and the residue was recrystallized from H_2O to yield 39.6 g (73%) of tan crystals, mp 93–96°. The analytical sample was obtained by repeated recrystallization from H_2O as colorless crystals of hydrated IX, mp 98–99°. Vacuum drying for 1 hr at 78° gave the anhydrous material IX, mp 162–163°. *Anal.* ($C_{12}H_{11}NO_3$) C, H, N.

1-Ethyl-1,4-dihydro-6,7-dihydroxy-4-oxo-3-quinolinecarboxylic Acid Hemihydrate (Xa).—A mixture of 19.6 g (0.075 mole) of IVb and 200 ml of 48% HBr was refluxed for 6 hr. The pH of the solution was adjusted to *ca.* 6.5 by addition of 50% aqueous NaOH with cooling. Filtration yielded 14.8 g (76%) of light tan solid, mp 291–293°. Recrystallization from H_2O yielded faint tan crystals which melted at 294–296° after drying *in vacuo* (100°, 0.01 mm) for 8 hr. *Anal.* ($C_{12}H_{11}NO_5 \cdot 0.5H_2O$) C, H, N, H_2O (Karl Fischer).

The N-methyl analog (Xb) was prepared similarly and recrystallized from 50% aqueous DMF to yield 82% of faint tan crystals of hemisolvate, mp 320–321°. *Anal.* ($C_{11}H_9NO_5 \cdot 0.5C_3H_7NO$) C, H, N.

Diethyl 2-[(3,4-Methylenedioxy-6-nitrophenyl)methylene]malonate (XII).—A mixture of 98 g (0.5 mole) of 6-nitropiperonal[9] (XI), 88 g (0.55 mole) of diethyl malonate, 34.5 g (0.25 mole) of anhydrous K_2CO_3, and 200 g of Ac_2O was heated for 3 hr on a steam bath. The mixture was poured onto 3 l. of ice and allowed to stand overnight. The solid was filtered and dissolved in 1 l. of Et_2O, and the Et_2O was washed successively with 500 ml of H_2O and 500 ml of 5% aqueous $NaHCO_3$. The Et_2O layer was dried ($MgSO_4$) and freed of solvent. The residue was crystallized by dissolving in toluene, adding 2 vol. of petroleum ether and cooling. Filtration gave 164 g (92%) of yellow XII, mp 52–54. Repeated recrystallization from $CHCl_3$–petroleum ether (1:4) gave the analytical material: mp 59–61°; pmr, 374 (2 s, O-CH_2-O), 414 (1 s, 2-H), 465 (1 s, vinyl H), 491 (1 s, 5-H). *Anal.* ($C_{15}H_{15}NO_8$) C, H, N.

Ethyl 5,6-Dihydro-6-oxo-1,3-dioxolo[4,5-*g*]quinoline-7-carboxylate (XIII).—Iron filings (10 g) were added to a solution of 10 g (0.03 mole) of XII, 50 ml of H_2O, and 200 ml of HOAc on a steam bath. The mixture was heated with stirring for 1 hr. More iron filings (20 g) were added in 4–5-g portions at 1-hr intervals with heating, and stirring was continued for an additional 2 hr. The mixture was filtered hot and the filter cake was extracted with 100 ml of boiling DMF. The combined filtrate was freed of solvents *in vacuo*, and the residue was recrystallized from absolute EtOH yielding 5.1 g (66%) of yellow-tan platelets, mp 272–275°. Recrystallization from 90% aqueous DMF gave the analytical sample: mp 276–277°; λ_{max} 214.5, 243, 264 sh, 298, and 376 mμ (ϵ 35,400, 25,000, 5300, 4800, and 8600); pmr (DMSO-d_6), 363 (2 s, O-CH_2-O), 404 (1 s, 4-H), 431 (1 s, 9-H), 495 (1 s, 8-H), 712 (1 s (broad), 5-H). *Anal.* ($C_{13}H_{11}NO_5$) C, H, N.

5,6-Dihydro-5-methyl-6-oxo-1,3-dioxolo[4,5-*g*]quinoline-7-carboxylic Acid (XIV).—Dimethyl sulfate, 5.1 g (0.04 mole), was added to a mixture of 6.0 g (0.023 mole) of XIII, 50 ml of 10% NaOH solution, and 10 ml of 95% EtOH, and the mixture was stirred for 3 hr. After leaving overnight, the mixture was refluxed for 2 hr, treated with charcoal, and filtered hot. To the cooled filtrate were added 50 ml of 5% NaOH solution and 2.5 g of Me_2SO_4, and the solution was stirred for 2 hr. Acidification with 12 *N* HCl yielded 5.1 g (85%) of tan XIV, mp 329–330°. The analytical sample, from 90% aqueous DMF, had mp 326–331°; λ_{max} (saturated solution in 95% EtOH) 221, 244.5, 264 (sh), 298, 306, 378, and 389 mμ. *Anal.* ($C_{12}H_9NO_5$) C, H, N.

