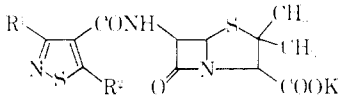
TABLE I
MINIMUM INHIBITORY CONCENTRATIONS (μg/ml) OF POTASSIUM 6-(4-ISOTHIAZOLYLCARBOXAMIDO)PENICILLANATES



			Gram-positive microorganisms			Penicillin G resistant	
No.	R^1	R^2	*D. pneumoniae*	*S. pyogenes*	*S. aureus* Smith	*S. aureus* BX1633-2	*S. aureus* 52-75
Ia	C_6H_5	H	0.031	0.031	0.031	1.6	3.1
Ib	C_6H_5	OCH_3	0.25	0.125	0.25	1.6	1.6
Ic	H	C_6H_5	0.016	0.031	0.031	3.1	12.5
Id	OCH_3	C_6H_5	0.125	0.031	0.125	0.8	0.8
Ie	OC_2H_5	C_6H_5	0.5	0.031	0.25	1.6	1.6
Oxacillin			0.031	0.031	0.062	0.4	0.4

Antibacterial Activity.—The compounds were tested for antibacterial activity by Dr. A. Gourevitch and his associates in the Microbiology Department of Bristol Laboratories, Syracuse, N. Y., using published techniques.[7]

In Table I the MIC values of the penicillins Ia–e against some gram-positive microorganisms and against two penicillinase-producing *Staphylococcus aureus* strains are compared with the values for oxacillin, obtained under the same conditions. Although all the compounds exhibit activity against the resistant *S. aureus* strains, only Id shows an activity comparable to that of oxacillin. When administered by the intramuscular route, the median curative dose in mice against *S. aureus* BX1633-2 was found to be 45 mg/kg for both Id and oxacillin.

Experimental Section[8]

5-Phenylisothiazole-4-carboxylic acid was obtained from 3-amino-4-bromo-5-phenylisothiazole[6] using procedures already described in the patent literature.[9] 4-Bromo-5-phenylisothiazole, mp 30–32°, obtained in 27% yield by the reductive deamination of 3-amino-4-bromo-5-phenylisothiazole,[6] when heated with cuprous cyanide in dimethylformamide, gave 4-cyano-5-phenylisothiazole, mp 103–107°, in 80% yield. The 4-cyano-5-phenylisothiazole on acid hydrolysis gave 5-phenylisothiazole-4-carboxylic acid, mp 174–176° (70%). *Anal.* ($C_{10}H_7NO_2S$) C, H, N, S; neut equiv, found 203.

5-Phenylisothiazole-4-carbonyl chloride, mp 72–75° (95%), was obtained by heating 5-phenylisothiazole-4-carboxylic acid with excess $SOCl_2$ under reflux for 1 hr.

3-Ethoxy-5-phenylisothiazole-4-carbonyl chloride, bp 138–140° (0.7 mm) (79%), was obtained from 3-ethoxy-5-phenylisothiazole[6] using identical procedures as described for 3-methoxy-5-phenylisothiazole-4-carbonyl chloride.[9] The intermediate compounds prepared were 4-bromo-3-ethoxy-5-phenylisothiazole, bp 128–131° (0.5 mm) (90%); 4-cyano-3-ethoxy-5-phenylisothiazole, mp 72–78° (93%); 3-ethoxy-5-phenylisothiazole-4-carboxamide, mp 165–180° (98%); 3-ethoxy-5-phenylisothiazole-4-carboxylic acid, mp 124–127° (90%). *Anal.* ($C_{12}H_{11}NO_3S$) C, H, N, S; neut equiv, found 247.

Acknowledgments.—The authors thank Professor R. U. Lemieux for guidance and advice in the conduct of this research and Messrs. R. A. Fortier and P. K. Wolfert for their capable technical assistance.

(7) A. Gourevitch, G. A. Hunt, J. R. Luttinger, C. C. Carmack, and J. Lein, *Proc. Soc. Exptl. Biol. Med.*, **107**, 455 (1961).

