Anal. Calcd. for $C_{10}H_{19}O_2N$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.75; H, 10.50; N, 7.70.

2-Amino-1-p-menthanols (III) *and* (VIII). Two teaspoons of Raney nickel catalyst were added to a solution of 20 g. of (VII) in 150 ml. of methanol and hydrogenation was carried out at 50 p.s.i. at 65°. Ninety-three % of the theoretical volume of hydrogen calculated for 2 moles was taken up in 70 min. The catalyst was removed by filtration and about one half of the methanol was evaporated from the filtrate at reduced pressure. Excess picric acid was added together with enough water to make the solution saturated at the boiling point. A picrate crystallized from the cooled solution as yellow needles, m.p. 88–94°, 22.6 g. [47% from (VII)]. This melting point was not improved after repeated recrystallizations from water. During vacuum drying at 64°, this picrate lost water of hydration and became an amorphous glass.

Anal. Calcd. for $C_{16}H_{24}O_8N_4$: C, 47.99; H, 6.04; N, 13.99. Found: C, 47.47; H, 5.91; N, 13.95.

The *cis* isomer of 2-amino-1-*p*-menthanol (VIII) was regenerated from the hydrated picrate (m.p. 88–94°) by treatment with dilute aqueous sodium hydroxide followed by ether extraction. Evaporation of the ether afforded colorless needles which were purified by vacuum sublimation. The sublimed material melted at 79.4–80.0°, $[\alpha]_D^{23}$ −97.72 (10% acetone solution).

Anal. Calcd. for $C_{10}H_{21}ON$: C, 70.12; H, 12.36; N, 8.18. Found: C, 69.85; H, 11.86; N, 8.26.

The filtrate from the above picrate (m.p. 88–94°) was evaporated to dryness under vacuum and the residue dissolved in water. A crystalline picrate m.p. 63–72° (10.4 g.) [21.7% from (VII)] separated slowly from the cooled solution. Several recrystallizations from water afforded pale yellow needles, m.p. 71–74°. After drying under vacuum at 85°, these crystals lost water of hydration and recrystallized to give the picrate of III, m.p. 130–132°. A mixture of this picrate with the picrate (m.p. 130–132°) prepared from (II) showed no melting point depression.

LAKE ALFRED, FLA.

[CONTRIBUTION FROM THE ORGANIC CHEMICALS DIVISION, ST. LOUIS RESEARCH DEPARTMENT, MONSANTO CHEMICAL COMPANY]

The Preparation and Bacteriostatic Activity of Substituted *m*-Nitrocarbanilides

D. J. BEAVER, D. P. ROMAN, AND P. J. STOFFEL

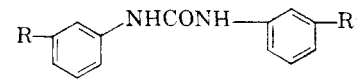
Received May 20, 1959

The preparation and *in vitro* bacteriostatic activity of some substituted *m*-nitrocarbanilides against *Staphylococcus aureus* are described. A discussion of specific activity as related to chemical structure is included.

The present paper is a continuation of work described previously[1,2] interrelating chemical structure with bacteriostatic activity. The remarkable specificity encountered in the tri- and tetra-chlorocarbanilides[3] has now been duplicated in the substituted nitrocarbanilides. In both cases, antimicrobial activity was enhanced or completely lost with slight modifications in chemical structure. The more effective nitrocarbanilides completely inhibited the growth of *Staphylococcus aureus* (SA) in dilutions of one to ten million.

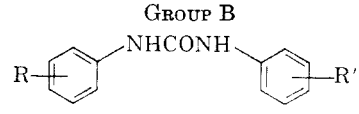
In the course of screening the carbanilides reported in this paper it was soon apparent that the substituted nitrocarbanilides were as specific in their structural requirements to obtain bacteriostatic activity as was found previously for the trichlorocarbanilides.[3] The 3-nitrocarbanilides were found to be inactive unless substituted with a halogen in the 3 position of the second phenyl ring when the maximum activity at a dilution of one part to ten million parts was obtained. The presence of either the nitro or the halogen in positions other than the 3 position completely inactivated the compounds. These data are shown in groups A and B. (The compounds are numbered consecutively for ready cross reference to Table I where their physical properties are listed)

GROUP A



No.	R	R'	SA[4]
4	Chloro	Chloro	0
8	Nitro	Nitro	0
6	Nitro	Chloro	10 Million

GROUP B



No.	R	R'	SA
24	2-Nitro	2-Nitro	0
5	2-Nitro	4-Chloro	0
23	3-Nitro	2-Nitro	0
35	3-Nitro	2-Methyl-5-nitro	0
7	3-Nitro	4-Chloro	0
34	4-Nitro	4-Nitro	0
1	4-Nitro	3-4-Dichloro	0
2	2-Nitro	3,4-Dichloro	0

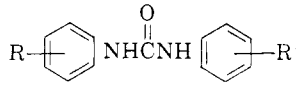
(1) D. J. Beaver and P. J. Stoffel, *J. Am. Chem. Soc.*, **74**, 3410 (1952).

