hydrogen peroxide (10 ml.) were added, and the solution was then refluxed for 3 hours. After refluxing, the solution was cooled and extracted several times with ether. The ether extracts were washed with a 10% bicarbonate solution, leaving some yellow neutral material in the ether layer. The bicarbonate washings were strongly acidified and extracted with ether. The ether was evaporated down leaving a yellow, oily residue of acidic material. Chloroform was added to the residue; the precipitate which formed was filtered off and washed with chloroform, leaving 0.401 g. (28.6%) of acid, m.p. 130–135°. Two recrystallizations from ether–petroleum ether raised the m.p. to 134.5–135.5° (0.35 g., 25%). An authentic sample of β-(2-carboxybenzoyl)-propionic acid[16] melted at 135–136.8°. The mixed melting point was 134.5–135.5°.

The neutral material from the first ether extraction, amounting to 81 mg., was identified as the dilactone of the above acid.

Norcarenone (XX).—The tosylate of 5-hydroxymethyl-2-cyclohexenone (9.2 g., 0.0328 mole), was dissolved in 450 ml. of 95% ethanol and cooled to 0°. Barium hydroxide (0.0892 *N*, 330 ml., 0.0295 equivalent) was added dropwise and with stirring over a period of 40 min. The base was added at such a rate as to maintain an average *p*H of 7.6–7.8. At no time was the *p*H allowed to go above *p*H 8. After all the base had been added, the solution was stirred until the *p*H of the solution fell to 6. The ethanol was then removed under reduced pressure. The aqueous solution was extracted three times with ether and the combined ether extracts washed with saturated salt solution. The ether was dried over sodium sulfate, which was removed by filtration, after which the ether was distilled off under reduced pressure. The residue was transferred to a small distillation flask with the aid of a small amount of benzene and distilled, giving the following fractions.

Fraction	B.p. °C.	Mm.	$n^{25}D$	Wt., g.
1	44	0.25	1.5150	0.1693
2	44	.25	1.5148	.3379
3	44–46	.25	1.5130	.3384
4	46–45	.25	1.5130	.4224
5	46–45	.25	1.5150	.2060
6	Forced over		1.5110	.2703

The ultraviolet showed λ_{max} 292, log ε 2.79; λ_{max} 218, log ε 4.94. These values indicate 10% of the 2,4-dienone and therefore the true value for pure norcarenone is log ε 4.98 (ε 9,530).

Anal. Calcd. for C_7H_8O: C, 77.75; H, 7.46. Found: C, 78.03; H, 7.47.

(16) W. Roser, *Ber.*, **17**, 2770 (1884).

Rearrangement of XX to Cycloheptadienone.—Norcarenone containing about 26% of the dienone (2.0 g., 0.0185 mole) was dissolved in ether; sodium hydroxide (0.8 g., 0.02 mole), dissolved in 25 ml. of water, was then added and the solution stirred. The aqueous layer turned red-brown almost immediately, while the ether layer became orange-yellow. The mixture was stirred for 5.5 hours, after which time the peak at 218 mμ had disappeared and the value for the peak at 292 mμ had increased markedly. The aqueous layer was then separated, acidified to *p*H 2 with dilute hydrochloric acid, and extracted three times with ether. The ether extracts were combined with the original ether layer and washed with saturated boric acid solution, followed by saturated salt solution. The ether solution was dried over sodium sulfate, the sodium sulfate removed by filtration, and the ether distilled under reduced pressure. The residue was transferred with the aid of a little ether and distilled into a Dry Ice–acetone cooled receiver. The material distilled at 34–36° at 0.8 mm., and amounted to 1.16 g. (58%), $n^{26}D$ 1.5305. The ultraviolet spectrum showed a peak at 292 mμ (log ε 3.81), indicating essentially complete purity.

Isolation of a Eucarvone Intermediate from Basic Treatment of Carvone Hydrobromide.—The carvone hydrobromide was treated under the conditions used for the conversion of tosylate XVIII to norcarenone. Nineteen grams (0.088 mole) of hydrobromide was dissolved in 200 ml. of 95% ethanol, and a 0.2 *N* solution of barium hydroxide was added at such a rate that the *p*H remained below 8.5 and above 8. The temperature of the reaction was maintained at about 20°.

After evaporating the alcohol, washing and extracting the aqueous layer with three 75-ml. portions of ether, 9.5 g. of crude material was obtained. After solvent evaporation, the material was distilled at 0.18–0.2 mm. Redistillation of the first fraction afforded 750 mg. of product, b.p. 52–54° (0.03 mm.), which was analyzed.

Fraction	B.p., °C.	Wt., g.
1	63–73	0.98
2	75–125	4.36
3	Residue	2.50

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.94; H, 9.41. Found: C, 79.45; H, 8.97.

Treatment of the first fraction (λ_{max} 235 mμ, ε 7200) with potassium hydroxide in methanol (1 *M*) gave a 36% spectral yield of eucarvone in 30 minutes (λ_{max} 303 mμ, ε 1880). It was found that eucarvone undergoes 45% deterioration in 2.5 hours under the same conditions, whereas carvone undergoes virtually no change.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MONSANTO CHEMICAL COMPANY]

The Preparation and Bacteriostatic Activity of Substituted Ureas

BY DAVID J. BEAVER, DANIEL P. ROMAN AND PAUL J. STOFFEL

RECEIVED AUGUST 23, 1956

The preparation and *in vitro* bacteriostatic activity of some ureas, carbanilides and related compounds against *Micrococcus pyogenes* var. *aureus* are described and the physical data of the compounds are tabulated. A discussion of the relation of antimicrobial action to structure is included.

Introduction

The present paper is a continuation of work described previously[1,2] on the relationship of chemical structure to bacteriostatic properties. The search for compounds more stable to light and less soluble in alkaline soap solutions than the previously described bis- and tris-phenols prompted the present study and it was found that certain substituted ureas overcame these limitations of the phenols. The parent compound urea[3] was first mentioned as a bacteriostat in 1906 and reviewed[4] in 1944 and the anthelmintic[5] and bac-

(1) D. J. Beaver and P. J. Stoffel, THIS JOURNAL, **74**, 3410 (1952).
(2) D. J. Beaver, R. S. Shumard and P. J. Stoffel, *ibid.*, **75**, 5579 (1953).
(3) G. Peju and J. Rajat, *Compt. rend. soc. biol.*, **61**, 477 (1906).
(4) L. Weinstein and A. McDonald, *Science*, **101**, 44 (1944).
(5) M. Shimotani, *J. Pharm. Soc. Japan*, **72**, 440 (1952).

teriostatic[6] properties of thioureas were reviewed recently.

Outstanding antimicrobial activity is reported for specific tri- and tetrachlorocarbanilides, some of which completely inhibit the growth of *Micrococcus pyogenes* var. *aureus* (MPA) in dilutions of 1 to 10–30 million. They are compatible with and stable in the alkaline media normally found in soap stocks, are non-toxic to higher order animals, are retained on the skin and show no tendency toward discoloration or staining.

Discussion

In the course of screening the compounds covered in this paper, it was soon apparent that the bacteriostatic properties of ureas as a group were remarkably specific in that activity was greatly enhanced or lost completely with slight changes in chemical structure. The physical data on these compounds are shown in Tables II to IX and are numbered consecutively for cross reference with their bacteriostatic activities which are summarized in Table I.

TABLE I

Max. diln. at which growth of MPA is inhibited	Compound
Thirty million	125, 126
Ten million	54, 129, 130, 166, 167, 205
One million	20, 55, 82, 93, 103, 110, 111, 133, 158, 169, 171, 199
One hundred thousand	91, 109, 118, 137, 150, 160, 161, 164, 170, 173, 175

All other compounds were less active than one part in 100,000.

The ureas reported in Tables II, III and IV do not inhibit bacterial growth of MPA in dilutions greater than one to one thousand until chlorine is introduced into the molecule. A superior order of activity is found in the phenylureas and carbanilides, reaching a maximum in 3,3′,4-trichlorocarbanilide (125) and 3,4,4′-trichlorocarbanilide (126). The remarkable specificity of these compounds when compared to numerous analogs and homologs suggests a "lock and key" combination as one of the essential properties to successful inhibition of bacterial growth. No appreciable effectiveness is found among the carbanilides, Group A, until *both* phenyl rings are chlorinated and that effectiveness is at a maximum when chlorine is present in the 3- *and* 4-positions of one ring and the 3- *or* 4-position of the second ring (125 and 126). Effectiveness is reduced to a minimum with the introduction of chlorine in *any ortho* position (126 *vs.* 124, 127).

With compound 126 selected as a standard, the 3,4-dichlorophenyl moiety was retained and analogs and isosteric derivatives were studied. Group B illustrates the effect of replacing the 4′-chlorine with other groups.

A similar trend is observed for substitution of chlorine in the *meta* position.

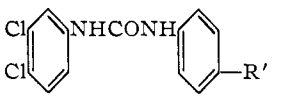
Since the introduction of an *ortho* chlorine reduces activity to a minimum, it is desirable to determine the effect of a similarly substituted positive group. In group C, it is shown again that activity is drastically reduced by *ortho* substitution regardless of the electronic character of the substituting group.

(6) D. C. Shroeder, *Chem. Revs.*, **55**, 186 (1955).

