Antibacterial Agents. Some New Halomethyl Aryl Ketones

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The antibacterial activity of chloroacetyl, dichloroacetyl, and dibromoacetyl derivatives of biphenyl, diphenylmethane, diphenylethane, diphenyl ether, diphenyl sulfide, diphenyl sulfoxide, and diphenyl sulfone was studied. The chloromethyl aryl ketones and the dibromomethyl aryl ketones are active against the *Micrococcus pyogenes*, but their activity is greatly reduced in the presence of serum. The dichloromethyl aryl ketones are active against *Mycobacterium tuberculosis* and their activity is not reduced by serum.

The dichloroacetamido group of chloramphenicol is essential for the antibacterial activity of this antibiotic,[3] and the same group greatly increases the antituberculous activity of other parent amino compounds, for example, that of 4-aminosalicylic acid.[4] In two recent patents,[5,6] these observations have been extended to mono- and dichloro- and bromomethyl aromatic ketones which also exhibit antibacterial activity. In continuation of our studies[7-10] on chemotherapeutically active derivatives of biphenyl, diphenyl ether, diphenyl sulfide, diphenyl sulfoxide, diphenyl sulfone, and diphenylmethane and -ethane, we considered it of interest to attach mono- and dihalogenoacetyl groups to the 4- and 4,4′-positions of these ring systems. Such halo ketones are reported in this paper. In addition, haloacetyl radicals have been attached to the 3- and 2,2′-positions of biphenyl, and the 4-positions of 3′-chloro-4′-methoxy-, 3′,5′-dichloro-4′-methoxy-, and 3′,5′-dichloro-4′-hydroxybiphenyl, as well as of 4′-chlorodiphenyl ether.

Chemistry.—Six general methods were employed for the preparation of these compounds. Method A involves the reaction of a substituted benzoyl chloride with diazomethane and is convenient for the preparation of some monochloroacetyl derivatives. Several mono- and bischloroacetyl derivatives of biphenyl were were obtained by modified Friedel–Crafts reactions (methods B-1, B-2, B-3) (for experimental details, see Table II). The halogeno ketones of diphenyl sulfoxide and diphenyl sulfone were prepared from the corresponding derivatives of diphenyl sulfide by oxidation with hydrogen peroxide in acetic acid (method C). The mono- and dibromoacetyl compounds were obtained from the corresponding acetyl derivatives by bromination with stoichiometric amounts of bromine in acetic acid or chloroform solution (method D). Some dichloroacetyl derivatives were prepared from the corresponding acetyl derivatives by chlorination in acetic acid (method E) or in acetic acid–acetic anhydride solution (method F).

The position of the side chain of the compounds obtained by methods B, D, E, and F was determined by oxidation to the corresponding aromatic acids.

In the chlorination of 4-acetyl-3′-chloro-4′-methoxybiphenyl (LVIII) and of 4-acetyl-4′-hydroxybiphenyl (LIX), the nucleus was also substituted, 4-dichloroacetyl-3′,5′-dichloro-4′-methoxybiphenyl (XX) and 4-dichloroacetyl-3′,5′-dichloro-4′-hydroxybiphenyl (XXI)

TABLE I

CHARACTERISTIC INFRARED FREQUENCIES[a]

	ν (OH) phenol cm.⁻¹	ν (C=O) -COOH (aromatic), cm.⁻¹	γ (C—H) p-disubstituted aromatic ring, cm.⁻¹
LXI	3460 (sharp peak)	1706 and 1686	800
LXII	3422 (broad band)	1686	851
LXIII	3367 (broad band)	1680	831

[a] Infrared spectra were measured in the solid state in KBr pellets with a Perkin-Elmer Model 12C spectrophotometer with NaCl optics.

