0.26 mole) of diethylaminomethyl ethyl ether[6d] in 75 cc. of dry ether. Gentle refluxing was induced by the reaction. After all the ether solution had been added, the mixture was heated for an hour at refluxing temperature and then hydrolyzed with 250 cc. of 15% sulfuric acid. The acid layer was separated and rendered alkaline with excess concentrated sodium hydroxide solution. The product was extracted with ether and the ether extracts washed well with water and dried over anhydrous potassium carbonate. The filtered ether solution was treated with excess alcoholic hydrogen chloride. After the solvent was removed under reduced pressure, the residual mass crystallized. It was triturated with ether and the crystals collected.

4-Guanyl-α-diethylamino-*o*-cresol (V 8).—A rapid stream of dry hydrogen chloride gas was passed for an hour through an ice-cooled suspension of 10 g. (0.04 mole) of 4-cyano-α-diethylamino-*o*-cresol hydrochloride (V 7) in 100 cc. of absolute alcohol. After standing for twenty-four hours, the solution was evaporated to dryness at room temperature under reduced pressure. Twelve grams of a red crystalline powder, considered to be the corresponding crude imino ether dihydrochloride, was obtained; m. p. 158–168° with vigorous decomposition. [A small sample was recrystallized as nearly white crystals; m. p. 167–169° (dec.)].

Half (6 g.) of the crude imino ether salt was placed in a pressure bottle with a ten-fold excess of alcoholic ammonia and the mixture shaken for fourteen hours, after which time the ammonia was neutralized with alcoholic hydrogen chloride. Precipitated ammonium chloride was separated several different times during the evaporation of the solvent. It was removed by filtration. When the volume was reduced to about 15 cc., the desired product crystallized. After two recrystallizations from alcohol, with charcoal treatments, 4.0 g. of crystalline hydrochloride was obtained.

Pharmacological Results[20]

Among the many α-aminocresols from this Laboratory which have been screened in avian malarial infections, 128 of them are grouped in the ten tables of this paper in order to simplify a study of the relationships of structure to antimalarial activity. An indication of the therapeutic effect of each chemical is expressed numerically along with its survey number.[21]

In Table I, none of the compounds, all of which contain the tetramethylbutyl group, were found to be more active than the first. Of those in Table II, number 31 proved to be the most effective, possibly because of its chemical relationship to the active *o*-phenylphenol types (*e. g.*, III 20). While the O-acetyl derivative of (III 21) was nearly as

(20) The facilities for testing the compounds described in this paper were provided by the Office of Scientific Research and Development through the Committee on Medical Research and by Dr. A. L. Tatum of the Department of Pharmacology in the University of Wisconsin.

(21) The SN numbers are part of the system set up by the Survey Office of the National Research Council as a means of systematizing the various data reported from cooperating laboratories. B4 (*P. gallinaceum* in chicks), D1 (*P. lophurae* in ducks), D2 (*P. cathemerium* in ducks), and J1 (*P. cathemerium* in canaries) designate the avian test procedures of, respectively, Drs. R. J. Porter and L. T. Coggeshall; Dr. E. K. Marshall, Jr.; and Dr. A. L. Tatum. All infections are trophozoite induced. An indication of the therapeutic effect of each compound tested is expressed numerically as a quinine equivalent (q. equiv.). For example, 0.2 represents the activity of a drug that is one-fifth as a effective as quinine; 0.2i shows that a drug is inactive at five times the effective dose of quinine; and 0.2t designates a drug that is both toxic to the bird and inactive at five times the effective dose of quinine. Dr. Tatum usually reported activities without reference to quinine. In such cases, conversions were made by the authors for purposes of this report.