(2) D. J. Beaver, R. S. Shumard, and P. J. Stoffel, *J. Am. Chem. Soc.*, **75**, 5579 (1953).

(3) D. J. Beaver, D. P. Roman, and P. J. Stoffel, *J. Am. Chem. Soc.*, **79**, 1236 (1957).

(4) In groups A–F, the figures under "SA" refer to the maximum dilution which will completely inhibit the growth *in vitro* of the organism *Staphylococcus aureus*. The bacteriostatic test procedure is described in ref. (3).

TABLE I



No.	R	R′	Yield %	M.P. °C	Empirical Formula	Molecular Weight	Nitrogen Analysis % Chlorine* Calcd.	Found
1	4-Nitro	3,4-Dichloro	95.3	294–295	$C_{13}H_9Cl_2N_3O_3$	326.2	12.88	13.23
2	2-Nitro	3,4-Dichloro	87.0	229.7–230.3	$C_{13}H_9Cl_2N_3O_3$	326.2	21.75*	21.73*
3	3-Nitro	3,4-Dichloro	99.5	241.8–242.7	$C_{13}H_9Cl_2N_3O_3$	326.2	21.75*	21.76*
4	3-Chloro	3-Chloro	93.0	252–253[a]	$C_{13}H_{10}Cl_2N_2O$	281.2	25.20*	25.00*
5	2-Nitro	4-Chloro	89.7	208.7–209.2[b]	$C_{13}H_{10}ClN_3O_3$	291.7	12.18*	12.20*
6	3-Nitro	3-Chloro	88.0	187.5–188.1[c]	$C_{13}H_{10}ClN_3O_3$	291.7	12.18*	12.11*
7	3-Nitro	4-Chloro	79.5	223.2–224.0[d]	$C_{13}H_{10}ClN_3O_3$	291.7	12.18*	12.37*
8	3-Nitro	3-Nitro	93.4	249.5–250.2[e]	$C_{13}H_{10}N_4O_5$	302.2		
9	3-Nitro	3-Methyl	96.4	193.1–193.7[f]	$C_{14}H_{13}N_3O_3$	271.2		
10	3-Nitro	Hydrogen	94.7	199.3–200.2[g]	$C_{13}H_{11}N_3O_3$	257.1		
11	3-Nitro	3-Carboxy	91.3	263 decomp.	$C_{14}H_{11}N_3O_5$	301.2	13.94	14.40
12	3-Nitro	3-Chloro-2-methyl	94.7	222.7–223.4	$C_{14}H_{12}ClN_3O_3$	305.7	11.62*	11.56*
13	3-Nitro	2,5-Dichloro	94.0	252.3–252.8	$C_{13}H_9Cl_2N_3O_3$	326.2	21.75*	21.69*
14	3-Nitro	3-Chloro-4-methyl	89.0	218.9–219.5	$C_{14}H_{12}ClN_3O_3$	305.7	11.62*	11.81*
15	3-Nitro	3-Aceto	88.7	214 decomp.	$C_{15}H_{13}N_3O_4$	299.2	14.08	13.85
16	3-Nitro	3-Ethoxy	84.0	154.7–155.3	$C_{15}H_{16}N_3O_4$	301.2	13.94	14.08
17	3-Nitro	3-Acetamino	72.7	181 decomp.	$C_{15}H_{14}N_4O_4$	314.2	17.83	17.99
18	3-Nitro	4-Ethoxy	77.2	194.5–195.0	$C_{15}H_{15}N_3O_4$	301.2		
19	3-Nitro	4-Methyl	95.5	211.5–212.1[h]	$C_{14}H_{13}N_3O_3$	271.2		
20	3-Nitro	4-Acetamino	99.8	325 decomp.	$C_{15}H_{14}N_4O_4$	314.2	17.83	17.69
21	3-Nitro	4-Carboxy	99.0	267 decomp.	$C_{14}H_{11}N_3O_5$	301.4	13.95	13.64
22	3-Nitro	2-Methoxy	85.5	186.4–187.3[i]	$C_{14}H_{13}N_3O_4$	288.1		
23	3-Nitro	2-Nitro	84.7	246.7–247.2[j]	$C_{13}H_{10}N_4O_5$	302.2		
24	2-Nitro	2-Nitro		224.7–225.2[k]	$C_{13}H_{10}N_4O_5$	302.2		
25	3-Nitro	5-Chloro-2-methyl	98.8	251.4–252.0	$C_{14}H_{12}ClN_3O_3$	305.7	11.62*	11.75*
26	3-Nitro	2-Methoxy-5-nitro	97.7	280–281	$C_{14}H_{12}N_4O_6$	332.1	16.88	17.02
27	3-Nitro	3-Ethyloxycarbonyl	82.5	170.9–171.5	$C_{16}H_{15}N_3O_5$	329.3	12.75	13.06
28	3-Nitro	3-Dimethylamino		187.7–188.4	$C_{15}H_{16}N_4O_3$	300.3	18.50	18.36
29	3-Nitro	5-Chloro-2-methoxy	94.3	215.4–216.1	$C_{14}H_{12}ClN_3O_4$	321.7	11.03*	11.12*
30	3-Nitro	2,5-Dichloro	97.7	246.5–247.3	$C_{13}H_9Cl_2N_3O_3$	326.2	21.75*	21.70*
31	3-Nitro	3-Bromo	96.0	211.9–212.6	$C_{13}H_{10}BrN_3O_3$	336.2	12.49	12.70
32	3-Nitro	4-Hydroxy-2-methyl	82.0	205.5–206.1	$C_{14}H_{13}N_3O_4$	288.1	14.63	14.40
33	3-Chloro	2-Methyl-5-nitro	92.0	252.8–253.6	$C_{14}H_{12}ClN_3O_3$	305.7	11.62*	11.88*
34	4-Nitro	4-Nitro	89.4	318–319[l]	$C_{13}H_{10}N_4O_5$	302.2		
35	3-Nitro	2-Methyl-5-nitro	98.5	271–272	$C_{14}H_{12}N_4O_5$	316.3	17.74	17.84
36	3-Nitro	2-Methyl-4-nitro	74.7	235.7–236.3	$C_{14}H_{12}N_4O_5$	316.3	17.74	17.59
37	3,4-Dichloro	2-Methyl-5-nitro	89.5	273–274	$C_{14}H_{11}Cl_2N_3O_3$	340.3	20.85*	21.09*
38	3-Nitro[m]	3-Chloro	93.3	79.9–80.7	$C_{15}H_{14}ClN_3O_3$	319.5	11.11*	11.17*
39	3-Nitro[n]	3-Chloro	76.1	113.7–114.2	$C_{14}H_{10}ClN_3O_4$	319.5	11.11*	11.42*
40	3-Nitro[p]	3-Chloro	92.3	147.7–148.5	$C_{13}H_{10}ClN_3O_2S$	307.7	11.60*	11.66*
41	3-Nitro[p]	3,4-Dichloro	55.0	162–163	$C_{13}H_9Cl_2N_3O_2S$	342.1	20.6*	20.0