TABLE II

EXPERIMENTAL CONDITIONS FOR FRIEDEL–CRAFTS REACTIONS (METHOD B-1, B-2, B-3)

Compound no.	Method	Temp. of addition, °C.	Solvent	Reaction temp., °C.	Time, hr.
L	B-1	10, 20	CS_2	Reflux	6
VI	B-1	−5, 0	CS_2	5, 10	3
	B-2	−5	$C_2H_4Cl_2$	−5	3
VII	B-1	−5, 0	CS_2	5, 10	3
II	B-1	10, 20	CS_2	Reflux	6
VIII	B-1	0	CS_2	0	6
X	B-1	0, 5	CS_2	5, 10	6
	B-1	0, 5	$C_2H_4Cl_2$	5, 10	6
	B-2	0	$C_2H_4Cl_2$	0, 5	5
XI	B-1	10, 20	CS_2	20, 30	18
XVIII	B-2	0, 5	$C_2H_4Cl_2$	20, 30	2
XIX	B-1	30	$C_2H_4Cl_2$	20, 30	96
XXIII	B-1	10, 20	CS_2	Reflux	6
XXV	B-1	0, 5	CS_2	5, 10	6
XXVII	B-3	−15	$C_2H_4Cl_2$	−10	6
XXIX	B-1	0, 5	CS_2	5, 10	6
XXX	B-1	10, 20	CS_2	20, 30	18
XXXI	B-1	10, 20	CS_2	20, 30	9
XXXII	B-1	0	CS_2	5, 10	9

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TABLE III
$RCOCH_2Cl$

Compound no.	R	Method	Yield, %	B.p., °C. (mm.)	M.p., °C.	Solvent of cryst.[a]	Formula
III	*m*-$C_6H_5C_6H_4$-	A[c]	79	140 (0.1)			$C_{14}H_{11}ClO$
L	*p*-(4-$CH_3OC_6H_4$)C_6H_4-	A	50		132	L	$C_{15}H_{13}ClO_2$
		B-1[d]	15				
II	*p*-(3-Cl-4-$CH_3OC_6H_3$)C_6H_4-	B-1	65	200–205 (0.5)	114–115	A	$C_{15}H_{12}Cl_2O_2$
V	*o,o'*-$C_6H_4C_6H_4$-	A[c]	65		110–112	L	$C_{16}H_{12}Cl_2O_2$
VI	*p*-$C_6H_5CH_2C_6H_4$-	B-1	49	165 (0.2)	58	H	$C_{15}H_{13}ClO$
		B-2					
VII	*p,p'*-$C_6H_4CH_2C_6H_4$-	B-1	20	240–250 (0.2)	118–120	A	$C_{17}H_{14}Cl_2O_2$
VIII	*p*-$C_6H_5CH_2CH_2C_6H_4$-	B-1	18	190 (1)	55–57	A	$C_{16}H_{15}ClO$
X	*p*-$C_6H_5OC_6H_4$-	B-1	50	155–160 (0.2)	56–57	H	$C_{14}H_{11}ClO_2$
		B-2					
XI	*p*-(4-ClC_6H_4)C_6H_4-	B-1	70		68–70	L	$C_{14}H_9Cl_3O_2$
XV	*p*-$C_6H_5SOC_6H_4$-	C	30		102–103	A	$C_{14}H_{11}ClO_2S$
LI	*p,p'*-$C_6H_4SOC_6H_4$-	C	70		165	C	$C_{16}H_{12}Cl_2O_3S$
XVI	*p*-$C_6H_5SO_2C_6H_4$-	C[e]	60		111–113	A	$C_{14}H_{11}ClO_3S$
XVII	*p,p'*-$C_6H_4SO_2C_6H_4$-	C[e]	90		175	C	$C_{16}H_{12}Cl_2O_3S$

[a] L = ligroin; A = ethanol; H = hexane; C = ethyl acetate. [b] Reference corresponds to literature data for the substituted benzoic acids obtained by oxidation from halomethyl aryl ketones. [c] Ethyl ether was used as solvent. The solution of the acid chloride was dropped in at −5° and the mixture was saturated with hydrogen chloride at room temperature. [d] In this way a partial demethoxyl-