TABLE VI

FUSED RING α-AMINO-*o*-CRESOLS

No.	SN	Q. equiv B4		Name	Procedure	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	7299	0.1	2.0	2-Diethylaminomethyl-1-naphthol	II	150[d]	57	$C_{15}H_{19}NO\cdot HCl$	67.78	67.72	7.53	7.14
2	6806		0.1t	1-Diethylaminomethyl-2-naphthol	I	164[e]	78	$C_{15}H_{19}NO\cdot HCl$	67.76	67.76	7.53	7.33
3		.05i	.33t	7-Dimethylaminomethyl-8-quinolinol	V	186[d]	74	$C_{12}H_{14}N_2O\cdot HCl$	60.37	60.16	6.33	6.43
4		.11		7-1′-Piperidylmethyl-8-quinolinol[a]	II	194[d]	52	$C_{15}H_{18}N_2O\cdot HCl$[c]	58.91	59.08	7.25	7.29
5			.33t	8-Diethylaminomethyl-7-quinolinol[b]	I	220[d]	37	$C_{14}H_{18}N_2O\cdot 2HCl$	55.45	55.19	6.65	6.33

[a] Free base (m. p. 117) prepared: German Patent 92,309; *Frdl.*, **4**, 103 (1899). [b] Intermediate 7-quinolinol prepared by the directions of Skraup, *Monatsh.*, **5**, 533 ("Beilstein," **10**, 167). [c] Contains in addition 1.5 moles of water; *anal.* for N: calcd. 8.84. Found 8.79. [d] From ethanol. [e] From ethanol–acetone.

TABLE VII

α,α′-*bis*-(AMINO)-4,4′-BI-*o*-CRESOLS (DIHYDROCHLORIDES)[c]

No.	SN	Q. equiv. B4	J1	Substituents	Procedure	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	6894	0.17t	0.5i	*bis*-(Diethylamino)	I	225[e]	55	$C_{22}H_{32}N_2O_2$	61.53	61.60	7.98	7.99
2	10271	4.0		α,α-*bis*-(Diethylamino)5,5′-bi-*o*-cresol[b]	II	106[e]	92	$C_{22}H_{32}N_2O_2$[d]	74.12	74.38	9.05	9.06
3	7824	0.75		6,6′-Dimethyl-*bis*-(diethylamino)[b]	I	215[f]	64	$C_{24}H_{36}N_2O_2$	63.00	62.63	8.37	8.18
4	7827	1.0		6,6′-Di-*n*-propyl-*bis*-(diethylamino)[b]	I	221[f]	70	$C_{28}H_{44}N_2O_2$	65.47	65.60	9.02	8.89
5		2.5		6,6′-Di-(2-chloroallyl)-*bis*-(diethylamino)[b]	I	208[g]	34	$C_{28}H_{38}Cl_2N_2O_2$	58.13	58.24	6.97	7.00
6	8379	0.11t		6,6′-Di-(2-methallyl)-*bis*-(diethylamino)[b]	I	263[f]	17	$C_{30}H_{44}N_2O_2$	67.02	66.70	8.62	8.76
7	8316	4.0	.5	6,6′-Diallyl-*bis*-(dimethylamino)[b]	I	241[g]	47	$C_{24}H_{32}N_2O_2$	63.56	63.26	7.56	7.53
8	6771	2.0	.5[a]	6,6′-Diallyl-*bis*-(diethylamino)	I	209[e]	67	$C_{28}H_{40}N_2O_2$	65.97	65.78	8.31	8.47
9	8315	1.0	.5	6,6′-Diallyl-*bis*-(di-*n*-propylamino)	I	187[g]	38	$C_{32}H_{48}N_2O_2$	67.94	67.99	8.91	8.92
10	8380	0.25		6,6′-Diallyl-*bis*-(di-*n*-butylamino)	I	178[g]	57	$C_{36}H_{56}N_2O_2$	69.54	69.60	9.40	9.46
11	9558	.5		6,6′-Diallyl-*bis*-(1-piperidyl)	I	250[f]	78	$C_{30}H_{40}N_2O_2$	67.52	67.20	7.93	7.99
12	10150	.05		6,6′-Diallyl-*bis*-(4-morpholinyl)	I	251[h]	70	$C_{28}H_{36}N_2O_4$	62.56	62.17	7.11	7.47
13	9187	.6		6,6′-Diallyl-*bis*-(2-hydroxyethyl)	I	111[i]	24	$C_{24}H_{32}N_2O_4$[d]	69.87	69.73	7.82	7.81
14	9188	.06		6,6′-Diallyl-*bis*-(di-2-hydroxyethyl)	I	130[j]	20	$C_{28}H_{40}N_2O_6$[d]	67.17	67.33	8.05	7.98
15	9635	1.3		0,0′-Diacetyl-6,6′-diallyl-*bis*-(diethylamino)	VI	224[k]	90	$C_{32}H_{44}N_2O_4$	64.74	64.81	7.81	7.75
16	11000	0.8		0,0′-Dipropionyl-6,6′-diallyl-*bis*-(diethylamino)	VI	185[l]	30	$C_{34}H_{48}N_2O_4$	65.68	65.42	8.10	8.37

