

and the residue was recrystallized from H₂O to yield 39.6 g (73%) of tan crystals, mp 93–96°. The analytical sample was obtained by repeated recrystallization from H₂O 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.* (C₁₂H₁₁NO₃) 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 H₂O yielded faint tan crystals which melted at 294–296° after drying *in vacuo* (100°, 0.01 mm) for 8 hr. *Anal.* (C₁₂H₁₁NO₃·0.5H₂O) C, H, N, H₂O (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.* (C₁₁H₉NO₃·0.5C₃H₇NO) C, H, N.

Diethyl 2-[(3,4-Methylenedioxy-6-nitrophenyl)methylene]-malonate (XII).—A mixture of 98 g (0.5 mole) of 6-nitropiperonal⁹ (XI), 88 g (0.55 mole) of diethyl malonate, 34.5 g (0.25 mole) of anhydrous K₂CO₃, and 200 g of Ac₂O 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 Et₂O, and the Et₂O was washed successively with 500 ml of H₂O and 500 ml of 5% aqueous NaHCO₃. The Et₂O layer was dried (MgSO₄) 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 CHCl₃-petroleum ether (1:4) gave the analytical material: mp 59–61°; pmr, 374 (2 s, O-CH₂-O), 414 (1 s, 2-H), 465 (1 s, vinyl H), 491 (1 s, 5-H). *Anal.* (C₁₈H₁₅NO₅) 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 H₂O, 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-d₆), 363 (2 s, O-CH₂-O), 404 (1 s, 4-H), 431 (1 s, 9-H), 495 (1 s, 8-H), 712 (1 s (broad), 5-H). *Anal.* (C₁₃H₁₁NO₅) 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 Me₂SO₄, 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.* (C₁₂H₉NO₅) C, H, N.

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Some New *p*-Chlorophenoxy-carbanilides and Their Bacteriostatic Activities

D. COBERN AND A. P. RHODES

Unilever Research Laboratory, Colworth House,
Sharnbrook, Bedford, England

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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 NaNO₂ 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 Stoffel¹ was used. A solution of the isocyanate (0.005 mole) in

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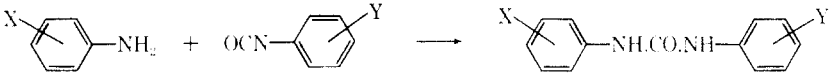
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TABLE I
CARBANILIDES



Carbanilide	X	Y	Yield, %	Mp, °C	Formula	Calcd, %				Found, %			
						C	H	Cl	N	C	H	Cl	N
1	2-(p-ClC ₆ H ₄ O)	H	78	200	C ₁₉ H ₁₅ ClN ₂ O ₂	67.3	4.4	10.7	8.5	67.4	4.5	10.5	8.3
2	2-(p-ClC ₆ H ₄ O)-5-Cl	4-Cl	45	184-185	C ₁₉ H ₁₃ Cl ₂ N ₂ O ₂	56.0	3.2	26.1	6.9	55.9	3.0	25.8	6.6
3	2-(p-ClC ₆ H ₄ O)	4-Cl	16.5	284-285	C ₁₉ H ₁₄ Cl ₂ N ₂ O ₂	61.1	3.8	19.0	7.5	60.5	3.6	19.2	7.7
4	2-(p-ClC ₆ H ₄ O)-4,5-Cl ₂	3,4-Cl ₂	69	229-230	C ₁₉ H ₁₁ Cl ₃ N ₂ O ₂	47.9	2.3	37.2	5.9	47.8	2.2	37.1	6.1
5	3-Cl-4-(p-ClC ₆ H ₄ O)	4-Cl	60	208-209	C ₁₉ H ₁₃ Cl ₂ N ₂ O ₂	56.0	3.2	26.1	6.9	56.2	2.8	25.4	6.8
6	3-Cl-4-(p-ClC ₆ H ₄ O)	3,4-Cl ₂	68.5	208-211	C ₁₉ H ₁₂ Cl ₃ N ₂ O ₂	51.6	2.7	32.1	6.35	50.8	2.45	31.2	6.2
7	2-(p-ClC ₆ H ₄ O)-5-Cl	3-Cl	81.5	188-189	C ₁₉ H ₁₃ Cl ₂ N ₂ O 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 × 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 Et₂O or C₆H₆. The resulting solution was boiled under reflux with stirring for 1 hr. A precipitate formed which was filtered, washed with Et₂O, 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 Bell⁷ was followed. A solution of the acyl chloride in Me₂CO was added dropwise with vigorous stirring to an excess of NaN₃ in H₂O 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 C₆H₆ at 60°, or toluene at 100°, during which a vigorous evolution of N₂ occurred. The mixture was kept at 60° (100° for toluene) for 1 hr and was then dried (MgSO₄). 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-Trichloronitrobenzene¹¹ (22.6 g), K₂CO₃ (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 H₂O. The aqueous solution was extracted with four 200-ml portions of CHCl₃, and the CHCl₃ extracts were washed successively with H₂O, 2 N KOH, 4 N HCl, and H₂O. The solution was dried (MgSO₄) and distilled; yield 10.4 g (33%), bp 170-180° (1 mm).

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Aminodiphenyl Ethers.—The nitro compounds were reduced by Zn dust in boiling, aqueous ethanolic CaCl₂.¹² The resulting amino compounds were isolated in CHCl₃ and recrystallized from Et₂O-C₆H₆.

Rates of Hydrolysis.—The hydrolyses were carried out in 2 N KOH in DMSO-H₂O (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 completely dissolved. Aliquots (5 ml) were removed from the reaction flasks at 1-hr intervals, H₂O was added to precipitate unreacted carbanilide, and the mixture was then extracted thoroughly with Et₂O 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 NaNO₂ solution to form the diazonium salt, the end point being detected by the blue color imparted to starch-iodide paper.

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Synthesis and Antimalarial Evaluation of Some 1,7-Naphthyridines and 2,9-Diazaanthracenes¹

PING-LU CHIEN AND C. C. CHENG

Midwest Research Institute,
Kansas City, Missouri 64110

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Chloroquine, quinaquine, 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

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