TABLE IV
$RCOCHCl_2$

Compound no.	R	Method	Yield, %	B.p., °C. (mm.)	M.p., °C.	Solvent of cryst.[a]	Formula
XVIII	*p*-$C_6H_5C_6H_4$-	B-2	56			A	$C_{14}H_{10}Cl_2O$
		E	90	165–170 (0.2)	95–96	D–W	
XXII	*m*-$C_6H_5C_6H_4$-	E[c]	80	115–120 (0.05)			$C_{14}H_{10}Cl_2O$
XIX	*p*-(3-Cl-4-$CH_3OC_6H_3$)C_6H_4-	B-1	31	203–208 (0.01)			$C_{15}H_{11}Cl_3O_2$
XX	*p*-(3,5-Cl_2-4-$CH_3OC_6H_2$)C_6H_4-	E[d]	75		148	A	$C_{15}H_{10}Cl_4O_2$
XXI	*p*-(3,5-Cl_2-4-HOC_6H_2)C_6H_4-	E[d]	60		104–105	D–W	$C_{14}H_8Cl_4O_2$
XXIII	*p,p'*-$C_6H_4C_6H_4$-	B-1	25		184–185	D	$C_{16}H_{10}Cl_4O_2$
		E	65			A	
XXIV	*o,o'*-$C_6H_4C_6H_4$-	E	63		167–170	D	$C_{16}H_{10}Cl_4O_2$
XXV	*p*-$C_6H_5CH_2C_6H_4$-	B-1	65		78–79	C	$C_{15}H_{12}Cl_2O$
XXVI	*p,p'*-$C_6H_4CH_2C_6H_4$-	E	70		112	I	$C_{17}H_{12}Cl_4O_2$
XXVII	*p*-$C_6H_5CH_2CH_2C_6H_4$-	B-3		166–172 (0.01)	50–51	P	$C_{16}H_{14}Cl_2O$
XXVIII	*p,p'*-$C_6H_4CH_2CH_2C_6H_4$-	E	55		161–162	C	$C_{18}H_{14}Cl_4O_2$
						A	
XXIX	*p*-$C_6H_5OC_6H_4$-	B-1	55	205–210 (0.2)	68	A	$C_{14}H_{10}Cl_2O_2$
XXX	*p*-(4-ClC_6H_4O)C_6H_4-	B-1	79		70–71	L	$C_{14}H_9Cl_3O_2$
						A–W	
XXXI	*p,p'*-$C_6H_4OC_6H_4$-	B-1	49		117–118	A	$C_{16}H_{10}Cl_4O_3$
		E[c]	90				
XXXII	*p*-$C_6H_5SC_6H_4$-	B-1	40	195–200 (0.6)	67	H	$C_{14}H_{10}Cl_2OS$
XXXIII	*p,p'*-$C_6H_4SC_6H_4$-	F	63		126–128	A	$C_{16}H_{10}Cl_4O_2S$
						L	
XXXIV	*p*-$C_6H_5SOC_6H_4$-	C	68		98	I	$C_{14}H_{10}Cl_2O_2S$
XXXV	*p*-$C_6H_5SO_2C_6H_4$-	C[e]	80		102	A	$C_{14}H_{10}Cl_2O_3S$
		E	78			I	
XXXVI	*p,p'*-$C_6H_4SO_2C_6H_4$-	E	68		201–202	D	$C_{16}H_{10}Cl_4O_3S$

[a] A = ethanol; D = acetic acid; W = water; C = ethyl acetate; I = isopropyl alcohol; P = benzene; L = ligroin; H = hexane. [b] Reference corresponds to literature data for the substituted benzoic acids obtained by oxidation from halomethyl aryl ke-

being obtained, respectively. Evidence for these reactions was obtained by oxidizing XX to 3′,5′-dichloro-4′-methoxybiphenyl-4-carboxylic acid (LX) and by oxidizing XXI to 3′,5′-dichloro-4′-hydroxybiphenyl-4-carboxylic acid (LXI), which could then be methylated with diazomethane to methyl 3′,5′-dichloro-4-methoxybiphenyl-4-carboxylate, which upon saponification gave LX. One of the two nuclear chlorine atoms must have entered position 3′ since the ketone XX had already been prepared from 4-acetyl-3′-chloro-4′-methoxybiphenyl (LVIII)[11] and because of the identity of LX with the product of oxidation and methylation of XXI. The 5′-position of the second nuclear chlorine atom may be deduced from a comparison of its infrared spectra with those of 3′-chloro-4′-hydroxybiphenyl-4-carboxylic acid (LXII)[12] and 4′-hydroxybiphenyl-4-carboxylic acid (LXIII).[13]

The position of the second chlorine atom *ortho* to the phenolic hydroxyl group is supported also by the infrared absorption of (O–H) which, in LXI, presents a sharp peak at 3460 cm.$^{-1}$. This contrasts with the broader bands at lower frequencies found in LXII, with