[a] Q 0.5 by D1 and Q1–2 by D2. [b] Intermediate biphenol from Dow Chemical Company. [c] All compounds, except 2, 13 and 14, contain 2HCl. [d] Obtained as the free base. [e] From ethanol. [f] From methanol–acetone. [g] From ethanol–ether. [h] Ethanol–acetone. [i] From benzene. [j] From benzene–ethyl acetate. [k] From ether–ethyl acetate. [l] From ether–acetone.

TABLE VIII

bis-(α-DIETHYLAMINO-*o*-CRESOLS)

No.	SN	Q. Equiv B4	Name	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	5918	1.0[a]	4,4′-Oxy-*bis*-(α-diethylamino-*o*-cresol)[b,c]	99	66[g]	$C_{22}H_{32}N_2O_3$					7.52	7.51
2	8450	0.21	4,4′-Oxy-*bis*-(6-allyl-α-diethylamino-*o*-cresol)[b,d]	240	47[h]	$C_{24}H_{32}N_2O_3$[f]					5.97	5.99
3	7737	.09	4,4′-Isopropylidene-*bis*-(6-methyl-α-diethylamino-*o*-cresol)[d]	210	48[i]	$C_{27}H_{42}N_2O_2$[f]					5.61	5.56
4	9186	.5	4,4′-Isopropylidene-*bis*-(6-phenyl-α-diethylamino-*o*-cresol)[d,e]	75	77[j]	$C_{37}H_{46}N_2O_2$	80.68	80.01	8.42	8.67		
5	7828	.2	4,4′-[(α,β-Diethyl-α,β-dihydroxy)-ethylene]-*bis*-(α-diethylamino-*o*-cresol)[d]	153	23[k]	$C_{28}H_{44}N_2O_4$	71.14	70.87	9.38	9.51		
6	7826	.4	4,4′-[(α,β-Dietnyl)-vinylene]-*bis*-(α-diethylamino-*o*-cresol)[d]	110	50[k]	$C_{28}H_{42}N_2O_2$	76.65	76.89	9.65	9.68		
7	8583	1.4	4,4′,4″,4‴-[Ethylenediethylidyne]-*tetrakis*-(α-diethylamino-*o*-cresol)[d,e]	150	6[l]	$C_{50}H_{74}N_4O_4$	75.52	75.25	9.38	9.36		

[a] Other activity figures: 1.0(J1), 0.09(D1) and 0.5(D2). [b] See Experimental part for the preparation of intermediate oxybiphenol. [c] Prepared by Procedure III. [d] Prepared by Procedure I. [e] Phenolic intermediate from Dow Chemical Company. [f] Contains also 2HCl. [g] From dilute ethanol. [h] From isopropanol. [i] From ethanol–ethyl acetate. [j] A suitable crystallizing solvent was not found; compound purified by neutralization of an acid solution. [k] From methanol. [l] From methanol–ethyl acetate.

active as the parent compound, the corresponding O-methyl compound (III 22) was both inactive and toxic at greater than the effective dosage of quinine. The benzyl-α-diethylamino-*o*-cresols (Table IV) appear to offer little promise. Despite their relationships to active types,[16,18] V 5 and 8