(8) As most of the experimental procedures have already been described in a recent patent,[9] only new compounds are reported here. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(9) R. U. Lemieux and R. G. Micetich, U. S. Patent 3,311,611 (1967).

Quinolone Antibacterial Agents. Oxolinic Acid and Related Compounds

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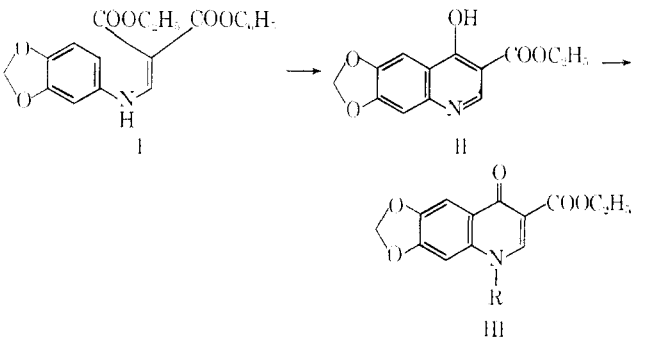
Extension of our efforts[1] at preparing more efficient agents *vs.* gram-negative organisms led to the discovery of oxolinic acid (IVb).[2] In order to investigate a possible structure-activity relationship, we prepared a number of analogs and derivatives. Condensation of 3,4-methylenedioxyaniline with diethyl ethoxymethylenemalonate gave the unsaturated ester I, and thermal cyclization in refluxing Dowtherm A[3] resulted in 70–95% yields of II. The quinolone ethyl esters (III) (see Table I) were prepared by alkylation of II, with the appropriate alkyl or substituted-alkyl halide. The free acids were obtained by basic and/or acid hydrolysis of the esters. No evidence of hydrolysis of the methylenedioxy group was noted during 1–6 hr (reflux) with 2–10% aqueous caustic or with 5–10% hydrochloric acid. In the case of III (R = ethyl), hydrolysis gave



IVb, which, upon treatment with thionyl chloride, gave the acid chloride V. Treatment of this acid chloride with an appropriate alcohol gave the desired ester of IV. In a similar manner the esters of other N-

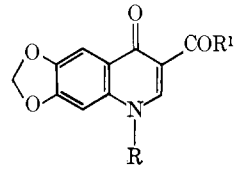
(1) D. Kaminsky and R. I. Meltzer, U. S. Patent 3,172,811 (March 9, 1965).

(2) Generic name for 5-ethyl-5,8-dihydro-8-oxo-1,3-dioxolo[4,5-*g*]quinoline-7-carboxylic acid.

(3) A eutectic mixture containing 26.5% diphenyl and 73.5% diphenyl ether.

TABLE I

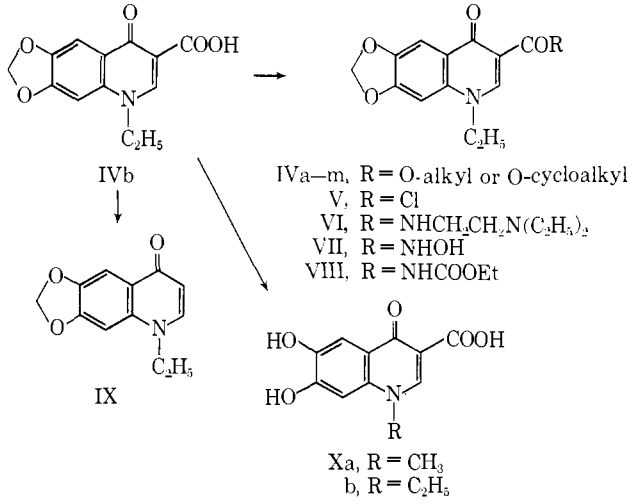
7-CARBONYL DERIVATIVES OF 5-SUBSTITUTED 5,8-DIHYDRO-8-OXO-1,3-DIOXOLO[4,5-*g*]QUINOLINES