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% Calcd.					% Found					
C	H	Cl	S	CH_3O	C	H	Cl	S	CH_3O	Ref.[b]
72.88	4.81	15.37			72.85	4.74	15.07			
69.09	5.02	13.60		11.93	69.15	4.75	13.74		12.22	15
61.03	4.10	24.02		10.51	61.23	4.01	24.10		10.80	16
62.55	3.93	23.08			62.60	3.89	23.20			
73.62	5.35	14.48			73.65	5.07	14.90			17
63.56	4.39	22.08			63.96	4.12	22.08			18
74.27	5.84	13.70			74.38	5.96	13.91			19
68.16	4.49	14.37			68.09	4.33	14.72			20
59.80	3.58	25.22			60.17	3.64	25.00			21
		12.76	11.54				13.00	11.49		
		19.95	9.02				19.90	9.00		
57.04	3.76	12.02	10.88		57.04	3.81	12.22	10.85		
51.76	3.23	19.10	8.63		51.91	3.21	19.20	8.86		

ation occurs. For that reason the purification was difficult and several crystallizations were necessary. [c] An excess of hydrogen peroxide was used.

% Calcd.					% Found					
C	H	Cl	S	CH_3O	C	H	Cl	S	CH_3O	Ref.[b]
63.41	3.80	26.74			63.38	3.86	26.79			22
63.41	3.80	26.74			63.18	3.69	26.08			
54.65	3.36	32.27			54.93	3.07	32.90			16
49.85	2.76	38.95		8.52	49.70	2.80	38.90		8.40	
48.04	2.30	40.51			48.00	2.23	40.40			
51.09	2.68	37.71			51.28	2.61	37.70			23
51.09	2.68	37.71			50.96	2.45	37.21			24
64.53	4.33	25.40			64.44	4.23	25.57			17
52.33	3.10	36.35			51.80	3.38	36.50			18
65.54	4.81	24.18			65.70	4.63	24.18			19
53.49	3.49	35.10			53.66	3.47	35.09			25
59.80	3.58	25.22			59.89	3.57	25.30			20
53.27	2.87	33.70			53.30	2.66	34.00			21
49.01	2.57	36.17			49.20	2.41	35.98			26
56.59	3.39	23.85	10.79		56.73	3.20	23.98	11.10		27
47.08	2.46	34.75			47.03	2.43	34.41			28
		22.64	10.25				22.40	10.50		
51.07	3.66	21.54	9.74		51.02	3.37	21.30	9.65		27
43.65	2.29	32.22			43.65	2.17	32.26			28

tones. [c] Reaction temperature 40°. [d] Reaction temperature 25°. [e] An excess of hydrogen peroxide was used.

only one chlorine atom *ortho* to OH, and in LXIII, where no chlorine atoms are present. The intramolecular hydrogen bonding between OH and the two *o*-chlorine atoms in LXI does not permit intermolecular hydrogen bonding which is responsible for the displacement and broadening of the bands to lower frequencies (see LXIII).

Experimental[14]

4-Chloroacetyl-4'-methoxybiphenyl (Method A).—To 250 ml. of an ethereal solution of diazomethane, prepared from 25 g. of nitrosomethylurea, 6.15 g. (0.025 mole) of 4'-methoxybiphenyl-

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TABLE V
$RCOCH_2Br$

Compound no.	R	Method	Yield, %	B.p., °C. (mm.)	M.p., °C.	Solvent of cryst.[a]	Formula
LII	*m*-$C_6H_5C_6H_4$-	D	25	85 (0.05)			$C_{14}H_{11}BrO$
LIII	*p*-(4-$NO_2C_6H_4$)-*m*-$NO_2C_6H_3$-	D	60		143	B–W	$C_{14}H_9BrN_2O_5$
LIV	*p*,*p*′-$C_6H_4C_6H_4$-	D	62		204–206	C	$C_{16}H_{12}Br_2O_2$
LVI	*p*-$C_6H_5SO_2C_6H_4$-	D	80		127–128	A	$C_{14}H_{11}BrO_3S$
LV	*p*-$C_6H_4SO_2C_6H_4$-	D	90		178–179	F–W	$C_{16}H_{12}Br_2O_4S$

[a] B = acetone; W = water; C = ethyl acetate; A = ethanol; F = dioxane. [b] Reference corresponds to literature data for the