GROUP A

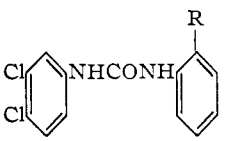
No.	R	R′	Max. diln. against MPA
..	H	H	None
67	H	4-Chloro	1–10 thousand
79	4-Chloro	4-Chloro	1–1 thousand
80	4-Chloro	2,4-Dichloro	1–10 thousand
81	4-Chloro	2,5-Dichloro	1–10 thousand
83	2,4-Dichloro	2,4-Dichloro	1–10 thousand
115	3,4-Dichloro	H	1–10 thousand
124	3,4-Dichloro	2-Chloro	1–10 thousand
127	3,4-Dichloro	2,4-Dichloro	1–10 thousand
125	3,4-Dichloro	3-Chloro	1–30 million
126	3,4-Dichloro	4-Chloro	1–30 million
129	3,4-Dichloro	3,4-Dichloro	1–10 million
130	3,4-Dichloro	3,4,5-Trichloro	1–10 million

GROUP B



No.	R′	Max. diln. against MPA
126	Chloro	1–30 million
118	Methoxy	1–100 thousand
137	Sulfamyl	1–100 thousand
115	Hydrogen	1–10 thousand
116	Methyl	1–10 thousand
123	Phenyl	1–10 thousand
136	Nitro	1–10 thousand
135	Hydroxy	1–10 thousand
134	Anilino	1–10 thousand
119	Dimethylamino	1–10 thousand
120	Amino	1–1 thousand

GROUP C



No.	R	Max. diln. against MPA
124	Chloro	1–10 thousand
115	Hydrogen	1–10 thousand
122	Phenyl	1–10 thousand
117	Methoxy	1–1 thousand

The marked lowering of activity by both electronegative and positive groups would again suggest a unique and specific "lock and key" relationship as one of the essential factors for bacterial inhibition.

Again retaining the 3,4-dichlorophenyl moiety, the compounds shown in groups D and E, and reported in Tables V and VI, were prepared to determine the effect of replacing the second phenyl ring with other aryl and alkyl groups. None of these compounds were active at dilutions higher than one part in ten thousand against MPA.

TABLE II

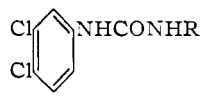
TYPE, R·NHC(=X)NHR'

No.	R	X	R	Procedure	Yield, %	M.p., °C.	Empirical formula	Analysis % nitrogen Calcd.	Found
1	H	O	2-Naphthyl	C	96.8	212 dec.[a]	$C_{11}H_{10}N_2O$	15.05	15.05
2	H	O	4-Biphenylyl	C	97.0	209 dec.[b]	$C_{13}H_{12}N_2O$	13.18	12.64
3	1-Naphthyl	O	1-Naphthyl	D	49.8	295–296[c]	$C_{21}H_{16}N_2O$	9.00	9.15
4	2-Naphthyl	O	2-Naphthyl	D	86.7	305–306[c]	$C_{21}H_{16}N_2O$	9.00	9.29
5	2-Naphthyl	O	3-Methoxypropyl	A	80.0	142.5–143.0	$C_{15}H_{18}N_2O_2$	10.84	10.57
6	1-Naphthyl	O	Cyclohexyl	A	100.0	237.0–238.0	$C_{17}H_{20}N_2O$	10.43	10.30
7	2-Naphthyl	O	Dicyclohexyl	A	99.3	177.3–177.8	$C_{23}H_{30}N_2O$	8.02	8.02
8	Cyclohexyl	O	Cyclohexyl	E	30.2	226.0–227.0[d]	$C_{13}H_{24}N_2O$	12.58	12.77
9	Dicyclohexyl	O	Ethyl	A	87.4	146.8–147.5	$C_{15}H_{28}N_2O$	11.10	11.11
10	Dicyclohexyl	O	Dicyclohexyl	E	36.5	81.0–81.7	$C_{25}H_{44}N_2O$	7.25	7.29
11	Cyclohexyl	S	Phenyl	A5	91.5	150.1–150.9[e]	$C_{13}H_{18}N_2S$	11.93	11.97
12	Cyclohexyl	S	4-Ethoxyphenyl	B	74.5	122.2–123.0	$C_{15}H_{22}N_2OS$	10.05	9.88
13	Cyclohexyl	S	4-Dimethylaminophenyl	B	91.0	127.0–127.8	$C_{15}H_{23}N_3S$	15.15	15.20
14	Cyclohexyl	S	1-Naphthyl	B	74.2	141.8–142.5	$C_{17}H_{20}N_2S$	9.86	9.72
15	Cyclohexyl	S	Dicyclohexyl	B	49.2	103.2–103.6	$C_{19}H_{34}N_2S$	8.68	8.70
16	Phenyl	S	4-Dimethylaminophenyl	B	84.2	154.4–154.8	$C_{15}H_{17}N_3S$	15.50	15.70
17	Phenyl	S	2-Naphthyl	B	83.6	158.2–159.0[f]	$C_{17}H_{14}N_2S$	10.07	10.05
18	Phenyl	S	Dicyclohexyl	B	63.7	86.5–87.3[g]	$C_{19}H_{28}N_2S$	8.85	8.76
19	Phenyl	S	4-Ethoxyphenyl	A5	89.8	133.9–134.3[h]	$C_{15}H_{16}N_2OS$	10.30	10.35
20	3,4-Dibromophenyl	S	4-Bromophenyl	A7	47.5	125.0–126.1	$C_{13}H_9Br_3N_2S$	51.55[i]	51.58[i]

NOTE: Tables II and VII headed X, O = oxygen, S = sulfur.

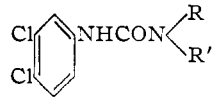
[a] W. Wlodkowsky and Z. Darst, *J. prakt. Chem.*, [2] **59**, 277 (1899), gives m.p. 213°. [b] M. J. Van Gelderen, *Rec. trav. chim.*, **52**, 977 (1933), gives m.p. 210°. [c] T. L. Davis and H. W. Underwood, Jr., THIS JOURNAL, **44**, 2601 (1922), give m.p. 286° for 1-naphthyl, 296° for 2-naphthyl. [d] A. Skita and H. Rolfes, *Ber.*, **53**, 1248 (1920), give m.p. 229–230°. [e] K. N. Campbell, B. K. Campbell and S. J. Patelski, *Proc. Indiana Acad. Sci.*, **53**, 119 (1943), give m.p. 148°. [f] K. Mainzer, *Ber.*, **15**, 1417 (1882), gives m.p. 156°. [g] Reference *e* gives m.p. 88–89°. [h] R. F. Hunter and J. W. Jones, *J. Chem. Soc.*, **133**, 2206 (1930), give m.p. 148°. [i] Analysis is % bromine.

GROUP D



No.	R	Max. dilu. against MPA
126	4-Chlorophenyl	1–30 million
115	Phenyl	1–10 thousand
84	Hydrogen	1–10 thousand
85	Ethyl	1–10 thousand
86	*t*-Octyl	1–10 thousand
88	1-Naphthyl	1–10 thousand
89	2-Naphthyl	1–10 thousand
90	2-Hydroxypropyl	1–1 thousand
92	Tetrahydrofurfuryl	1–1 thousand
87	Cyclohexyl	1–1 thousand

GROUP E

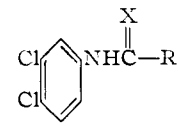


No.	R	R'	Max. dilu. against MPA
84	H	H	1–10 thousand
96	2-Hydroxyethyl	2-Hydroxyethyl	1–10 thousand
94	Allyl	Allyl	1–1 thousand
97	2-Chloroallyl	2-Chloroallyl	1–1 thousand
100	3-Chloroallyl	3-Chloroallyl	1–1 thousand
108	Cyclohexyl	Cyclohexyl	1–1 thousand
107	Phenyl	Phenyl	1–1 thousand
104	Butyl	Phenyl	1–1 thousand
102	2-Chloroallyl	Phenyl	1–1 thousand

Table VII describes the heterocyclic carboxanilides in which one nitrogen of the urea moiety is bound in the hetero group. Varying degrees of activity were found, but a review of 25 derivatives fails to disclose any group equivalent to 3,4,4′-trichlorocarbanilide. Compounds 150, 160, 161 and 164 were the most active but they were effective at a maximum dilution of 1:100,000.

In group F is shown a comparison of substituted ureas with similarly substituted thioureas. The thio derivatives are invariably less effective.

GROUP F



No.	X	R	Max. dilu. against MPA
126	O	4-Chlorophenylamino	1–30 million
166	S	4-Chlorophenylamino	1–10 million
129	O	3,4-Dichlorophenylamino	1–10 million
170	S	3,4-Dichlorophenylamino	1–100 thousand
115	O	Anilino	1–10 thousand
168	S	Anilino	1–1 thousand
150	O	4-Morpholinyl	1–100 thousand
151	S	4-Morpholinyl	1–1 thousand
158	O	1-Pyrrolidine-2-thione	1–1 million
159	S	1-Pyrrolidine-2-thione	1–1 thousand

Several bromocarbanilides prepared for direct comparison with the chloro derivatives show a decreasing order of activity in both the urea and thiourea series as shown in group G.