No.	R	R'	Mp, °C	Yield,[c] %	Solvent[a]	Formula[d]	MIC[f] *In vitro*	ED_{50}, mg/kg[g] *In vivo* Po	*In vivo* Sc
IIa	H	OC_2H_5	301–302	56	A	$C_{13}H_{11}NO_5$	>500	...	...
IIb	H	OH	313–315	92	A	$C_{11}H_7NO_5$	62	>50	>50
IIIa	CH_3	OC_2H_5	202–203	81	B	$C_{14}H_{13}NO_5$	>500	...	...
IIIb	C_2H_5	OC_2H_5	177–178	63	B	$C_{15}H_{15}NO_5$	16	4.9	5.4
IIIc	C_2H_5	OC_3H_7-*n*	159–160	70	B	$C_{16}H_{17}NO_5$	8	...	...
IIId	C_2H_5	OC_4H_9-*n*	131–133	72	B	$C_{17}H_{19}NO_5$	62	4.9	2.9
IIIe	C_2H_5	OC_5H_{11}-*t*	172–173	54	B	$C_{18}H_{21}NO_5$	<4	...	...
IIIf	C_2H_5	OC_6H_{13}-*n*	90–92	61	B	$C_{19}H_{23}NO_5$	8	6.8	6.2
IIIh	C_2H_5	OC_6H_{11}[b]	204–206	86	B	$C_{19}H_{21}NO_5$	>500	4.9	4.3
IIIi	C_2H_5	$OC_{10}H_{21}$-*n*	99–101	54	B	$C_{23}H_{31}NO_5$	>500	8.0	>50
IIIj	C_3H_7-*n*	OC_2H_5	146–148	82	B	$C_{16}H_{17}NO_5$	>500	...	...
IIIk	C_4H_9-*n*	OC_2H_5	116–118	76	B	$C_{17}H_{19}NO_5$	>500	...	...
IVa	CH_3	OH	341–343	71	A	$C_{12}H_9NO_5$	0.8	20	>50
IVb	C_2H_5	OH	313–314	93	A	$C_{13}H_{11}NO_5$	0.4	4.7	2.3
IVc	CH_2COOH	OH	316–317	71	A	$C_{13}H_9NO_7$	31	>50	>50
IVd	CH_2CH_2OH	OH	303–305	84	A	$C_{13}H_{11}NO_6$	<4	17	3.6
IVe	$CH_2CH{=}CH_2$	OH	282–284	66	A	$C_{14}H_{11}NO_5$	<4	32	>50
IVf	C_3H_7-*n*	OH	271–273	72	A	$C_{14}H_{13}NO_5$	<4	41	>50
IVg	C_3H_7-*i*	OH	297–299	52	A	$C_{14}H_{13}NO_5$	<4	16	17.5
IVh	C_4H_9-*n*	OH	233–234	61	A	$C_{15}H_{15}NO_5$	16	>50	>50
IVi	C_4H_9-*i*	OH	286–288	49	A	$C_{15}H_{15}NO_5$	31	>50	>50
IVj	C_4H_9-*s*	OH	254–256	24	A	$C_{15}H_{15}NO_5$	<4	>50	>50
IVk	C_6H_{13}-*n*	OH	183–185	58	A	$C_{17}H_{19}NO_5$[e]	>500	>50	>50
IVl	C_8H_{17}-*n*	OH	158–160	56	A	$C_{19}H_{21}NO_5$	>500	>50	>50
IVm	$CH_2C_6H_5$	OH	312–313	63	A	$C_{18}H_{13}NO_5$	>500	>50	>50
VIa	C_2H_5	$NH(CH_2)_2N(C_2H_5)_2$	199–201	86	C	$C_{19}H_{25}N_3O_4$	>500	...	...
VIb	C_2H_5	$NHC_6H_4OCH_3$-*m*	240–241	88	A	$C_{20}H_{18}N_2O_5$	250	>50	>50
VII	C_2H_5	NHOH	269–270	83	C	$C_{13}H_{12}N_2O_5$	<4	20	16.5
VIII	C_2H_5	$NHCOOC_2H_5$	277–279	68	A	$C_{16}H_{16}N_2O_6$	<4	25–50	25–50
Nalidixic acid							3.1	12.5	10.1

[a] Solvent of recrystallization: A = aqueous DMF, B = $CHCl_3$–Skellysolve B, C = aqueous EtOH. [b] C_6H_{11} = cyclohexyl. [c] Of analytical material. [d] All compounds analyzed for C, H, N. [e] *Anal.* H, N; C: calcd, 64.34; found, 64.70. [f] μg/ml. [g] b.i.d. × 1.