TABLE VI
$RCOCHBr_2$

Compound no.	R	Method	Yield, %	M.p., °C.	Solvent of cryst.[a]	Formula
XXXVII	*p*-$C_6H_5C_6H_4$-	D	55	118–119	D	$C_{14}H_{10}Br_2O$
LVII	*p*-(4-$NO_2C_6H_4$)-*m*-$NO_2C_6H_3$-	D	61	126	B–W A	$C_{14}H_8Br_2N_2O_5$
XXXVIII	*p*,*p*′-$C_6H_4C_6H_4$-	D[c]	60	169–170	D–W	$C_{16}H_{10}Br_4O_2$
XXIX	*o*,*o*′-$C_6H_4C_6H_4$-	D	54	182–183	D	$C_{16}H_{10}Br_4O_2$
XL	*p*-$C_6H_5CH_2C_6H_4$-	D	90	44	P	$C_{15}H_{12}Br_2O$
XLI	*p*,*p*′-$C_6H_4CH_2C_6H_4$-	D	72	104–105	M	$C_{17}H_{12}Br_4O_2$
XLII	*p*-$C_6H_5CH_2CH_2C_6H_4$-	D	98	77	M–W	$C_{16}H_{14}Br_2O$
XLIII	*p*,*p*′-$C_6H_4CH_2CH_2C_6H_4$-	D	78	146	B–W	$C_{18}H_{14}Br_4O_2$
XLIV	*p*-$C_6H_5OC_6H_4$-	D	60	54–56	A	$C_{14}H_{10}Br_2O_2$
XLV	*p*,*p*′-$C_6H_4OC_6H_4$-	D	95	110	B W	$C_{16}H_{10}Br_4O_3$
XLVI	*p*-$C_6H_5SC_6H_4$-	D	50	80–81	A	$C_{14}H_{10}Br_2OS$
XLVII	*p*,*p*′-$C_6H_4SC_6H_4$-	D	50	118–120	C	$C_{16}H_{60}Br_4O_2S$
XLVIII	*p*-$C_6H_5SO_2C_6H_4$-	D	50	136–138	A	$C_{14}H_{10}Br_2O_3S$
LI	*p*,*p*′-$C_6H_4SO_2C_6H_4$-	D	85	195	B–W C	$C_{16}H_{10}Br_4O_4S$

[a] D = acetic acid; B = acetone; W = water; A = ethanol; P = benzene; M = methanol; C = ethyl acetate. [b] Reference corresponds to literature data for the substituted benzoic acids obtained by oxidation from halomethyl aryl ketones. [c] Reaction

carbonyl chloride, dissolved in 250 ml. of anhydrous benzene, was added dropwise at 20°. After 48 hr. at 20°, the solution was saturated with anhydrous hydrogen chloride, concentrated under reduced pressure until crystallization began, and cooled. The product was filtered off and recrystallized from ligroin (see Table III).

3-Chloro-4-chloroacetyl-4′-methoxybiphenyl (II) (Method B-1).—Chloroacetyl chloride (11.2 g., 0.1 mole) was added dropwise at 10–20° to a stirred mixture of 21.85 g. (0.1 mole) of 3-chloro-4-methoxybiphenyl, 100 ml. of anhydrous carbon disulfide, and 13.3 g. (0.1 mole) of aluminum chloride. After stirring and refluxing for 6 hr., the reaction mixture was poured into ice-water and acidified with hydrochloric acid, and the crude product was extracted with methylene chloride, washed, dried, and fractionated.

The yields, chemical and physical data, and analyses of this substance and of the other products prepared by this method are listed in Tables III and IV. The solvent, the temperature, and the time of reaction of other products prepared by this method are listed in Table II.

4-Chloroacetyldiphenylmethane (VI) (Method B-2).—A mixture of 33.6 g. (0.2 mole) of diphenylmethane, 100 ml. of ethylene chloride, and 22.6 g. (0.2 mole) of chloroacetyl chloride was added dropwise at −5° with stirring to a mixture of 26.6 g. (0.2 mole) of aluminum chloride and 100 ml. of ethylene chloride. After stirring at −5° for 3 hr. the mixture was poured into ice-water, acidified with hydrochloric acid, separated, and the water layer was extracted with ethylene chloride. The extracts were washed with water. After drying and concentration, the residue was distilled at reduced pressure. The yields, chemical and physical data, and analyses of this substance and of the other products prepared by this method are listed in Tables III and IV.