With the maximum order of activity apparently attained in compound 126, a series of 33 isosteric

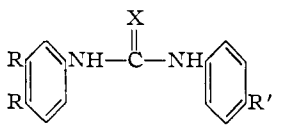
TABLE III

TYPE R—C6H4—NHCONR'R''

No.	R	R'	R''	Procedure	Yield, %	M.p., °C.	Empirical formula	Analysis % nitrogen Calcd.	Found
21	H	H	H	C	61.5	148.5–149.0[a]	$C_7H_8N_2O$	20.58	20.38
22	H	H	3-Diethylaminopropyl	A6	100.0	69.5–70.0	$C_{14}H_{23}N_3O$	16.85	16.62
23	H	H	3-Isopropylaminopropyl	A2	58.0	143.7–144.2	$C_{13}H_{21}N_3O$	17.87	17.73
24	H	H	3-Methoxypropyl	A7	100.0	87.5–88.2	$C_{11}H_{16}N_2O_2$	13.45	13.20
25	H	H	Cyclohexyl	A7	97.3	186.3–187.1[b]	$C_{13}H_{18}N_2O$	12.83	12.86
26	H	H	2-Naphthyl	A5	73.3	233.0–234.0	$C_{17}H_{14}N_2O$	10.73	10.57
27	H	Cyclohexyl	Cyclohexyl	A	79.4	180.3–181.3[c]	$C_{19}H_{28}N_2O$	9.37	9.47
28	H	Allyl	Allyl	A2	100.0	65.5–66.0	$C_{13}H_{18}N_2O$	12.92	12.83
29	H	$C_6H_5NHCONHCH_2CH_2CH_2$–	$C_6H_4NHCONHCH_2CH_2CH_2$–	A6	100.0	132 decomp.	$C_{27}H_{32}N_6O_3$	17.10	16.84
30	H	Butyl	Butyl	A6	98.6	82.7–83.0	$C_{15}H_{24}N_2O$	13.00	12.90
31	H	Heptyl	Heptyl	A	76.0	.....	$C_{21}H_{36}N_2O$	8.42	8.32
32	H	2-Ethylhexyl	2-Ethylhexyl	A7	93.7	.....	$C_{33}H_{40}N_2O$	7.77	7.88
33	H	Phenyl	Phenyl	A7	86.8	136.0–136.6[d]	$C_{13}H_{12}N_2O$	9.73	9.75
34	2-Methyl	H	Cyclohexyl	A	95.1	196.1–196.5	$C_{14}H_{20}N_2O$	12.03	11.91
35	2-Methyl	Cyclohexyl	Cyclohexyl	A	86.0	142.2–142.8	$C_{20}H_{30}N_2O$	8.93	9.21
36	4-Methyl	H	Cyclohexyl	A	100.0	205.2–205.8	$C_{14}H_{20}N_2O$	12.03	11.92
37	4-Methyl	Cyclohexyl	Cyclohexyl	A	91.5	173.4–173.7	$C_{20}H_{30}N_2O$	8.93	9.07
38	2-Methoxy	Cyclohexyl	Cyclohexyl	A	100.0	155.3–156.0	$C_{20}H_{30}N_2O_2$	8.49	8.43
39	2-Ethoxy	H	3-Methoxypropyl	A6	78.0	86.6–87.2	$C_{13}H_{20}N_2O_3$	11.10	11.11
40	2-Ethoxy	H	2-Naphthyl	A	71.0	177.5–178.2	$C_{19}H_{18}N_2O_2$	9.15	9.04
41	2-Ethoxy	Cyclohexyl	Cyclohexyl	A	65.2	99.8–100.4	$C_{21}H_{32}N_2O_2$	8.13	8.02
42	4-Ethoxy	H	Ethyl	A	85.3	151.9–152.4[e]	$C_{11}H_{16}N_2O_2$	13.45	13.49
43	4-Ethoxy	H	1-Naphthyl	A	97.6	238.0–239.0	$C_{19}H_{18}N_2O_2$	9.14	9.00
44	4-Ethoxy	H	2-Naphthyl	A	99.3	237.4–238.0	$C_{19}H_{18}N_2O_2$	9.14	8.98
45	4-Ethoxy	H	Cyclohexyl	A	95.6	182.6–183.0	$C_{15}H_{22}N_2O_2$	10.70	10.56
46	4-Ethoxy	Cyclohexyl	Cyclohexyl	A	91.8	149.6–150.2	$C_{21}H_{32}N_2O_2$	8.15	8.18
47	Dodecyl	Cyclohexyl	Cyclohexyl	A2	100.0	.....	$C_{31}H_{52}N_2O$	6.13	6.20
48	4-Dimethylamino	1-Naphthyl	H	A	96.0	227.5–228.5	$C_{19}H_{19}N_3O$	13.79	13.89
49	4-Dimethylamino	2-Naphthyl	H	A	91.3	252–253	$C_{19}H_{19}N_3O$	13.79	13.95
50	2-Phenyl	H	Ethyl	A	88.0	114.6–115.2[f]	$C_{15}H_{16}N_2O$	11.67	11.59
51	2-Phenyl	H	3-Diethylaminopropyl	A6	100.0	76.4–77.0	$C_{20}H_{27}N_3O$	12.90	12.60
52	2-Phenyl	Cyclohexyl	Cyclohexyl	A	100.0	110.0–110.7	$C_{25}H_{32}N_2O$	7.43	7.39
53	4-Chloro	Formyl	2,4-Dichlorophenyl	A7	85.3	118.5–119.1	$C_{14}H_9Cl_3N_2O_2$	8.16	7.99
54	4-Chloro	Formyl	3,4-Dichlorophenyl	A7	63.0	122.5–123.5	$C_{14}H_9Cl_3N_2O_2$	8.16	8.00
55	4-Chloro	Allyl	3,4-Dichlorophenyl	A2	87.2	151.2–152.0	$C_{16}H_{13}Cl_2N_2O$	30.00[g]	30.09[g]
56	2-Methoxy	Formyl	2,5-Dichlorophenyl	A7	71.0	152.5–153.0	$C_{15}H_{12}Cl_2N_2O_3$	8.26	8.19

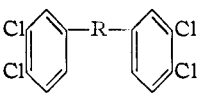
[a] A. Steiner, *Ber.*, **8**, 518 (1875), gives m.p. 149°. [b] A. Skita and H. Rolfes, *ibid.*, **53**, 1248 (1920), give m.p. 182°. [c] P. Sabatier and J. B. Senderens, *Ann. chim.*, [8] **4**, 379 (1905), give m.p. 169°. [d] W. Michler, *Ber.*, **9**, 398 (1876), gives m.p. 136°. [e] H. F. J. Lorang, *Rec. trav. chim.*, **46**, 635 (1927), gives m.p. 152°. [f] M. H. Werther, *ibid.*, **52**, 670 (1933), gives m.p. 118°. [g] Analysis is % chlorine.

GROUP G



No.	X	R	R'	Max. diln. against MPA
125	O	3,4-Dichloro	3-Chloro	1–30 million
133	O	3,4-Dichloro	3-Bromo	1–1 million
82	O	3,4-Dibromo	3-Chloro	1–1 million
167	S	3,4-Dichloro	3-Chloro	1–10 milion
169	S	3,4-Dichloro	3-Bromo	1–1 million

GROUP H



No.	R	Max. diln. against MPA
129	—NHCONH—	1–10 million
174	—NHCO—	1–10 thousand
180	—N=CH—	1–1 thousand
185	—NHCOCONH—	1–10 thousand
186	—NHC=NH·NH—	1–10 thousand
192	—NHCONHCH$_2$—	1–1 thousand
195	—NHSONH—	1–10 thousand
203	—NH·CH=N—	1–10 thousand
205	—NHCOO—	1–10 million

derivatives were screened to determine the overall effect of the urea linkage connecting both the 3,4-dichlorophenyl (group H) and 4-chlorophenyl (group J) moieties.

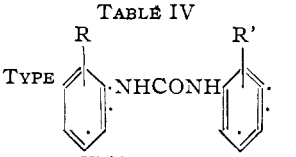
None of these compounds approach the activity of 129 or 126 except the symmetrical carbanilate 205.

No explanation is offered except to point out this frequently recurring phenomenon wherein a slight change in structure has resulted in enormous variations in activity and reversals of trends when changing from one series to another no matter how closely related. A similar investigation of the carbanilates will be reported in a forthcoming paper.

Experimental

The compounds described in Tables II–IX have been prepared following one of the procedures A–E as noted. The reactants, when commercially available, were used as received without further purification. When unavailable,

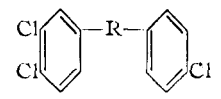
TABLE IV

TYPE 

No.	R	R'	Procedure	Yield, %	M.p., °C.	Empirical formula	Analysis % nitrogen Calcd.	Found
57	H	2-Methoxy	A	84.3	146.2–146.8[a]	$C_{14}H_{14}N_2O_2$	11.57	11.47
58	H	2-Ethoxy	A	94.4	173.8–174.2[b]	$C_{15}H_{16}N_2O_2$	10.94	10.69
59	H	4-Ethoxy	A	100.0	188.2–188.8[c]	$C_{15}H_{16}N_2O_2$	10.94	10.85
60	H	2-Ethyl	A	61.2	184.9–185.5	$C_{15}H_{16}N_2O$	11.66	11.43
61	H	4-Dimethylamino	A	94.0	208.0–208.8[d]	$C_{15}H_{17}N_3O$	16.46	16.32
62	H	4-Diethylamino	A	88.8	178.7–179.3	$C_{17}H_{21}N_3O$	14.83	14.71
63	H	2-Phenyl	A	95.7	173.0–173.6	$C_{19}H_{16}N_2O$	9.73	9.67
64	H	4-Phenyl	A	85.5	240–241[e]	$C_{19}H_{16}N_2O$	9.73	9.48
65	H	4-Amino	A	78.5	>400[f]	$C_{13}H_{13}N_3O$	18.43	18.10
66	H	4-Anilino	A	98.2	212.8–213.8[g]	$C_{19}H_{17}N_3O$	13.88	13.85
67	H	4-Chloro	A	95.0	250–251[h]	$C_{13}H_{11}ClN_2O$	11.35	11.35
68	2-Methoxy	2,4-Dichloro	A	99.5	222.3–223.0	$C_{14}H_{12}Cl_2N_2O_2$	22.79[p]	23.15[p]
69	4-Methoxy	2,4-Dichloro	A	58.0	230.0–230.5	$C_{14}H_{12}Cl_2N_2O_2$	22.79[p]	22.65[p]
70	2-Ethoxy	4-Ethoxy	A	65.2	146.4–147.0[i]	$C_{17}H_{20}N_2O_3$	9.35	9.16
71	4-Ethoxy	2-Methyl	A	84.0	202.0–202.4[j]	$C_{16}H_{18}N_2O_2$	10.33	10.37
72	4-Ethoxy	4-Methyl	A	100.0	220.4–221.0[k]	$C_{16}H_{18}N_2O_2$	10.33	10.14
73	4-Ethoxy	4-Dimethylamino	A	91.1	211.8–212.2	$C_{17}H_{21}N_3O_2$	14.07	14.05
74	4-Ethoxy	Dodecyl	A2	100.0	.....	$C_{27}H_{40}N_2O_2$	6.60	6.81
75	4-Ethoxy	2-Phenyl	A	95.8	194.8–195.4	$C_{21}H_{20}N_2O_2$	8.44	8.44
76	2-Phenyl	4-Anilino	A	86.8	155.8–156.2	$C_{25}H_{21}N_3O$	11.06	11.01
77	2-Phenyl	2-Phenyl	A	74.0	182.2–182.8	$C_{25}H_{20}N_2O$	7.69	7.85
78	4-Phenyl	4-Phenyl	A	76.5	312 dec.[l]	$C_{25}H_{20}N_2O$	..	..
79	4-Chloro	4-Chloro	A	98.0	315–319[m]	$C_{13}H_{10}Cl_2N_2O$	..	..
80	4-Chloro	2,4-Dichloro	A	98.0	253.0–253.8[o]	$C_{13}H_9Cl_3N_2O$	33.70[p]	33.20[p]
81	4-Chloro	2,5-Dichloro	A	83.0	261.5–262.5	$C_{13}H_9Cl_3N_2O$	33.70[p]	33.40[p]
82	3-Chloro	3,4-Dibromo	A	94.0	208.5–209.0	$C_{13}H_9Br_2ClN_2O$	6.93	6.99
83	2,4-Dichloro	2,4-Dichloro	A	97.5	261–263[n]	$C_{13}H_8Cl_4N_2O$	..	..