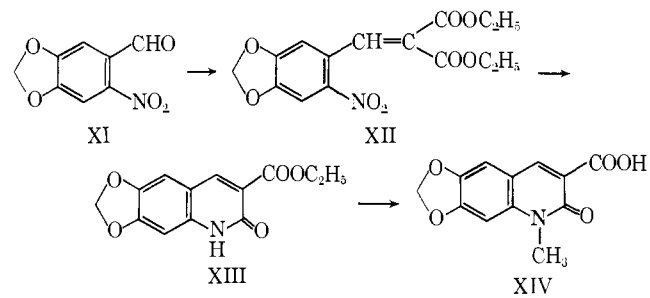
substituted quinolones were prepared from their unisolated acid chlorides. Treatment of V with N,N-diethylethylenediamine, hydroxylamine, and ethyl carbamate gave the amide VIa, the hydroxamic acid VII, and the acyl carbamate VIII, respectively.



Decarboxylation of IVb could not be accomplished by the usual methods[4] (*i.e.*, heating above the melting point; refluxing with copper and quinoline, etc.) but proceeded quite readily by heating at *ca.* 300° with copper in dibutyl phthalate to yield IX.

Hydrolysis of IVb by refluxing 48% hydrobromic acid led to the 6,7-dihydroxy compound Xb and a similar reaction with the N-methyl analog gave the corresponding N-methyl-6,7-dihydroxy compound Xa.

The isomeric quinolone XIII was prepared by treating nitropiperonal (XI) with diethyl malonate to yield XII which upon reductive cyclization gave the ester



(4) V. Migrdichian, "Organic Synthesis," Vol. 2, Reinhold Publishing Corp., New York, N. Y., 1957.

XIII. Alkylation with dimethyl sulfate followed by alkaline hydrolysis yielded XIV.

Microbiological Testing.—The compounds were tested against a single laboratory strain of *Proteus vulgaris* (WLRI 240), and the techniques used were those reported by Turner, *et al.*[5] The compounds are compared with nalidixic acid (1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid) in Table I. The *in vitro* values are derived from a two-fold serial dilution and are reported as minimum inhibitory concentration (MIC) in μg/ml. The *in vivo* values were obtained by two routes of administration of drug, orally (*po*) and subcutaneously (sc), and are reported as ED_{50} in mg/kg, bid × 1.

Compound IX was found to have only trace (~1000 μg/ml) activity in the *in vitro* test. The N-methyl compound Xa was inactive *in vitro;* however, the N-ethyl compound Xb exhibited an *in vitro* MIC value of 31 μg/ml and an *in vivo* ED_{50} greater than 100 mg/kg. Compounds XIII and XIV were inactive against *Proteus*.

Structure–Activity Relationship.—The accumulated data (Table I) (*in vitro vs. in vivo* values) suggest that the antiproteus activity resides in the free acid, whereas the activity of the esters and amides apparently depends upon solubility and rates of hydrolysis to the free acid. Although the data are limited, it would seem that the free carboxyl function, an N-ethyl (or substituted ethyl) and the 8-oxo functions are prerequisites for enhanced activity. Broad spectrum antigram-negative activity[6] suggests oxolinic acid (IVb) as the agent of choice in this group.

Experimental Section

Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.3% of the theoretical values. Melting points below 280° were measured with a Thomas–Hoover Uni-Melt apparatus, those >280° with a Mel-Temp apparatus; all are corrected. Ultraviolet spectra were determined in 95% EtOH using a DK-1 spectrophotometer. Pmr spectra were determined with a Varian A-60 spectrometer (TMS as internal standard) with $CDCl_3$ as solvent, unless otherwise noted. The pertinent assignments are reported in cps with the number of protons followed by s (for singlet), d (for doublet), or q (for quartet). Infrared spectra were as expected for the respective structures.