TABLE IX

α-DIETHYLAMINO-*p*-CRESOLS

No.	SN	Q. equiv. B4	Q. equiv. J1	Q. equiv. D1	Substituents	Procedure	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	8999	0.04i			3,6-Dimethyl	II	104[e]	20	$C_{13}H_{21}NO$	75.31	75.10	10.21	10.08
2	9001	.05			3-Methyl-6-isopropyl[a]	II	93[f]	..	$C_{15}H_{25}NO$	76.54	76.69	10.71	10.61
3	6772	1.2	2.0	0.13	2-Phenyl[b]								
4	8050	0.4	2.0	.5i	2-Chloro-6-phenyl[c]	II	162[g]	80	$C_{17}H_{20}ClNO\cdot HCl$	62.58	62.61	6.49	6.70
5	8388	.4		.25t	2-Allyl-6-phenyl[d]	II	128[g]	66	$C_{20}H_{25}NO\cdot HCl$	72.38	72.33	7.90	8.10
6	10210	.12	1.0i		2,6-Diphenyl[c]	I	189[h]	57	$C_{23}H_{25}NO\cdot HCl$	75.08	75.14	7.12	7.14

[a] Microanalyses by Arlington Laboratories. [b] Preparation and proof of structure will appear in a later publication. [c] Intermediate phenol from Dow Chemical Company. [d] Intermediate 2-allyl-6-phenylphenol described by Auwers and Wittig, *J. prakt. Chem.*, [2] **108**, 99 (1924). [e] From ligroin–acetone. [f] From ligroin. [g] From isopropanol. [h] From methanol–acetone.

TABLE X

POLY-(AMINOMETHYL)-PHENOLS

No.	SN	Q. equiv. B4	Q. equiv. J1	Name	M. p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	7357	0.05	0.17i	2,6-*bis*-(Dimethylaminomethyl)-phenol[a]									
2	7638	.06	.17i	2,4-*bis*-(Dimethylaminomethyl)-6-methylphenol[a]									
3	7736	.25		2,4-*bis*-(Diethylaminomethyl)-6-cyclohexylphenol[b,c]	199[e]	..	$C_{22}H_{38}N_2O\cdot 2HCl$	62.99	62.74	9.61	10.03	6.68	6.70
4	7358	1.3	.5	2,4-*bis*-(Diethylaminomethyl)-6-phenylphenol[b,c]	207[f]	95	$C_{22}H_{32}N_2O\cdot 2HCl$	63.91	63.58	8.29	8.35		
5	7356	0.23		2,5-*bis*-(Diethylaminomethyl)-hydroquinone[d]	107[f]	62	$C_{16}H_{28}N_2O_2$	68.53	68.46	10.07	9.81	9.99	9.83
6	6793	.03	.17i	2,4,6-*tris*-Dimethylaminomethyl)-phenol[a]									
7	6795	.02i		2,4,6-*tris*-(4-morpholinylmethyl)-phenol[a]									

[a] Sample from Rohm and Haas Company. [b] Intermediate phenol from Dow Chemical Company. [c] Prepared by Procedure I. [d] Prepared by Procedure II. [e] From ethyl acetate. [f] From alcohol.

were ineffective. VI 1 was twice as active as quinine in the canary; this effectiveness demonstrates how the α-aminocresol grouping may confer antimalarial activity upon compounds containing various nuclei. The bis-(dialkylamino)-bi-*o*-cresols of Table VII offer evidence of nuclear variations that increase activity. Although the efficacy of VIII 1 in avian malaria has been of considerable interest, the nuclear introduction of allyl groups patterned after the VII 7 series resulted in the inactive compound VIII 2. The only compounds of note in Tables IX and X were derived from *o*-phenylphenol.

Detailed pharmacological data on all the compounds included in this paper will appear elsewhere, along with descriptions of the testing methods used. Also, clinical reports on several of the compounds will be published elsewhere.

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Summary

Establishment of the effectiveness of α-dimethylamino-4-(1,1,3,3-tetramethylbutyl)-*o*-cresol in avian malaria has resulted in the synthesis and study of hundreds of compounds. This first report includes 128 compounds, most of which were prepared by the Mannich reaction; 109 are new. For the purpose of studying the relationships of chemical structure to activity, the compounds have been classified in ten tables.

Several of these agents range in effectiveness from one to four times that of quinine. The following are representative of some of the most interesting types thus far prepared in this particular group: 4-*t*-butyl-α-diethylamino-6-phenyl-*o*-cresol, 2-diethylaminomethyl-1-naphthol, 6,6′-diallyl-α,α′-*bis*-(dimethylamino)-4,4′-bi-*o*-cresol, and 4,4′-oxy-*bis*-(α-diethylamino-*o*-cresol).

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