[a] J. H. Ransom, *Am. Chem. J.*, **23**, 40 (1900), gives m.p. 144°. [b] R. Leuckart, *J. prakt. Chem.*, [2] **41**, 327 (1890), gives m.p. 170°. [c] G. Abati and P. Gallo, *Chem. Zentr.*, **I**, 246 (1907), give m.p. 178°. [d] H. Staudinger and R. Endle, *Ber.*, **50**, 1045 (1917), give m.p. 208°. [e] M. J. Van Gelderen, *Rec. trav. chim.*, **52**, 977 (1933), reports m.p. 240°. [f] E. Lellmann and E. Wurthner, *Ann.*, **228**, 225 (1885), give no data. [g] A. Krammer, *J. prakt. Chem.*, [2] **86**, 361 (1912), gives m.p. 213.5°. [h] H. Goldschmidt, *Ber.*, **25**, 1364 (1892), gives m.p. 238°. [i] A. F. McKay, *Can. J. Chem.*, **30**, 227 (1952), gives m.p. 148°. [j] A. F. McKay, *ibid.*, **30**, 227 (1952), gives m.p. 210°. [k] A. F. McKay, *ibid.*, **30**, 227 (1952), gives m.p. 217°. [l] Reference *e* gives m.p. 312°. [m] F. D. Chattaway and K. P. Orton, *Ber.*, **34**, 1074 (1901), give m.p. 310°. [n] F. D. Chattaway and K. P. Orton, *ibid.*, **34**, 1074 (1901), give m.p. 273°. [o] G. Young and A. E. Dunstan, *J. Chem. Soc.*, **93**, 1058 (1908), give m.p. 262°. [p] Analysis is % chlorine.

GROUP J



No.	R	Max. dilu. against MPA
126	—NHCONH—	1–30 million
175	—CONH—	1–100 thousand
176	—CSNH—	1–10 thousand
177	—CH_2NH—	1–1 thousand
178	—$NHCH_2$—	1–1 thousand
179	—NHCO—	1–10 thousand
181	—N=CH—	1–1 thousand
182	—$NH{\cdot}CH_2CO$—	1–1 thousand
193	—$CH_2NHCONH$—	1–1 thousand
204	—NHCOO—	1–1 thousand

they were prepared in this Laboratory as described under "Preparation of Intermediates."

Compounds described under procedures A-A7 and B were prepared by treating the appropriate isocyanate or isothiocyanate with amine in a suitable solvent. The solvents and amines were anhydrous to prevent reaction of the isocyanates to form the symmetrical carbanilides.

Procedure A.[7] **3,4-Dichlorocarbanilide (115).**—A solution of 11.9 g. (0.1 mole) of phenyl isocyanate in 50 ml. of ether was added dropwise, with constant stirring to 16.2 g. (0.1 mole) of 3,4-dichloroaniline in 50 ml. of ether. The product separated during addition as fine white plates. The slurry was held for 2 hours, filtered, washed with 20 ml. of ether and dried; yield theoretical. (In several cases, the reaction is sufficiently exothermic to evaporate the ether and additional ether was added to maintain a stirrable slurry.) One recrystallization from ethanol gave fine, colorless needles.

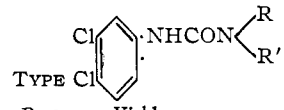
An unexpected result was obtained on preparing the carbanilide from 3,4-dichlorophenyl isocyanate and *p*-phenylenediamine. Irrespective of molar ratios, when reacting in ether the disubstituted derivative was obtained (191); but when run in benzene only the mono-substituted derivative could be formed (120). The reduction of 3,4-dichloro-4'-nitrocarbanilide (136) gave a product identical with (120).

Sub-procedures A were carried out exactly as described in A substituting the reactant solvent as

A2	Skellysolve "D" (heptane fraction)
A3	Benzene
A4	Acetone
A5	Abs. ethanol
A6	No solvent
A7	No solvent 90°, 4 hr.

(7) P. P. Sah, *Rec. trav. chim.*, **59**, 231 (1940).

TABLE V



No.	R	R'	Procedure	Yield, %	M.p., °C.	Empirical formula	Analysis % chlorine Calcd.	Found
84	H	H	C	93.7	155.6–156.3	$C_7H_6Cl_2N_2O$	34.58	34.45
85	H	Ethyl	A	100.0	179.5–180.1[a]	$C_9H_{10}Cl_2N_2O$	12.10[b]	12.32[b]
86	H	*t*-Octyl	A	100.0	145.8–146.6	$C_{15}H_{22}Cl_2N_2O$	22.37	22.70
87	H	Cyclohexyl	A	100.0	188.0–188.7	$C_{13}H_{16}Cl_2H_2O$	24.70	24.85
88	H	1-Naphthyl	A	97.0	265–266	$C_{17}H_{12}Cl_2N_2O$	21.41	21.17
89	H	2-Naphthyl	A	97.2	267–268	$C_{17}H_{12}Cl_2N_2O$	21.41	21.34
90	H	2-Hydroxypropyl	A	100.0	152.0–152.8	$C_{10}H_{12}Cl_2N_2O_2$	26.92	26.73
91	H	3-Hydroxypropyl	A	98.8	126.5–128.0	$C_{10}H_{12}Cl_2N_2O_2$	26.92	26.80
92	H	Tetrahydrofurfuryl	A	100.0	144.1–144.9	$C_{12}H_{14}Cl_2N_2O_2$	24.50	24.28
93	Ethyl	4-Chlorophenyl	A	77.0	116.0–116.8	$C_{15}H_{13}Cl_3N_2O$	31.00	31.02
94	Allyl	Allyl	A2	100.0	62.5–63.5	$C_{13}H_{14}Cl_2N_2O$	24.83	25.01
95	Allyl	Isopropyl	A	93.4	84.0–84.5	$C_{13}H_{16}Cl_2N_2O$	24.70	24.70
96	2-Hydroxyethyl	2-Hydroxyethyl	A	65.0	156.8–157.6	$C_{11}H_{14}Cl_2N_2O_3$	24.20	24.15
97	2-Chloroallyl	2-Chloroallyl	A	100.0	100.7–101.4	$C_{13}H_{12}Cl_4N_2O$	40.00	40.00
98	2-Chloroallyl	Isopropyl	A	100.0	84.7–85.2	$C_{13}H_{15}Cl_3N_2O$	33.13	32.90
99	2-Chloroallyl	*t*-Butyl	A	100.0	93.9–95.0	$C_{14}H_{17}Cl_3N_2O$	31.70	31.91
100	3-Chloroallyl	3-Chloroallyl	A	100.0	156.0–156.6	$C_{13}H_{12}Cl_4N_2O$	40.00	39.96
101	2-Chloroallyl	3-Methoxypropyl	A2	100.0	.....	$C_{14}H_{17}Cl_3N_2O_2$	30.30	29.85
102	2-Chloroallyl	Phenyl	A7	92.9	118.7–119.4	$C_{16}H_{13}Cl_3N_2O$	29.92	29.90
103	H	2,3-Dichloroallyl	A	61.2	105.1–105.9	$C_{10}H_8Cl_4N_2O$	45.20	44.90
104	Butyl	Phenyl	A	96.5	98.5–99.4	$C_{17}H_{18}Cl_2N_2O$	21.03	21.34
105	2-Cyanoethyl	Phenyl	A	89.3	114.7–115.5	$C_{16}H_{13}Cl_2N_3O$	21.20	21.12
106	Isopropyl	2-Propynyl	A	71.1	84.4–85.1	$C_{13}H_{14}Cl_2N_2O$	24.50	24.61
107	Phenyl	Phenyl	A	39.5	148.3–149.1	$C_{19}H_{14}Cl_2N_2O$	19.85	20.30
108	Cyclohexyl	Cyclohexyl	A	98.0	177.6–178.4	$C_{19}H_{26}Cl_2N_2O$	7.60[b]	7.49[b]
109	Cyclohexyl	3-Chloro-2-butenyl	A	88.7	160.4–160.8	$C_{17}H_{21}Cl_3N_2O$	28.31	28.37
110	Allyl	4-Ethoxyphenyl	A	100.0	.....	$C_{15}H_{18}Cl_2N_2O_2$	19.41	19.40
111	Allyl	3,4-Dichlorophenyl	A2	87.3	116.8–117.5	$C_{16}H_{12}Cl_4N_2O$	36.25	36.43
112	2-Propynyl	3,4-Dichlorophenyl	A	69.0	145.2–146.0	$C_{16}H_{10}Cl_4N_2O$	36.58	36.44
113	Butyl	Phenyl	A	96.5	98.5–99.4	$C_{17}H_{18}Cl_2N_2O$	21.03	21.34
114	H	2-Thiazolyl	A4	99.0	225 dec.	$C_{10}H_7Cl_2N_3OS$	24.60	24.62

[a] C. W. Todd, U. S. Patent 2,655,447, no data given. [b] Analysis is % nitrogen.