Acknowledgment.—We are indebted to Mrs. Unni Zeek and staff for the microanalyses, Mr. R. Puchalski and staff for the spectra, Dr. S. Ringel, Mr. D. Kronish and staffs for the *in vitro* screening, and Mr. F. Turner, Mr. P. Storino, and staff for the *in vivo* testing. We should also like to acknowledge the aid of Mr. J. Genzer and Mr. F. Fontsere of the Chemical Development Department for supplying kilogram quantities of several of these compounds.

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Some New *p*-Chlorophenoxycarbanilides and Their Bacteriostatic Activities

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Received June 21, 1967

The antibacterial properties of various carbanilides, especially when substituted with halogen and trifluoromethyl groups, are well known,[1,2] and some of these compounds are widely incorporated into toilet soaps for the control of skin flora.[3]

We now report the synthesis of some new compounds of this class bearing 4-chlorophenoxy substituents, most of which show very high *in vitro* activity against *Staphylococcus aureus*.

Details of the new carbanilides are given in Table I. They were synthesized by reaction of an aminodiphenyl ether with an aryl isocyanate and characterized spectroscopically and by elemental analysis. The required isocyanates can either be obtained commercially or can be readily synthesized by the Curtius reaction, and the aminodiphenyl ethers were obtained by reduction of the corresponding nitrodiphenyl ethers, synthesized by the Ullmann reaction. In the Ullmann synthesis of 2-nitro-4,5,4′-trichlorodiphenyl ether, we have assumed that the *o*- rather than the *p*-chlorine atom of 2,4,5-trichloronitrobenzene reacts, in view of the relative reactivities of 2- and 4-halogenonitrobenzenes.[4]

A preliminary screening test of bacteriostatic activity was carried out in the manner discussed by Gibbs and Stuttard.[5] Bacteriostatic activities of the new compounds, together with those of certain reference compounds, are shown in Table II. The results show that compounds **2–4**, **6**, and **7** are extremely potent antibacterials, having minimum inhibitory concentrations (MIC) to *S. aureus* of less than 1 ppm.

In view of possible applications of such germicides in soaps, where hydrolysis might conceivably give rise to toxic anilines,[6] we compared the rates of alkali-catalyzed hydrolysis of the new compounds. Each carbanilide was hydrolyzed by 2 *N* KOH in aqueous DMSO at 95.2°, and the liberated anilines were estimated by titration with $NaNO_2$ solution. The results given in Table II show that generally substituents have rather small effects on the rate constant. A significant difference can be noted between the 2- and the 4-(4-chlorophenoxy)carbanilides, the former being hydrolyzed almost ten times faster (compare **6** and **7**). However, none of the compounds seem appreciably more resistant to hydrolysis than the commercially used 3,4,4′-trichlorocarbanilide.

Experimental Section

Carbanilides.—The general method of Beaver, Roman, and Stoffel[1] was used. A solution of the isocyanate (0.005 mole) in

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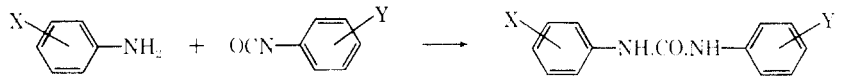
TABLE I
CARBANILIDES



Carbanilide	X	Y	Yield, %	Mp, °C	Formula	Calcd, % C	H	Cl	N	Found, % C	H	Cl	N
1	2-(*p*-ClC_6H_4O)	H	78	200	$C_{19}H_{15}ClN_2O_2$	67.3	4.4	10.7	8.5	67.4	4.5	10.5	8.3
2	2-(*p*-ClC_6H_4O)-5-Cl	4-Cl	45	184–185	$C_{19}H_{13}Cl_3N_2O_2$	56.0	3.2	26.1	6.9	55.9	3.0	25.8	6.6
3	2-(*p*-ClC_6H_4O)	4-Cl	16.5	284–285	$C_{19}H_{14}Cl_2N_2O_2$	61.1	3.8	19.0	7.5	60.5	3.6	19.2	7.7
4	2-(*p*-ClC_6H_4O)-4,5-Cl_2	3,4-Cl_2	69	220–230	$C_{19}H_{11}Cl_5N_2O_2$	47.9	2.3	37.2	5.9	47.8	2.2	37.1	6.1
5	3-Cl-4-(*p*-ClC_6H_4O)	4-Cl	60	208–209	$C_{19}H_{13}Cl_3N_2O_2$	56.0	3.2	26.1	6.9	56.2	2.8	25.4	6.8
6	3-Cl-4-(*p*-ClC_6H_4O)	3,4-Cl_2	68.5	208–211	$C_{19}H_{12}Cl_4N_2O_2$	51.6	2.7	32.1	6.35	50.8	2.45	31.2	6.2
7	2-(*p*-ClC_6H_4O)-5-Cl	3-Cl	81.5	188–189	$C_{19}H_{13}Cl_3N_2O_2$	56.0	3.2	26.1	6.9	56.0	3.0	25.8	6.7