4-Dichloroacetyldiphenylethane (XXVII) (Method B-3).—Dichloroacetyl chloride (14.74 g., 0.1 mole) was added dropwise with stirring at 20° to a mixture of 16.07 g. (0.125 mole) of aluminum chloride and 50 ml. of ethylene chloride. Stirring at 20° was continued for 30 min., the solution was decanted from excess aluminum chloride and added, at −15°, to a solution of 18.2 g. (0.1 mole) of diphenylethane in 50 ml. of ethylene chloride. After stirring the reaction mixture at −10° for 6 hr., it was poured into water and worked up as usual. For data, see Table IV.

4-Chloroacetyldiphenyl Sulfoxide (XV) (Method C).—To a solution of 5.24 g. (0.02 mole) of 4-chloroacetyldiphenyl sulfide in 100 ml. of glacial acetic acid was added 2.38 ml. (0.02 mole) of 30% hydrogen peroxide. After standing at room temperature for 48 hr., the mixture was poured into 2 l. of ice-water, and the product was filtered off and crystallized (see Tables III and IV).

General Directions for Mono- and Dibromoacetyl Derivatives (Method D).—To a solution of 0.1 mole of the aryl methyl ketone in (a) glacial acetic acid or (b) chloroform, the required amount of bromine was added at 30–40° and the mixture was stirred until the color disappeared. When acetic acid was used, water was added to precipitate the product, which was filtered, washed with water, and crystallized or distilled. If the reaction was carried out in chloroform, the solution was washed with water, dried, evaporated, and the residue crystallized from a suitable solvent (see Tables V and VI).

4-Dichloroacetylbiphenyl (XVIII) (Method E).—A solution of 19.6 g. (0.1 mole) of 4-acetylbiphenyl in 250 ml. of acetic acid, warmed at 60°, was saturated with a stream of chlorine. Nitrogen was bubbled in to remove excess chlorine and hydrogen chloride, and the 4-dichloroacetylbiphenyl crystallized on addition of water. It was filtered, washed, and recrystallized (see Table IV).

4,4′-Bis-(dichloroacetyl)diphenyl Sulfide (XXXIII) (Method F).—A stream of chlorine and nitrogen was passed through a solution of 27 g. (0.1 mole) of 4,4′-bis(acetyldiphenyl) sulfide in 250 ml. of glacial acetic acid and warmed at 60° until the solution was saturated with chlorine. It was cooled, and the product, which crystallized, was filtered, washed with water, and recrystallized (see Table IV).

3′,5′-Dichloro-4′-hydroxybiphenyl-4-carboxylic Acid (LXI).—A solution of 3.5 g. (0.01 mole) of 4-dichloroacetyl-3′,5′-dichloro-4′-hydroxybiphenyl (XXI) in 20 ml. of dioxane was refluxed for 5 hr. with a solution of 3.16 g. (0.02 mole) of potassium perman-

% Calcd.					% Found					
C	H	Br	N	S	C	H	Br	N	S	Ref.[b]
61.11	4.03	29.05			60.67	3.75	29.11			29
45.79	3.02	21.76	7.67		46.00	2.62	21.99	7.50		30
49.51	3.05	40.35			49.16	3.15	40.07			23
49.56	3.27	23.56			49.31	3.27	23.90			27
41.76	2.63	34.73		6.97	41.39	2.56	35.28		6.94	28

substituted benzoic acids obtained by oxidation from halomethyl aryl ketones.

% Calcd.					% Found					
C	H	Br	N	S	C	H	Br	N	S	Ref.
47.48	2.84	45.14			47.61	2.88	45.36			22
37.86	1.81	35.99	6.31		38.19	1.94	35.90	6.18		30
34.69	1.82	57.71			34.68	1.71	57.62			23
34.69	1.82	57.71			34.68	1.63	57.94			24
48.94	3.29	43.42			49.19	3.41	43.19			17
35.95	2.13	56.29			36.12	1.97	56.19			18
50.29	3.69	41.83			50.85	3.81	41.44			19
37.15	2.42	54.93			37.54	2.45	54.78			25
45.43	2.72	43.19			45.68	2.66	42.59			20
33.72	1.77	56.09			33.96	2.04	55.54			26
43.55	2.61	41.40			43.37	2.64	41.59			27
32.79	1.72	54.55			33.33	1.51	54.48			28
40.21	2.41	38.23			40.35	2.62	38.09			27
31.09	1.63	51.73		5.18	31.43	1.45	51.60		5.30	28

temperature 80–90°.