Procedure B.[8] **3,3',4,4'-Tetrachlorothiocarbanilide (170).**—A solution of 20.4 g. (0.1 mole) of 3,4-dichlorophenyl isothiocyanate and 16.2 g. (0.1 mole) of 3,4-dichloroaniline in 75 ml. of absolute ethanol was held at reflux for 1 hour. On cooling, the product separated in a white granular mass which was filtered, washed with 30 ml. of ethanol and dried. One recrystallization from ethanol gave fine, white granules.

Procedure C.[9] **Phenylurea (21).**—A solution of 11.9 g. (0.1 mole) of phenyl isocyanate in 400 ml. of ether was held at 20° while passing anhydrous ammonia through the solution until precipitation was complete. The crude product was filtered and recrystallized from ethanol to give small, white plates.

Procedure D.[10] **1,3-Di-2-naphthylurea (4).**—A dry mixture of 60.0 g. (0.42 mole) of 2-naphthylamine and 24.0 g. (0.2 mole) of urea was heated gradually to 160° and held for 3 hours until the evolution of ammonia was complete. The crude mass was pulverized and extracted with three 200-ml. portions of boiling alcohol, discarding the filtrates. The extracted cake was recrystallized from glacial acetic acid to give a white microcrystalline powder.

Procedure E.[11] **1,3-Dicyclohexylurea (8).**—A solution of 60.0 g. (0.6 mole) of cyclohexylamine and 800 ml. of toluene was held at 100° while passing in phosgene until no more solids formed. The heavy slurry of cyclohexamine HCl salt was filtered and discarded. The filtrate was evaporated under vacuum and the crude residue was recrystallized from ethanol to give small colorless needles.

Preparation of Intermediates.—The preparations of only those compounds which are new are described. The number in parentheses following the compounds corresponds to the product in Tables II–IX for which it was used.

N-Formyl-3,4-dichloroaniline[12] **(54).**—A solution of 32.4 g. (0.2 mole) of 3,4-dichloroaniline and 18.4 g. (0.4 mole) of 95% formic acid was refluxed for 6 hours. On cooling, the product separated and was filtered. One recrystallization from benzene gave fine, colorless plates.

N-(2-Propynyl)-3,4-dichloroaniline[13] **(112).**—A 162.1-g. (1.0 mole) charge of 3,4-dichloroaniline was held at 75–80° with vigorous stirring while adding dropwise 60.0 g. (0.5 mole) of propargyl bromide. After addition was completed, the resultant slurry was held at 85° for 3 hours. The reaction mix was cooled and held at 20° using an ice–salt-bath while neutralizing with a solution of 30 g. (0.75 mole) of sodium hydroxide in 500 ml. of water. The oil which separated was extracted with two 300-ml. portions of ether and dried over calcium chloride. The ether was removed under light vacuum and the remaining oil was distilled. After removal of the 3,4-dichloroaniline, the product was obtained as a mobile yellow oil b.p. 152.7–153.4° (7 mm.), $n^{25}D$ 1.5991.

N-Allyl-3,4-dichloroaniline[13] **(111).**—Prepared as above using allyl chloride and held 18 hours at 80–85°. Lemon

(8) T. Otterbacher and F. C. Whitmore, THIS JOURNAL, **51**, 1909 (1929).

(9) P. P. Sah and K. S. Chang, *Ber.*, **69**, 2762 (1936).

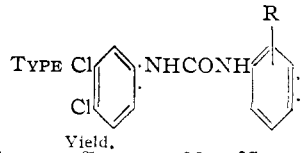
(10) T. L. Davis and H. W. Underwood, Jr., THIS JOURNAL, **44**, 2601 (1922).

(11) A. W. Hofmann, *Ann.*, **70**, 140 (1849).

(12) F. D. Chattaway, K. J. Orton and W. H. Hurtley, *Ber.*, **32**, 3636 (1899).

(13) T. J. Nolan and H. W. Clapham, *J. Soc. Chem. Ind., London*, **44**, 220T (1925).

TABLE VI

TYPE 

No.	R	Procedure	Yield, %	M.p., °C.	Empirical formula	Analysis % chlorine Calcd.	Found
115	H	A	100.0	217.2–217.7	$C_{13}H_{10}Cl_2N_2O$	25.11	25.03
116	4-Methyl	A	100.0	258.0–259.0	$C_{14}H_{12}Cl_2N_2O$	23.96	23.87
117	2-Methoxy	A	95.2	173.8–174.3	$C_{14}H_{12}Cl_2N_2O_2$	22.78	22.56
118	4-Methoxy	A	93.5	233.1–234.0	$C_{14}H_{12}Cl_2N_2O_2$	22.78	22.83
119	4-Dimethylamino	A	95.0	229.6–230.4	$C_{15}H_{15}Cl_2N_3O$	21.83	21.90
120	4-Amino	A3	96.0	>360	$C_{13}H_{11}Cl_2N_3O$	23.92	24.15
121	Dodecyl	A7	98.0	.....	$C_{25}H_{34}Cl_2N_2O$	15.78	15.70
122	2-Phenyl	A	91.6	183.3–184.1	$C_{19}H_{14}Cl_2N_2O$	19.85	20.30
123	4-Phenyl	A	84.5	233.0–234.0	$C_{19}H_{14}Cl_2N_2O$	19.85	20.04
124	2-Chloro	A	87.0	220.0–220.6	$C_{13}H_9Cl_3N_2O$	33.70	33.78
125	3-Chloro	A	91.5	210.7–211.3	$C_{13}H_9Cl_3N_2O$	33.70	33.80
126	4-Chloro	A	88.0	255.2–256.0	$C_{13}H_9Cl_3N_2O$	33.70	33.80
127	2,4-Dichloro	A	97.3	238.5–239.2	$C_{13}H_8Cl_4N_2O$	40.57	40.63
128	2,5-Dichloro	A	94.2	242.2–242.6	$C_{13}H_8Cl_4N_2O$	40.57	40.67
129	3,4-Dichloro	A	100.0	281–282	$C_{13}H_8Cl_4N_2O$	40.57	40.52
130	3,4,5-Trichloro	A	100.0	308–310	$C_{13}H_7Cl_5N_2O$	46.09	45.86
131	3-Chloro-4-hydroxy	A	95.4	237.4–238.0	$C_{13}H_9Cl_2N_2O_2$	8.46[a]	8.18[a]
132	3,5-Dichloro-4-hydroxy	A	92.4	272–273	$C_{13}H_8Cl_4N_2O_2$	7.66[a]	7.53[a]
133	3-Bromo	A	100.0	208.5–209.2	$C_{13}H_9BrCl_2N_2O$	7.78[a]	7.71[a]
134	4-Anilino	A	100.0	208.8–209.5	$C_{19}H_{15}Cl_2N_3O$	19.04	19.00
135	4-Hydroxy	A3	82.5	213.8–214.5	$C_{13}H_{10}Cl_2N_2O_2$	23.86	23.78
136	4-Nitro	A	95.3	294–295	$C_{13}H_9Cl_2N_3O_3$	21.72	21.59
137	4-Sulfamyl	A4	83.6	258.5–259.5	$C_{13}H_{11}Cl_2N_3O_3S$	11.68[a]	11.62[a]
138	4-(2-Thiazolesulfamyl)	A4	82.8	271–272	$C_{16}H_{13}Cl_2N_4O_3S_2$	15.85	15.81
139	4-(2-Pyrimidinesulfamyl)	A4	79.0	290 dec.	$C_{17}H_{13}Cl_2N_5O_3S$	16.15	15.98

[a] Analysis is % nitrogen.

yellow oil, darkening rapidly, b.p. 159.0–161.0° (7.5 mm.), $n^{25}D$ 1.5895.

3,4-Dichlorophenyl Isocyanate.[14]—One liter of ethyl acetate was saturated with phosgene and held at reflux while adding a solution of 324 g. (2.0 mole) of 3,4-dichloroaniline in 1.5 l. of ethyl acetate in a fine stream over 2–3 hours. Phosgene was passed into the reaction flask throughout the reaction so as to maintain an excess of phosgene at all times. When all the amine was added, the phosgene was cut off and the solution held at reflux for 1 hour. Approximately 1.5 l. of ethyl acetate was distilled at atmospheric pressure, removing practically all dissolved phosgene. The remaining solvent was removed under vacuum gradually dropping the pressure during the distillation. Following a small precut, the product was obtained as a mobile colorless liquid b.p. 116.7–118.1° (10.5 mm.) which gradually set to a hard crystalline mass, c.p. 40–41° (90.5%). *Anal.* Calcd. for $C_7H_3Cl_2NO$: N, 7.45. Found: N, 7.45.

