γ(A,A)] (Fig. 12). The subsequent slow alkaline hydrolysis of β(B) could be assigned to the solvolysis of the carbamate at position 10 to give γ(B,B) which could be deduced to be VI, where the resultant spectrophotometric pK_a of *ca.* 7 can still be assigned to the phenolic hydroxyl.

Although the λ_{max}^{NaOH} is shifted from 360 mμ (a = 67) for β(B) (V) to 233 mμ (a = 52) for γ(B,B) (VI) the shapes of the absorption curves and the absorptivities are similar.

The extremely fast hydrolysis of γ(B,B) (VI) to δ(B,B,A) (IV) on acidification of the solution can be assigned on the basis of these postulated structures to the solvolysis of the aziridine ring to give IV (with a spectrophotometric pK_a *ca.* 5 as expected) plus other rearranged products. The actual δ(B,B,A) appears to be a mixture of products.

Further alkaline solvolysis of γ(B,B) to δ(B,B,B) kinetically demonstrates a new pK_a value of *ca.* 11 absent in β(B) and which could be assigned to an uncharged acid. The acid and basic forms due to this pK_a did not significantly affect the chromophore of γ(B,B). This leads to the preference of structure VI for γ(B,B) rather than a hydroxymethyl at the 9-position. δ(B,B,B) also reacted quickly on mild acidification to indicate further that the aziridine group is not readily attacked by alkali. The further alkaline hydrolysis of γ(B,B) so diminished the chromophoric absorptivities that more drastic structural changes should be postulated although VII is a reasonably major product.

Except for γ(B,B) which has been explained on other grounds, the kinetically observed pK_a *ca.* 11–13 of a weak uncharged acid was demonstrated only when these structure assignments were consistent with the presence of the secondary ethanolamine function[14] assigned to positions 1 and 2 as in β(A), γ(A,A), and γ(B,A). It is probable that this group has weak acid character.

Structure and Biological Activity.—The fascinating change of biological activity with the physicochemical transformations of porfiromycin permit definitive assignment of action. Porfiromycin (I) had both Gram-positive and Gram-negative activity. In all cases when the postulated fused ring aziridine[14] may be considered intact as in porfiromycin (I), β(B) (*i.e.*, V), or γ(B,B) (*i.e.*, VI), antibacterial activity was retained. Modification of other portions of the molecule as in V and VI by alkali only modified the kind and degree of biological activity. For example, the replacement of the 7-amino by a hydroxyl group reduced the Gram-positive activity, whereas Gram-negative activity was retained in both β(B) and γ(B,B). The loss of all activities can be considered concomitant with the loss of the aziridine ring on acid solvolysis.

Acknowledgments—The author is greatly indebted to Mrs. Lillian G. Snyder and Mr. Dennis J. Weber for excellent technical assistance, to Dr. G. B. Whitfield and associates for microbiological assays, and to Dr. W. Schroeder and Mr. C. DeBoer for their discussion and interest.

The Preparation and Bacteriostatic Activity of Halogenated Carbanilates

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The preparation and *in vitro* bacteriostatic activity of some halogenated carbanilates against *Staphylococcus aureus* is described. The relationship of chemical structure to specific activity is discussed.

The relationship of bacteriostatic activity to the chemical structure of two series of substituted carbanilides[1] has been reported previously. The effect of substitution on the phenyl rings of the carbanilides was fairly well established and further investigation was directed toward replacing the urea bridge with isoteric and non similar bridges. This paper reports the series of highly active halogenated carbanilates, several of which are active in dilutions of 1–10 million. The physical data for 107 carbanilates are given in Tables I to III which are numbered consecutively for easy cross reference with their bacteriostatic activities. Throughout this paper, the figures given under activity refer to the maximum dilution which will completely inhibit the growth *in vitro* of the test organism *Staphylococcus aureus*. The bacteriostatic test procedure is given in the Experimental part.

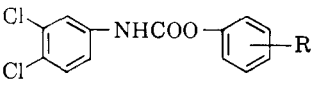
As reported previously, maximum activity in the halogenated carbanilides was obtained when chlorine was introduced into the 3- and 4-positions of one phenyl ring and the 3- and/or 4-positions of the second ring (1) but substitution of any *ortho* position reduced drastically or completely suppressed activity. Since the phenyl esters of carbanilic acid may be viewed as being formed by replacing the urea bridge, –NHCONH–, with the carbamate bridge, NHCOO–, the compounds given in Table I show, in most cases, the same specificity as was found in the urea series. The maximum activity was obtained when chlorine was introduced into the 3- and 4-positions of the carbanilic phenyl ring and the 3- and 4-positions of the phenyl ester ring (**91**). However, unlike the carbanilides, activity was lost or lowered when the phenyl ester ring was only monosubstituted in the 3- or 4-positions (**89–90**).

At this point the 3,4-dichlorophenyl moiety was retained as an essential element for activity and a series of aliphatic esters was prepared.

Activity appears to improve gradually as the carbon chain increases in length, reaching a maximum and plateauing at C_4 to C_8, but dropping in effectiveness

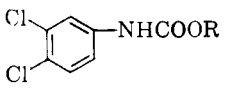
(1) D. J. Beaver, D. P. Roman, and P. J. Stoffel, *J. Am. Chem. Soc.*, **79**, 1236 (1957); *J. Org. Chem.*, **24**, 1676 (1959).