Florisil[7] was generally used as an aid in decolorization during recrystallizations. Skellysolve B refers to commercial heptane (bp 60–90°), and petroleum ether was the fraction boiling at 30–60°.

Diethyl 2-[(3,4-Methylenedioxyanilino)methylene]malonate (I).—A mixture of 26.9 g (0.2 mole) of 3,4-methylenedioxyaniline[8] and 43.2 g (0.2 mole) of diethyl ethoxymethylenemalonate was heated on a steam bath for 3 hr at atmospheric pressure and for 1 hr at *ca.* 10–15 mm. The residue was recrystallized from Skellysolve B to yield 52.7 g (86.5%) of yellow, crystalline I, mp 100–102°. The analytical sample was obtained by a second crystallization; mp 101–102°; pmr, 364 (2 s, O–CH_2–O), 407 (1 d, 2-H, *meta* coupling, $J \simeq 2$ cps), 405 (2 q, 5-H, 6-H, $J = 8$ cps, upfield legs split by *meta* coupling, $J \sim 2$ cps), 505 (1 d, vinyl H, $J \sim 13.5$ cps), ~760 (1 q, broad, NH, $J \sim 13.5$ cps). *Anal.* ($C_{15}H_{17}NO_6$) C, H, N.

Ethyl 8-Hydroxy-1,3-dioxolo[4,5-*g*]quinoline-7-carboxylate (IIa).—A mixture of 48 g (0.16 mole) of I and 500 ml of Dowtherm A was heated to reflux during 1 hr and maintained at this temperature for 1 hr. The liberated alcohol was collected in a Dean Stark trap. The mixture was filtered. The filter cake was washed with petroleum ether and dried *in vacuo*, yielding 31.2 g (76%) of crude product, mp 282–285° (see Table I).

Ethyl 5-Ethyl-5,8-dihydro-8-oxo-1,3-dioxolo[4,5-*g*]quinoline-7-carboxylate (IIIb).—A mixture of 15.6 g (0.06 mole) of IIa, 250 ml of DMF, and 3.0 g (0.12 mole) of NaH powder was heated with stirring for 0.5 hr at 80–90°. EtI (15.6 g, 0.1 mole) was added dropwise over 0.5 hr. The temperature was maintained above 70° for an additional 2 hr. This was followed by an additional 7.8 g (0.05 mole) of EtI and 2 hr of stirring at 70°. After leaving overnight at room temperature, the solvents were removed at *ca.* 60° (0.1 mm), and the residue was triturated in 250 ml of hot $CHCl_3$. The $CHCl_3$ solution was decolorized with charcoal, diluted with an equal volume of petroleum ether, cooled, and filtered to yield 13.6 g (78%) of almost colorless IIIb: mp 172–175° (Table I); pmr, 366 (2 s, O–CH_2–O), 411 (1 s, 4-H), 468 (1 s, 9-H), 499 (1 s, 6-H).

Acids IVa–m were obtained by hydrolysis of the esters in refluxing aqueous alkali or acid for 1–2 hr and were purified by recrystallization from aqueous DMF. Properties of the acids are reported in Table I. The uv spectra of the N-substituted free acids IVa–m exhibited the same maxima (±1 mμ): λ_{max} 220, 255.5 (sh), 259.5, 268, 298 (sh), 311 (sh), 321, and 326 mμ ($\epsilon \times 10^{-3}$ (±5%) 14.8, 36.8, 38.4, 6.4, 9.2, 10.8, and 11.2).