3,4-Dichlorophenyl Isothiocyanate.[15]—A solution of 58.0 ml. of 38% hydrochloric acid and 350 ml. of water was held at 10–15° with vigorous agitation while adding 80.0 g. (0.7 mole) of thiophosgene during ½ hour. The cooling bath was removed, and a solution of 128.0 g. (0.7 mole) of 3,4-dichloroaniline in 400 ml. of toluene was added in a fine stream allowing the temperature to rise to 40–45° over ½ to 1 hour. The flask was then gradually heated to 85° and held for 3 hours. A small amount of solid material was filtered and discarded. The toluene layer was separated. The aqueous layer was twice extracted with 30-ml. aliquots of toluene, and the extracts combined. The toluene phase was twice washed with 50-ml. aliquots of water, separated and distilled. The solvent, water and low-boiling material was removed gradually reducing the pressure to 20 mm. at 180°. Following a small precut the product was obtained as a yellow mobile oil, b.p. 134.8–135.9° (7.0 mm.); (95.1%). *Anal.* Calcd. for $C_7H_3Cl_2NS$: S, 15.70; N, 6.87. Found: S, 15.80; N, 6.90.

3,4-Dibromophenyl Isothiocyanate.[15]—Prepared as above from 3,4-dibromoaniline. The crude product did not distil at 180° (2 mm.) and when signs of decomposition were noted, heating was discontinued and the crude product used as such. On standing the product set to a soft, buff, crystalline mass (86.5%). *Anal.* Calcd. for $C_7H_3Br_2NS$: S, 10.91; N, 4.78. Found: S, 10.88; N, 4.83.

Miscellaneous—Preparation of Carbanilide Analogs. Table IX.—Compounds 174 through 205 are new. Footnotes refer to methods of preparation. Analyses of all compounds are given in Table IX.

3,3′,4,4′-Tetrachlorobenzanilide[16] **(174).**—A solution of 16.2 g. (0.1 mole) of 3,4-dichloroaniline in 75 ml. of pyridine was stirred vigorously while adding dropwise 20.9 g. (0.1 mole) of 3,4-dichlorobenzoyl chloride. The temperature rose to 60° during the addition and stirring was continued for 2 hours. The crude oil was poured into 1 l. of cold water forming a buff-colored, granular solid. One recrystallization from acetone gave fine white needles.

3,4,4′-Trichlorobenzanilide[16] **(175).**—Prepared as above from 3,4-dichlorobenzoyl chloride and *p*-chloroaniline; fine white needles from ethanol.

N-(3,4-Dichlorobenzyl)-*p*-chloroaniline[17] **(177).**—A solution of 65.2 g. (0.33 mole) of 3,4-dichlorobenzyl chloride, 42.5 g. (0.33 mole) of *p*-chloroaniline and 42.0 g. (0.33 mole) of sodium bicarbonate in 400 ml. of water was refluxed for 72 hours. The liquid was cooled to 20° and extracted with four 100-ml. aliquots of ether. The ether extracts were combined, dried over calcium chloride and the ether removed under vacuum leaving a brown crystalline mass. One recrystallization from heptane gave small colorless granules.

3,4,4′-Trichlorothiobenzanilide[18] **(176).**—A solution of 8.0 g. (0.03 mole) of 3,4,4′-trichlorobenzanilide in 70 ml. of

(14) W. H. Horne and R. L. Shriner, THIS JOURNAL, **53**, 3186 (1931).

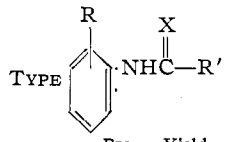
(15) G. M. Dyson and H. J. George, *J. Chem. Soc.*, **125**, 1702 (1924).

(16) A. H. Blatt, "Organic Syntheses," Coll., Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1946, p. 99.

(17) A. H. Blatt, ref. 16, p. 103.

(18) E. Klingsberg and D. Papa, THIS JOURNAL, **73**, 4988 (1951).

TABLE VII



No.	R	X	R′	Procedure	Yield, %	M.p., °C.	Empirical formula	Analysis % nitrogen Calcd.	Found
140	H	O	4-Morpholinyl	A	74.5	159.3–160.0[a]	$C_{11}H_{14}N_2O_2$	13.60	13.75
141	H	S	4-Morpholinyl	B	72.6	132.6–133.4[b]	$C_{11}H_{14}N_2OS$	12.62	12.49
142	H	O	2-Methyl-1-piperidyl	A	94.5	115.4–116.0[c]	$C_{13}H_{18}N_2O$	12.85	12.47
143	H	O	1,2-Dihydro-2,2,4-trimethyl-1-quinolyl	A	71.0	125.5–126.2[d]	$C_{19}H_{20}N_2O$	9.57	9.72
144	H	O	1,2-Dihydro-6-ethoxy-2,2,4-trimethyl-1-quinolyl	A	94.2	146.6–147.0	$C_{21}H_{24}N_2O_2$	8.35	8.16
145	H	O	1,2-Dihydro-6-phenyl-2,2,4-trimethyl-1-quinolyl	A	40.5	148.0–149.1	$C_{25}H_{24}N_2O$	7.61	7.55
146	4-Methoxy	O	4-Morpholinyl	A2	95.7	124.5–125.0	$C_{12}H_{16}N_2O_3$	11.88	11.84
147	2-Chloro	O	4-Morpholinyl	A2	93.8	132.2–132.8	$C_{11}H_{13}ClN_2O_2$	14.72[e]	14.72[e]
148	3-Chloro	O	4-Morpholinyl	A2	98.3	129.7–130.3	$C_{11}H_{13}ClN_2O_2$	14.72	14.78
149	4-Chloro	O	4-Morpholinyl	A2	91.4	200.8–201.4	$C_{11}H_{13}ClN_2O_2$	14.72	14.89
150	3,4-Dichloro	O	4-Morpholinyl	A	90.0	157.1–157.8	$C_{11}H_{12}Cl_2N_2O_2$	10.18	10.00
151	3,4-Dichloro	S	4-Morpholinyl	B	96.8	197.5–198.1	$C_{11}H_{12}Cl_2N_2OS$	24.35[e]	24.34[e]
152	3,4-Dichloro	O	1-Piperidyl	A	100.0	175.0–175.8	$C_{12}H_{14}Cl_2N_2O$	25.97[e]	25.82[e]
153	3,4-Dichloro	O	2-Methyl-1-piperidyl	A2	97.5	171.4–171.9	$C_{13}H_{16}Cl_2N_2O$	24.63[e]	24.49[e]
154	3,4-Dichloro	O	3-Methyl-1-piperidyl	A	56.5	115.7–116.7	$C_{13}H_{16}Cl_2N_2O$	24.63[e]	24.70[e]
155	3,4-Dichloro	O	4-Methyl-1-piperidyl	A2	92.5	144.0–144.8	$C_{13}H_{16}Cl_2N_2O$	24.63[e]	24.69[e]
156	3,4-Dichloro	O	1-Pyrrolidyl	A	97.8	176.8–177.4	$C_{11}H_{12}Cl_2N_2O$	27.37[e]	27.53[e]
157	3,4-Dichloro	O	1-Pyrrolidyl-2-one	A	89.3	151.8–152.7	$C_{11}H_{10}Cl_2N_2O_2$	25.95[e]	25.93[e]
158	3,4-Dichloro	O	1-Pyrridyl-2-thione	A4	90.5	171.9–172.8	$C_{11}H_{10}Cl_2N_2OS$	24.55[e]	24.67[e]
159	3,4-Dichloro	S	1-Pyrrolidyl-2-thione	A7	52.6	126.7–127.2	$C_{11}H_{10}Cl_2N_2S_2$	23.23[e]	22.96[e]
160	3,4-Dichloro	O	3-Methyl-1-pyrazinyl-5-one	A4	62.3	228.0–229.0	$C_{11}H_9Cl_2N_3O_2$	24.80[e]	25.04[e]
161	3,4-Dichloro	O	2,4,6-Trimethyl-1-piperidyl	A	85.5	135.3–136.1	$C_{15}H_{20}Cl_2N_2O$	22.43[e]	22.23[e]
162	3,4-Dichloro	O	Decahydro-1-quinolyl	A	99.7	160.5–161.4	$C_{16}H_{20}Cl_2N_2O$	21.63[e]	21.70[e]
163	3,4-Dichloro	O	Decahydro-2-isoquinolyl	A	90.4	144.0–145.0	$C_{16}H_{20}Cl_2N_2O$	21.63[e]	22.24[e]
164	3,4-Dichloro	O	1,2-Dihydro-6-ethoxy-2,2,4-trimethyl-1-quinolyl	A	54.0	139.3–140.2	$C_{21}H_{22}Cl_2N_2O_2$	17.44[e]	17.76[e]

[a] R. A. Henry and W. M. Dehn, THIS JOURNAL, **71**, 2297 (1949), give m.p. 162°. [b] R. A. Henry and W. M. Dehn, *ibid.*, **72**, 2806 (1950), give m.p. 130.5°. [c] Footnote *b*, m.p. 115.5°. [d] W. H. Cliffe, *J. Chem. Soc.*, **136**, 1327 (1933), gives m.p. 126°. [e] Analysis is % chlorine.

pyridine was held at reflux for 4 hours while adding 6.0 g. (0.03 mole) of phosphorus pentasulfide in six portions. The hot solution was quenched into 500 ml. of ice-water, in which the oily product gradually solidified. One recrystallization from ethanol gave a brilliant yellow microcrystalline powder.