[a] H. Vittenet, *Bull. soc. chim. France*, [3] **21**, 151 (1899), gives m.p. 245°. [b] C. H. Kao, H. Y. Fang, and P. P. T. Sah, *J. Chinese Chem. Soc.*, **3**, 137 (1935), gives m.p. 206°. [c] P. P. T. Sah, *J. Chinese Chem. Soc.*, **4**, 513 (1936), gives m.p. 248°. [d] K. C. Meng and P. P. T. Sah, *J. Chinese Chem. Soc.*, **4**, 75 (1936), gives m.p. 212°. [e] Reference [a] gives m.p. 242°. [f] Ref. [d] gives m.p. 192°. [g] A. W. Hofmann, *Ann.*, **67**, 156, (1848) gives m.p. 195°. [h] Reference [d] gives m.p. 202°. [i] K. J. Karrman, *Svensk. Kem. Tid.*, **60**, 61 (1948), gives m.p. 207.° [j] C. Naegeli, A. Tyabji, and L. Conrad, *Helv. Chem. Acta*, **21**, 1127 (1938) gives m.p. 228°. [k] Ref. [a] gives m.p. 225°. [l] Ref. [a] gives m.p. 312°. [m] *N*-Ethyl derivative. [n] *N*-Formyl derivative. [p] These compounds are *thio*carbanilides.