5-Ethyl-5,8-dihydro-8-oxo-1,3-dioxolo[4,5-*g*]quinoline-7-carbonyl Chloride (V).—$SOCl_2$ (13.2 g, 0.11 mole) was added to a slurry of 26.1 g (0.1 mole) of pure IV in 100 ml of dry C_6H_6, and the mixture was refluxed for 12 hr. Petroleum ether (250 ml) was added, and the mixture was filtered to yield 29 g of yellow-brown solid, mp 235–236° dec. The crude solid was refluxed with 500 ml of CH_2Cl_2 and filtered hot to yield 24.3 g (87%) of insoluble, light brown solid (V), mp 245° dec. *Anal.* ($C_{13}H_{10}ClNO_4$) C, H, N, Cl.

Cyclohexyl Ester (IIIh).—A mixture of 14 g (0.05 mole) of V, 6 g (0.06 mole) of freshly distilled cyclohexanol, and 30 g of pyridine was heated for 2 hr on a steam bath. The volatiles were removed *in vacuo*, and the residue was triturated several times in water and filtered. The crude product was recrystallized from 3:1 CCl_4–Skellysolve B yielding 15.4 g (90%) of colorless crystals, mp 203–206° (Table I).

N-(2-Diethylaminoethyl)-5-ethyl-5,8-dihydro-8-oxo-1,3-dioxolo[4,5-*g*]quinoline-7-carboxamide (VIa).—A mixture of 8.4 g (0.03 mole) of V, 4.6 g (0.04 mole) of N,N-diethylethylenediamine, and 150 ml of C_6H_6 was refluxed for 8 hr. The volatiles were removed under aspirator vacuum, and the residue was triturated in 5% NaOH and recrystallized from aqueous *i*-PrOH yielding 10.2 g (94%) of colorless VIa (Table I).

5-Ethyl-5,8-dihydro-8-oxo-1,3-dioxolo[4,5-*g*]quinoline-7-hydroxamic Acid (VII).—Hydroxylamine hydrochloride (2.1 g, 0.03 mole) was added to a slurry of 4.2 g (0.015 mole) of V in 25 ml of pyridine. After 2 hr (stirring), the mixture was heated for 3 hr on a steam bath. The pyridine was removed under aspirator vacuum, and the residue was recrystallized from 90% aqueous EtOH to yield 4.0 g (96%) of light yellow VII, mp 265–268° (Table I).

Ethyl [(5-Ethyl-5,8-dihydro-8-oxo-1,3-dioxolo[4,5-*g*]quinolin-7-yl)carbonyl]carbamate (VIII).—A mixture of 8.4 g (0.03 mole) of V, 5.3 g (0.06 mole) of ethyl carbamate, and 100 ml of pyridine was refluxed for 8 hr. The solvent was removed *in vacuo*, and the residue was triturated in H_2O and recrystallized from 90% aqueous DMF yielding 76% of colorless VIII, mp 273–275° dec (Table I).

5-Ethyl-1,3-dioxolo[4,5-*g*]quinolin-8(5H)-one (IX).—A mixture of 60 g (0.23 mole) of IVb, 1 g of Cu powder, and 500 ml of di-*n*-butyl phthalate was heated with stirring at 285–295° until the evolution of CO_2 ceased (*ca.* 1 hr). The mixture was cooled and filtered, and the filtrate was diluted with an equal volume of $CHCl_3$. The solution was extracted with six 250-ml portions of 4 *N* HCl and discarded. The aqueous phase was cooled and made strongly basic with 50% aqueous NaOH. The precipitate and solution were extracted into four 500-ml portions of $CHCl_3$. The combined $CHCl_3$ extracts were stripped on a steam bath,

(5) F. J. Turner, F. L. Lindo, P. J. Storino, J. M. Daly, D. Allen, and B. S. Schwartz, *Antimicrobial Agents Chemotherapy*, 815 (1962).

(6) S. M. Ringel, F. J. Turner, D. Kaminsky, and B. S. Schwartz, presented at the 67th Annual Meeting of the American Society for Microbiology, New York, N. Y., April 30–May 4, 1967.

(7) Activated magnesium silicate.

(8) E. A. Steck, J. S. Buck, and L. T. Fletcher, *J. Am. Chem. Soc.*, **79**, 4414 (1957).

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.

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Some New *p*-Chlorophenoxycarbanilides and Their Bacteriostatic Activities

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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 $NaNO_2$ 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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