N-(4-Chlorobenzyl)-3,4-dichloroaniline[18] **(178)**.—A solution of 48.6 g. (0.3 mole) of 3,4-dichloroaniline and 24.2 g. (0.15 mole) of *p*-chlorobenzyl chloride was held at 95–100° for 76 hours. The slurry which formed was stirred with 100 ml. of ether and filtered. The ether was removed under vacuum. The brown oil was set aside for 2 weeks during which time the oil solidified. One recrystallization from heptane gave small colorless needles.

3′,4,4′-Trichlorobenzanilide[18] **(179)**.—Prepared following procedure for 174 from 3,4-dichloroaniline and *p*-chlorobenzoyl chloride.

N-(3,4-Dichlorobenzylidene)-3,4-dichloroaniline[19] **(180)**.—A solution of 8.7 g. (0.05 mole) of 3,4-dichlorobenzaldehyde and 8.2 g. (0.05 mole) of 3,4-dichloroaniline in 250 ml. of ethanol was refluxed for 4 hours. On cooling the product separated as fine yellow needles (86.5%).

N-(4-Chlorobenzylidene)-3,4-dichloroaniline[19] **(181)**.—Prepared as above from *p*-chlorobenzaldehyde and 3,4-dichloroaniline; fine yellow needles from ethanol.

α-(3,4-Dichloroanilino)-*p*-chloroacetophenone[16] **(182)**.—A solution of 16.3 g. (0.1 mole) of 3,4-dichloroaniline and 23.4 g. (0.1 mole) of *p*-chlorophenacyl bromide in 250 ml. of ethanol was refluxed for 6 hours. The product separated during reaction. The slurry was cooled to 70° and filtered, giving small canary yellow plates from acetone (80.0%).

3,3′,4,4′-Tetrachloromalonanilide[20] **(183)**.—A solution of 32.5 g. (0.2 mole) of 3,4-dichloroaniline and 64.0 g. (0.4 mole) of ethyl malonate was refluxed for 18 hours. The initial reflux temperature of 170° gradually fell to 110° during that time. On cooling the product separated as small white granules (28.7%).

1,5-Bis-(3,4-dichlorophenyl)-pentadien-3-one[21] **(184)**.—A solution of 35.0 g. (0.2 mole) of 3,4-dichlorobenzaldehyde and 5.8 g. (0.1 mole) of acetone in 150 ml. of ethanol was held at 30° with vigorous stirring while adding 2 ml. of 50% caustic. A heavy slurry formed almost at once and was filtered after holding 15 minutes. One recrystallization from benzene gave small colorless needles.

3,3′,4,4′-Tetrachlorooxanilide[20] **(185)**.—A solution of 32.5 g. (0.2 mole) of 3,4-dichloroaniline and 14.6 g. (0.1 mole) of ethyl oxalate was held at 160° for 16 hours. On cooling the liquid solidified. The crude product was recrystallized from ethanol to give fluffy white plates.

1,3-Bis-(3,4-dichlorophenyl)-guanidine[22] **(186)**.—A solution of 10.6 g. (0.1 mole) of cyanogen bromide in 40 ml. of ethanol was added with stirring at 60° to 32.4 g. (0.2 mole) of 3,4-dichloroaniline in 50 ml. of ethanol. On cooling, a solid product separated and was filtered. The crude product was refluxed for 10 minutes with 250 ml. of 10% hydrochloric acid, filtered and refluxed with 300 ml. of 10% so-

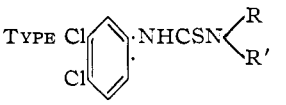
(19) H. Gilman and A. H. Blatt, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 80.

(20) A. G. Richardson, J. S. Pierce and E. E. Reid, THIS JOURNAL, **74**, 4011 (1952).

(21) P. T. Mora and T. Széki, *ibid.*, **72**, 3009 (1950).

(22) E. Lieber and G. B. Smith, *Chem. Revs.*, **25**, 213 (1939).

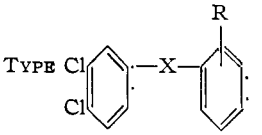
TABLE VIII



No.	R	R'	Procedure	Yield, %	M.p., °C.	Empirical formula	Analysis % chlorine Calcd.	Found
165	H	3-Hydroxypropyl	A2	99.0	34–35	$C_{10}H_{12}Cl_2N_2OS$	25.40	25.38
166	H	4-Chlorophenyl	B	82.0	154.2–154.9	$C_{13}H_9Cl_3N_2S$	32.10	32.09
167	H	3-Chlorophenyl	B	75.5	119.5–120.5	$C_{13}H_9Cl_3N_2S$	32.10	32.03
168	H	Phenyl	B	99.0	136.1–137.0	$C_{13}H_{10}Cl_2N_2S$	23.86	23.80
169	H	3-Bromophenyl	A7	74.6	107.5–108.3	$C_{13}H_9BrCl_2N_2S$	7.46[a]	7.49[a]
170	H	3,4-Dichlorophenyl	B	94.5	162.6–163.5	$C_{13}H_8Cl_4N_2S$	38.72	38.60
171	H	2-Thenyl	A	99.0	153.2–154.1	$C_{12}H_{10}Cl_2N_2S_2$	22.35	22.18
172	Isopropyl	Allyl	A2	93.4	80.8–81.6	$C_{13}H_{16}Cl_2N_2S$	23.40	23.35
173	Isopropyl	2-Propynyl	A2	88.7	77.2–77.8	$C_{13}H_{14}Cl_2N_2S$	23.52	23.35

[a] Analysis is % chlorine.

TABLE IX



No.	X	R	Yield, %	M.p., °C.	Empirical formula	Analysis % chlorine Calcd.	Found
174	—CONH—	3,4-Dichloro	86.5	232.6–233.3	$C_{13}H_7Cl_4NO$	42.25	42.50
175	—CONH—	4-Chloro	80.0	167.3–168.1	$C_{13}H_8Cl_3NO$	35.22	34.98
176	—CSNH—	4-Chloro	77.0	144.5–145.3	$C_{13}H_8Cl_3NS$	33.64	33.50
177	—CH_2NH—	4-Chloro	18.5	169.0–169.5	$C_{13}H_{10}Cl_3N$	37.12	37.40
178	—$NHCH_2$—	4-Chloro	18.0	122.3–123.1	$C_{13}H_{10}Cl_3N$	37.17	37.35
179	—NHCO—	4-Chloro	73.3	176.6–177.4	$C_{13}H_8Cl_3NO$	35.22	34.98
180	—N=CH—	3,4-Dichloro	86.5	132.3–133.0	$C_{13}H_7Cl_4N$	4.39[b]	4.33[b]
181	—N=CH—	4-Chloro	81.0	103.7–104.4	$C_{13}H_8Cl_3N$	4.92[b]	4.84[b]
182	—$NHCH_2CO$—	4-Chloro	80.0	182.5–183.7	$C_{14}H_{10}Cl_3NO$	33.81	33.76
183	—$NHCOCH_2CONH$—	3,4-Dichloro	28.7	227.8–228.6	$C_{15}H_{10}Cl_4N_2O_2$	36.20	36.05
184	—CH=CHCOCH=CH—	3,4-Dichloro	59.3	202.1–202.8	$C_{12}H_{10}Cl_4O$	38.10	37.98
185	—NHCOCONH—	3,4-Dichloro	27.3	228.2–229.1	$C_{14}H_8Cl_4N_2O_2$	37.50	37.37
186	—NHC(=NH)NH—	3,4-Dichloro	74.0	181.1–182.0[a]	$C_{13}H_9Cl_4N_3$	40.65	40.65
187	—NHCOCH=CHCONH—	3,4-Dichloro	85.0	227–229	$C_{16}H_{10}Cl_4N_2O_2$	35.10	34.75
188	—$NHCOOCH_2CH_2OCONH$—	3,4-Dichloro	79.3	217.3–218.0	$C_{16}H_{12}Cl_4N_2O_4$	32.17	32.30
189	—$NHCONH(CH_2)_4NHCONH$—	3,4-Dichloro	100.0	197.2–198.2	$C_{18}H_{18}Cl_4N_4O_2$	30.58	30.16
190	—$NHCOC_6H_4CONH$— *o*-	3,4-Dichloro	71.8	256–257	$C_{20}H_{12}Cl_4N_2O_2$	31.24	31.10
191	—$NHCONHC_6H_4NHCONH$— *p*-	3,4-Dichloro	94.3	>360	$C_{20}H_{14}Cl_4N_4O_2$	29.18	29.13
192	—$NHCONHCH_2$—	3,4-Dichloro	90.0	194.7–195.8	$C_{14}H_{10}Cl_4N_2O$	38.95	39.11
193	—$CH_2NHCONH$—	4-Chloro	88.8	213.2–213.7	$C_{14}H_{11}Cl_3N_2O$	32.32	32.11
194	—$NHCOOC_6H_4OCONH$— *p*-	3,4-Dichloro	84.5	279–280	$C_{20}H_{12}Cl_4N_2O_4$	29.18	29.23
195	—NHSONH—	3,4-Dichloro	70.6	49.5–50.2	$C_{12}H_8Cl_4N_2OS$	38.32	38.31
196	—$NHCOOCH_2CH_2SCH_2CH_2OCONH$—	3,4-Dichloro	87.3	141.4–142.5	$C_{18}H_{16}Cl_4N_2O_4S$	28.40	28.20
197	—CONHCONHCO—	3,4-Dichloro	70.0	199.6–200.4	$C_{15}H_8Cl_4N_2O_3$	34.75	34.60
198	—NHCSNHNHCSNH—	3,4-Dichloro	89.9	169 dec.	$C_{14}H_{10}Cl_4N_4S_2$	32.18	31.95
199	—NHCONHNHCONH—	3,4-Dichloro	88.8	233–234	$C_{14}H_{10}Cl_4N_4O_2$	34.90	35.50
200	—NHCONHNH—	H	97.8	172.2–173.1	$C_{13}H_{11}Cl_2N_3O$	23.92	24.29
201	—$NHCOO(CH_2)_4OCONH$—	3,4-Dichloro	86.0	170.9–171.8	$C_{18}H_{16}Cl_4N_2O_4$	30.40	30.48
202	CCl_3CH=	3,4-Dichloro	74.9	101.3–102.1	$C_{14}H_9Cl_7N_2$	54.70	54.80
203	—NHCH=N—	3,4-Dichloro	73.0	158.3–159.1	$C_{13}H_8Cl_4N_2$	8.38[b]	8.24[b]
204	—NHCOO—	4-Chloro	88.8	149.5–150.7	$C_{13}H_8Cl_3NO_2$	33.60	33.84
205	—NHCOO—	3,4-Dichloro	91.5	148.1–149.1	$C_{13}H_7Cl_4NO_2$	40.15	40.20

[a] N. S. Tohary, S. S. Guha and P. C. Guha, *Current Sci. (India)*, **21**, 84 (1952), give m.p. 173–175°. [b] Analysis is % nitrogen. [c] The preparation of all compounds in Table IX is given under Experimental—miscellaneous section.

dium hydroxide for 4 hours. The product was filtered, washed with three 100-ml. portions of water and recrystallized from toluene to give small buff granules.