TABLE II
BACTERIOSTATIC PROPERTIES AND HYDROLYSIS RATE CONSTANTS

Compd	MIC, ppm	$k \times 10^6$, sec^{-1}
1	100	4.7
2	0.02	
3	0.2	
4	0.15	4.5
5	10	0.84
6	0.25	0.76
7	0.5	6.0
Carbanilide	>200	3.2
3,4,4′-Trichlorocarbanilide	0.2	1.0

anhydrous ether or benzene was added dropwise with stirring to a solution of the aminodiphenyl ether (0.005 mole) in anhydrous Et_2O or C_6H_6. The resulting solution was boiled under reflux with stirring for 1 hr. A precipitate formed which was filtered, washed with Et_2O, and dried. The product was further purified if necessary by recrystallization from EtOH. All the carbanilides had characteristic "amide bands I–III" at 1600–1700, 1540–1560, and 1260–1320 cm^{-1}.

Isocyanates.—The method of Allen and Bell[7] was followed. A solution of the acyl chloride in Me_2CO was added dropwise with vigorous stirring to an excess of NaN_3 in H_2O at 10–15°. The mixture was then stirred for 1 hr, the aqueous layer was removed, and the organic layer (acyl azide) was added to a solution of C_6H_6 at 60°, or toluene at 100°, during which a vigorous evolution of N_2 occurred. The mixture was kept at 60° (100° for toluene) for 1 hr and was then dried ($MgSO_4$). The solvent was removed *in vacuo*, and, after the residue had been checked for absence of residual azide,[8] it was distilled. Yields of isocyanates by this method were 70–90%. The compounds had physical constants in agreement with the literature values and had a pronounced peak at 2280 cm^{-1} (N=C=O) in their infrared spectra.

Nitrodiphenyl Ethers.—The following compounds were prepared by the Ullmann synthesis, and had physical constants in agreement with the literature values: 2-nitro-4-chlorodiphenyl ether,[9] 2-nitro-4,4′-dichlorodiphenyl ether,[10] and 4-nitro-2,4′-dichlorodiphenyl ether.[10]

2-Nitro-4,5,4′-trichlorodiphenyl Ether.—2,4,5-Trichloronitrobenzene[11] (22.6 g), K_2CO_3 (39 g), *p*-chlorophenol (19.2 g), pyridine (1 ml), and Cu bronze (1 g) were heated at 200° for 2 hr (air condenser). The mixture was allowed to cool below 100°, then extracted with hot H_2O. The aqueous solution was extracted with four 200-ml portions of $CHCl_3$, and the $CHCl_3$ extracts were washed successively with H_2O, 2 *N* KOH, 4 *N* HCl, and H_2O. The solution was dried ($MgSO_4$) and distilled; yield 10.4 g (33%), bp 170–180° (1 mm).

Aminodiphenyl Ethers.—The nitro compounds were reduced by Zn dust in boiling, aqueous ethanolic $CaCl_2$.[12] The resulting amino compounds were isolated in $CHCl_3$ and recrystallized from Et_2O–C_6H_6.

Rates of Hydrolysis.—The hydrolyses were carried out in 2 *N* KOH in DMSO-H_2O (1:1 v/v) by heating in a thermostatic bath maintained at 95.2 ± 0.1°. The carbanilide was added quickly to the KOH solution at the reaction temperature, when, in all cases, it readily and completedly dissolved. Aliquots (5 ml) were removed from the reaction flasks at 1-hr intervals, H_2O was added to precipitate unreacted carbanilide, and the mixture was then extracted thoroughly with Et_2O to remove the carbanilide and anilines. The anilines were removed from this solution by extraction with 4 *N* HCl. The acid solution was titrated at 5° with standard $NaNO_2$ solution to form the diazonium salt, the end point being detected by the blue color imparted to starch-iodide paper.

Acknowledgments.—We thank Mr. L. W. Stuttard for the MIC determinations and Drs. Weiler and Strauss for the analytical results.

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Synthesis and Antimalarial Evaluation of Some 1,7-Naphthyridines and 2,9-Diazaanthracenes[1]

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Received May 29, 1967

Chloroquine, quinacrine, and other 4-aminoquinolines and 9-aminoacridines, which have been of great clinical value in the treatment of malaria, have all encountered the problem of parasite resistance.[2] This suggests that further synthetic designs involving the attachment of

(1) This investigation was supported by the Walter Reed Army Institute of Research (WRAIR), Walter Reed Army Medical Center, Department of the Army, and Headquarters, U. S. Army Medical Research and Development Command, Office of the Surgeon General, Contract No. DA-49-193-MD-2749. This paper is contribution No. 226 from the Army Research program on malaria.

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