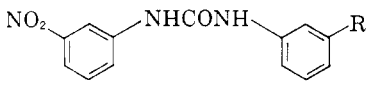
Group C illustrates the striking activity of the carbanilides having a nitro group in the 3 position of one phenyl ring and a halogen in the 3 position of the other phenyl ring.

These results confirm the data obtained previously in a homologous series in which the 3 chloro substituent is held constant while replacing the 3 prime nitro group.[3]

In group D are shown the results obtained by additional substitution in the 4 position of the phenyl ring containing the 3′ halogen. In general, the additional group had no effect on the activity of the compounds. As was found previously with the polychloro carbanilides,[3] the *thio* compounds were not as active as their oxygen analogues. In group E are tabulated the results obtained by additional substitution in either the 2 or 6 position of either phenyl ring of the 3-nitro-3′ halocarbanilide. In every case the biological activity of the compounds was lost.

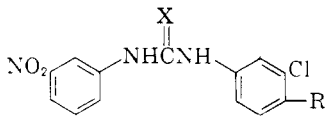
In Group F the data show that when 3-nitrocarbanilide is substituted in the 2 or 4 position of

GROUP C



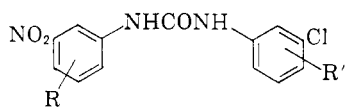
No.	R	SA
6	Chloro	10 Million
31	Bromo	10 Million
10	Hydrogen	0
8	Nitro	0
9	Methyl	0
11	Carboxy	0
27	Ethyloxycarbonyl	0
16	Ethoxy	0
15	Aceto	0
17	Acetamino	0
28	Dimethyl amino	0

GROUP D



No.	R	X	SA
6	Hydrogen	O	10 Million
40	Hydrogen	S	1 Million
3	Chloro	O	10 Million
41	Chloro	S	1 Million
14	Methyl	O	10 Million
38	Hydrogen (*N*-ethyl)	O	1 Million
39	Hydrogen (*N*-formyl)	O	1 Million

GROUP E

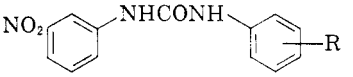


No.	R	R′	SA
6	Hydrogen	Hydrogen	10 Million
12	Hydrogen	2-Methyl	0
25	Hydrogen	6-Methyl	0
29	Hydrogen	2-Methoxy	0
30	Hydrogen	6-Chloro	0
33	6-Methyl	Hydrogen	0
37	6-Methyl	4-Chloro	0

the second phenyl ring, activity was lost completely.

The *in vivo* bacteriostatic activity of the nitro carbanilides given in Groups A–F show that the most active compounds have a 3-nitro group in one ring of the parent carbanilide and a 3′-halogen in the other ring. The presence of either the nitro group or the halogen in the 2 or 4 positions of either ring completely inactivated the compounds. The activity of the *thio*carbanilides parallels the structural requirements of their oxygen analogues.

GROUP F



No.	R	SA
23	2-Nitro	0
22	2-Methoxy	0
10	Hydrogen	0
36	2-Methyl-4-nitro	0
35	2-Methyl 5 nitro	0
26	2-Methoxy-5-nitro	0
13	2,5-Dichloro	0
7	4-Chloro	0
19	4-Methyl	0
18	4-Ethoxy	0
20	4-Acetamino	0
21	4-Carboxy	0
32	4-Hydroxy-2-methyl	0

EXPERIMENTAL

The compounds were prepared following Procedure A. The isocyanates and amines were commercially available or prepared in this laboratory[3] and used without further purification. The appropriate isocyanate and amine were reacted in ether or acetone under anhydrous conditions to prevent formation of the symmetrical carbanilides.

Procedure A.[3] *3-Chloro-3′-nitrocarbanilide* (6). A solution of 16.4 g. (0.1 mole) of *m*-nitrophenylisocyanate in 50 ml. of acetone was added dropwise with stirring to 12.8 g. (0.1 mole) of *m*-chloroaniline in 50 ml. of acetone. The product separated during the addition period. The slurry was held for 2 hr., filtered, and washed with 20 ml. of ether. Recrystallization from ethanol gave small white granules.

Conversely the product was prepared from 15.4 g. (0.1 mole) of *m*-chlorophenylisocyanate and 13.8 g. (0.1 mole) of *m*-nitro aniline.

Acknowledgment. The authors are indebted to Mr. John O'Sullivan and Mr. Ottmar Kring for the analyses and Mr. Paul D. McDonald for the bacteriostatic screening.

ST. LOUIS, MO.