3',3",4',4"-Tetrachlorofumaranilide (187).—A solution of 32.4 g. (0.2 mole) of 3,4-dichloroaniline in 100 ml. of ether was added gradually to 7.2 g. (0.05 mole) of fumaryl chloride in 100 ml. of ether. After two hours, the heavy slurry was filtered. The crude filter cake was taken up in 300 ml. of 10% sodium hydroxide, heated to 80° for 1 hour and filtered hot. The crude product was extracted twice with 500 ml. of boiling ethanol and filtered hot. The product was a white micro-crystalline powder.

1,2-Ethylenebis-(3,4-dichlorocarbanilate) (188).—A solution of 9.4 g. (0.05 mole) of 3,4-dichlorophenyl isocyanate and 1.6 g. (0.025 mole) of ethylene glycol was heated to 90°, and held 16 hours on the steam-bath. The hard crystalline

mass which formed was pulverized and recrystallized from ethanol to give a white micro-crystalline powder.

1,1'-Tetramethylenebis-(3,4-dichlorophenylurea) (189).—Prepared following procedure A from 3,4-dichlorophenyl isocyanate and 1,4-butanediamine as a white micro-crystalline powder.

N,N'-Bis-(3,4-dichlorophenyl)-phthalamide[16] (190).—Phthaloyl chloride, 10.4 g. (0.05 mole), was added dropwise with stirring to 16.2 g. (0.1 mole), of 3,4-dichloroaniline in 75 ml. of pyridine. The temperature rose to 70° during the addition, the solution turning a brilliant red. The solution was held for 3 hours and quenched into 800 ml. of ice-water. The crude product which separated was filtered and recrystallized from acetone to give a fine white powder.

1,1'-*p*-Phenylenebis-[3-(3,4-dichlorophenyl)-urea] (191).—The compound was prepared following procedure A using 3,4-dichlorophenyl isocyanate and *p*-phenylenediamine as a white microcrystalline powder.

p-Phenylenebis-(3,4-dichlorocarbanilate) (194).—Prepared from 3,4-dichlorophenyl isocyanate and hydroquinone following procedure for compound 188; large, white flakes from ethanol.

N,N'-Sulfinylbis-(3,4-dichloroaniline) (195).—A solution of 65.0 g. (0.4 mole) of 3,4-dichloroaniline in 600 ml. of ether was stirred while adding dropwise 1.9 g. (0.1 mole) of thionyl chloride. After 1 hour, the heavy slurry was filtered and washed with 50 ml. of ether. The filtrate and wash were combined and the ether removed under vacuum. The residue was recrystallized from heptane to give fine, yellow needles. *Anal.* Calcd. for $C_{12}H_8Cl_4N_2OS$: Cl, 38.32; S, 8.64; N, 7.58. Found: Cl, 38.31; S, 8.60; N, 7.51.

2,2'-Thiodiethanolbis-(3,4-dichlorocarbanilate) (196).—Prepared from 3,4-dichlorophenyl isocyanate and thiodiethanol following the procedure for compound 188 in fine, white granules from ethanol.

1,3-Bis-(3,4-dichlorobenzoyl)-urea (197).—Prepared from 3,4-dichlorobenzoyl chloride and urea following procedure D in fine, white granules from ethanol.

1,6-Bis-(3,4-dichlorophenyl)-2,5-dithiobiurea (198).—Prepared from 3,4-dichlorophenyl isothiocyanate and 85% hydrazine hydrate following procedure A.

1,6-Bis-(3,4-dichlorophenyl)-biurea (199).—Prepared from 3,4-dichlorophenyl isocyanate and 85% hydrazine hydrate following procedure A as a white, micro-crystalline powder. The product is known to be contaminated with the symmetrical tetrachlorocarbanilide.

4-(3,4-Dichlorophenyl)-1-phenylsemicarbazide (200).—Prepared from 3,4-dichlorophenyl isocyanate and phenylhydrazine following procedure A in colorless, felted needles from ethanol.

1,4-Butanediolbis-(3,4-dichlorocarbanilate) (201).—On mixing 18.8 g. (0.1 mole) of 3,4-dichlorophenyl isocyanate and 4.5 g. (0.05 mole) of 1,4-butanediol, a vigorous reaction set in forming a hard, crystalline mass within 15 minutes. Recrystallization from acetone gave fine, colorless needles.

2,2,2-Trichloro-N,N'-bis-(3,4-dichlorophenyl)-ethylidenediamine (202).—A solution of 16.3 g. (0.1 mole) of 3,4-dichloroaniline and 7.4 g. (0.05 mole) of chloral in 50 ml. of benzene was refluxed for 3 hours. The benzene was removed under 60 mm. vacuum leaving a brown sirup which slowly crystallized on standing. The crude product was dissolved in 800 ml. of heptane, treated with 5 g. of decolorizing charcoal for 30 minutes, filtered and set aside to crystallize as fine, colorless needles.

1,3-Bis-(3,4-dichlorophenyl)-formamidine[23] (203).—A solution of 16.3 g. (0.1 mole) of 3,4-dichloroaniline and 7.4 g. (0.05 mole) of triethyl orthoformate in 250 ml. of ethanol was refluxed for 6 hours. On cooling, the product crystallized in fine, colorless needles.

4-Chlorophenyl-3,4-dichlorocarbanilate (204).—A mixture of 9.4 g. (0.05 mole) of 3,4-dichlorophenyl isocyanate and 6.5 g. (0.05 mole) of *p*-chlorophenol was heated to 90° in an Erlenmeyer flask, stoppered and held at 90° for 16 hours. On cooling, the hard crystalline mass was recrystallized from ethanol in glistening white plates.

3,4-Dichlorophenyl-3,4-dichlorocarbanilate (205).—Prepared as above from 3,4-dichlorophenyl isocyanate and 3,4-dichlorophenol as fine, white needles from ethanol.

Bacteriostatic Test Procedure.—In the preliminary bacteriostatic tests 1–100 stock solutions are prepared by dissolving 100 mg. of the test compound in 10 ml. of acetone, alcohol or other suitable solvent. The stock solutions are diluted serially by pipetting 2 ml. of the stock solution into 18 ml. of sterile nutrient agar to obtain a 1:1000 dilution, and continuing in the same manner for dilutions of 1:10,000, 1:100,000, and 1:1,000,000. The agar is poured in Petri dishes, allowed to harden, and spot inoculated with one drop of a cell suspension of *Micrococcus pyogenes* var. *aureus*, prepared by suspending the growth from a 24-hour nutrient agar slant culture in 10 ml. of distilled water. The plates are incubated at 37° for 48 hours, and examined for presence or absence of growth.

Those compounds found active in the range 1–10 p.p.m. are tested for their activity in the presence of soap. Additional stock solutions of the test compound are prepared and diluted in solutions of "neutral white high-grade toilet soap" sufficient to yield a ratio of 1:50 compound to soap dilutions; inoculation and incubation are carried out as in the preliminary screening.

Acknowledgment.—The authors are indebted to Mr. Andrew A. Bybell for the analyses and to Mr. Paul D. McDonald for the bacteriostatic screening.

(23) H. J. Backer and W. L. Wanmaker, *Rec. trav. chim.*, **67**, 257 (1948).

ST. LOUIS, MISSOURI

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Allylmagnesium Bromide as a Selective Nucleophile toward Aza-aromatic Heterocycles

BY HENRY GILMAN, JOHN EISCH AND THEODORE SODDY

RECEIVED MARCH 2, 1956

In the interaction between allylmagnesium bromide and certain aza-aromatic heterocycles, the following reactivity series was observed: pyridine < quinoline ≃ isoquinoline < phenanthridine ≃ N-benzylideneaniline ≃ acridine < quinoxaline. Proof of structure of the resulting allyl derivatives was accomplished by synthesis, degradation and infrared analysis. The mechanism of the reaction is discussed as a nucleophilic attack of the Grignard reagent on the nitrogen heterocycle. The variation in reactivity of these heterocycles can be rationalized adequately in terms of the localization energies of the dihydro derivatives. In connection with the selectivity of allylmagnesium bromide, an explanation is advanced for the different behavior of butyllithium with these nitrogen heterocycles.

The interactions of Grignard reagents with aza-aromatic heterocycles such as pyridine, quinoline and acridine have been reported periodically, but the conditions employed have been so varied that the limitations of the reaction have not been drawn.[1]

(1) For an excellent survey of previous work see M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, pp. 1251–1259.