ganate in 40 ml. of 12% aqueous sodium hydroxide. After filtration from manganese dioxide, the precipitate, formed on acidification with hydrochloric acid, was recrystallized from acetic acid to give 2.7 g. (95%) of 3′,5′-dichloro-4′-hydroxybiphenyl-4-carboxylic acid, m.p. >300°.

Anal. Calcd. for $C_{13}H_8Cl_2O_3$: C, 55.15; H, 2.85. Found: C, 54 58; H, 2.72.

3′,5′-Dichloro-4′-methoxybiphenyl-4-carboxylic Acid (LX). (a).—A similar oxidation of the 4-dichloroacetyl-3′,5′-dichloro-4′-methoxybiphenyl (XX) afforded a 90% yield of 3′,5′-dichloro-4′-methoxybiphenyl-4-carboxylic acid (LX) which crystallized from acetic acid, m.p. 210°.

Anal. Calcd. for $C_{14}H_{10}Cl_2O_3$: C, 56.61; H, 3.39; Cl, 23.88. Found: C, 56.64; H, 3.43; Cl, 24.18.

(b).—To a well stirred solution of 2.83 g. (0.01 mole) of 3′,5′-dichloro-4′-hydroxybiphenyl-4-carboxylic acid (LXI) in ether, cooled at 5°, a solution of 0.88 g. (0.02 mole) of diazomethane in 40 ml. of ethyl ether was added dropwise. After 5 hr. standing at 5–8° the 3′,5′-dichloro-4′-methoxybiphenyl-4-carboxylic acid (LX) crystallized and was recrystallized from acetic acid, yield 2.08 g. (70%); m.p. 210–211°.

Anal. Calcd. for $C_{14}H_{10}Cl_2O_3$: C, 56.61; H, 3.39; Cl, 23.88; CH_3O, 10.44. Found: C, 55.81; H, 3.23; Cl, 24.01; CH_3O, 10.15.

Microbiology.—The antimicrobial activity of all compounds was tested *in vitro* by the usual procedures of the tube dilution method. In Table VII the minimal inhibiting concentrations are reported for *Micrococccus pyogenes* var. *aureus*, *Salmonella typhi*, and *Mycobacterium tuberculosis* H 37 RV.

For the tests 1% solutions in Carbowax were prepared. These solutions were then diluted with media to make a concentration of 100 γ/ml. The inoculum was 0.1 ml. of an 18-hr. broth culture (1:100) of *M. pyogenes* or *S. typhi*, or 0.1 ml. of a 7-day broth culture of *M. tuberculosis*. The incubation temperature was 37°.

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Results and Discussion

Table VII records the results of antibacterial screening. As can be seen from these data, the monochloromethyl aryl ketones tested clearly show activity against *M. pyogenes* var. *aureus* which, however, decreases in the presence of serum. Some of these substances are weakly active against *S. typhi*. Almost all of them also have slight activity against *M. tuberculosis* in the presence of serum. The chloromethyl ketones were not screened because of their irritating properties. The dichloromethyl aryl ketones are slightly active against *M. pyogenes* var. *aureus*, and inactive against *S. typhi*, but show considerable inhibitory activity against *M. tuberculosis* in the presence of serum. The corresponding dibromomethyl aryl ketones are less active against *M. tuberculosis* than their dichloromethyl analogs, but they show slight activity against *S. typhi* and good activity against *M. pyogenes;* this latter activity is, however, reduced by serum. The 2,2′-disubstituted derivatives of biphenyl are practically devoid of antibacterial activity.

As in a series of guanylhydrazones[10] previously tested, the 4,4′-disubstituted derivatives of biphenyl, diphenylethane, diphenyl ether, and diphenyl sulfide exhibited

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TABLE VII
MINIMAL INHIBITORY CONCENTRATION μG./ML. OF HALOMETHYL ARYL KETONES

	Test organism							
	Micrococcus pyogenes var. *aureus*[a]		*Micrococcus pyogenes* var. *aureus*[b]		*Salmonella typhi*[c]		*Mycobacterium tuberculosis* H 37 R. V.	
Compound no.	After 24 hr.	After 48 hr.	After 24 hr.	After 48 hr.	After 24 hr.	After 48 hr.	After 7 days	After 14 days
I[d]	6.25	6.25	12.5	25	6.25	100	12.5	12.5
III	3.12	3.12			50	50		
II	12.5	12.5	100	100	0[e]	0	50	50
IV[f]	3.12	3.12	50	50	0	0	12.5	12.5
V	0	0			0	0		
VI	6.25	6.25	25	25	25	100	25	25
VII	3.12	3.12	25	25	0	0	25	25
VIII	12.5	12.5	25	25	0	0	50	50
IX[g]	6.25	6.25	12.5	12.5	0	0	12.5	12.5
X	12.5	12.5	50	50	25	50	25	25
XI	12.5	12.5	25	25	50	50		
XII[h]	3.12	6.25	50	50	100	100	25	25
XIII[i]	12.5	12.5	50	50	0	0	25	25
XIV[j]	12.5	12.5	50	50	0	0	50	50
XV	3.12	6.25	25	25	25	50	25	25
XVI	1.56	3.12	25	50	50	50	100	100
XVII	1.56	6.25	0	0	0	0	0	0
XVIII	100	100	0	0	0		3.125	6.25
XIX	100	100	100	100	0		12.5	12.5
XX	0	0	100	100	0		6.25	6.25
XXI	0	0	100	100	0		6.25	6.25
XXII	100	100	50	100	0		6.25	12.5
XXIII	12.5	25	25	50	0		1.56	1.56
XXIV	50	50	0	0	0		0	0
XXV	0	0	0	0	0		6.25	12.5
XXVI	25	50	25	25	0		6.25	12.5
XXVII	0	0	0	0	0		6.25	6.25
XXVIII	12.5	12.5	12.5	25	0		0.78	0.78
XXIX	0	0	0	0	0		6.25	6.25
XXX	0	0	100	100	0		6.25	12.5
XXXI	25	50	25	50	0		1.56	3.12
XXXII	100	100	0	0	0		6.25	6.25
XXXIII	50	50	12.5	50	0		1.56	1.56
XXXIV	25	50	50	100	0		3.125	3.125
XXXV	25	25	100	100	0		6.25	12.5
XXXVI	6.25	12.5	25	25	0		0	0
XXXVII	3.12	3.12	6.25	12.5	12.5	25	12.5	12.5
XXXVIII	1.56	1.56	50	100	0	0	6.25	6.25
XXXIX	25	50	25	50	0	0	0	0
XL	1.56	1.56	100	0	50	50	12.5	12.5
XLI	1.56	1.56	6.25	6.25	0	0	6.25	12.5
XLII	1.56	1.56	100	0	50	50	12.5	12.5
XLIII	3.12	6.25	100	100	0	0	3.125	6.25
XLIV	1.56	1.56	100	100	25	25	25	25
XLV	1.56	1.56	100	0	50	50	25	25
XLVI	3.12	3.12	100	0	0	0	25	25
XLVII	1.56	3.12	100	100	50	50	6.25	6.25
XLVIII	3.12	6.25	100	100	25	50	0	0
IL	6.25	12.5	100	0	0	0	0	0

[a] Medium: Difco nutrient broth + 1% Tween 80. [b] Medium: Difco nutrient broth + 1% Tween 80 + 10% beef serum. [c] Medium: Difco Dubos broth base + 10% Bacto Dubos medium serum. [d] 4-Chloroacetylbiphenyl, see ref. 31. [e] The number zero indicates no activity under 100 μg./ml. [f] 4,4′-Bis(chloroacetyl)biphenyl, see ref. 32. [g] 4,4′-Bis-chloroacetyldiphenylethane, see ref. 33. [h] 4,4′-Bis(chloroacetyl)diphenyl ether, see ref. 34. [i] 4-Chloroacetyldiphenyl sulfide, see ref. 35. [j] 4,4′-Bis(chloroacetyl)diphenyl sulfide, see ref. 36.

the highest antibacterial activities, pointing to the significance of these "supporting" molecular moieties.

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