TABLE I



No.	R	Activity
91	3,4-Cl_2	10^7
89	3-Cl	10^6
90	4-Cl	+
88	2-Cl	+
92	4-Cl-3-CH_3	+
93	4-Cl-3,5-$(CH_3)_2$	+
94	2,4,5-Cl_3	10^5

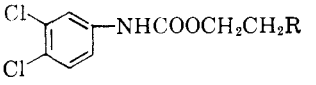
TABLE II



No.	R	Activity
1	Methyl	10^4
2	Ethyl	10^4
3	Propyl	10^5
4	Isopropyl	10^5
5	Butyl	10^6
6	Isobutyl	10^6
7	*sec*-Butyl	10^6
8	*t*-Butyl	10^6
9	2-Pentyl	10^7
10	3-Pentyl	10^7
11	Hexyl	10^7
12	Octyl	10^6
13	Decyl	10^5
14	Dodecyl	10^5

above C_8 (**4**–**12**). Branching *vs.* unbranched chain as indicated by propyl (**3**, **4**), butyl (**5**–**8**), amyl (**9**, **10**), has little or no effect on activity.

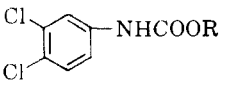
TABLE III



No.	R	Activity
2	H	10^4
3	CH_3	10^5
15	Cl	10^4
16	Br	10^6
41	CN	10^4
42	SCN	10^6
43	N-CHO	10^5
44	CF_3	10^6
45	OCH_3	10^5
46	OC_4H_9	10^5
47	$OCH_2CH_2OCH_3$	10^6
48	$OCH_2(CH_2OCH_2)_3CH_2OH$	10^6
49	$OCH_2(CH_2OCH_2)_6OC_{13}H_{27}$	+
50	SH	10^5
51	SCH_2CH_3	10^5
52	$SCH(CH_3)_2$	+
53	SC_6H_5	+
54	$SCH{=}CH_2$	10^4
55	$N(C_2H_5)_2$	10^6

In Table III, ethyl 3,4-dichlorocarbanilate (**2**) was chosen as a standard, and all other compounds in this table are viewed as β-substituted ethyl esters. While increases in activity are noted for some substituents, the data are not sufficient to afford a direction for additional synthesis. It is interesting to note, as pointed out in Table II, that whereas compounds containing long alkyl chains (C_{10} or longer) are inactive, a similarly long chain (**48**) made up of recurring ethoxy groups is active. If the chain is broken with oxygen at two-carbon intervals, it appears to act as a short active alkyl chain. Activity is once again lost, however, by terminating several ethoxy groups with a long unbroken alkyl chain (**49**).

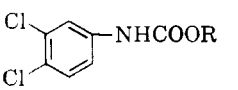
TABLE IV



No.	R	Activity
27	Allyl	10^5
28	2-Methylallyl	10^6
29	2-Propynyl	10^7
30	3-Butynyl	10^7
31	1,1-Dimethyl-2-propynyl	10^7
32	1-Ethyl-1-methyl-2-propynyl	10^6
33	1-Methyl-1-hexylpropynyl	10^6
34	1-Methyl-1-isopentylpropynyl	10^7

The unsaturated alkyl esters are listed in Table IV. Activity is improved 10- to 100-fold, carbon for carbon, as compared to the saturated esters shown in Table II, except for allyl, which is equivalent to propyl and isopropyl (**3**, **4**).

TABLE V

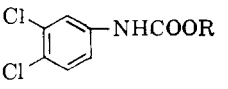


No.	R	Activity
15	2-Chloroethyl	10^4
16	2-Bromoethyl	10^5
18	2-(1-Chloropropyl)	10^6
17	3-Chloropropyl	10^6
19	3-Bromopropyl	10^5
20	2-(1,3-Dichloropropyl)	10^7
21	1-(2,3-Dichloropropyl)	10^6
22	4-Chlorobutyl	10^7
23	1-(2-Chloroallyl)	10^5
25	1-(3,3-Dichloroallyl)	10^5
24	1-(2,3-Dichloroallyl)	10^5
26	1-(4-Chloro-2-butynyl)	10^5

Table V lists halogenated esters, both saturated and unsaturated. A comparison of Table V with Tables II and III indicates that chlorination of the alkyl series tends to improve activity slightly whereas chlorination of the alkene series reduces activity slightly. The data seem only to point out the not too uncommon phenomena of two factors such as chlorination and unsaturation individually increasing activity but not necessarily cumulative when combined.

Table VI lists a series of cycloalkyl esters which were prepared. Activity of the 5-, 6-, and 7-membered rings

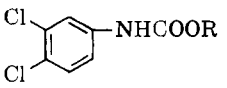
TABLE VI



No.	R	Activity
35	Cyclopentyl	10^6
36	Cyclohexyl	10^6
37	Cycloheptyl	10^6
38	Tetrahydrofurfuryl	+
40	1-Ethynylcyclohexyl	10^5
39	2-Cyclopentenyl	10^6

is equivalent to the unbranched chain alkyl counterparts. Heterocyclic rings or introducing unsaturation into the ring do not improve activity. Further synthesis was directed toward open chain esters as more promising leads.

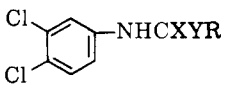
TABLE VII



No.	R	Activity
56	2-Nitrobutyl	10^7
57	2-Nitro-2-methylpropyl	10^6
58	3-(2-Methyl-2-nitrohexyl)	10^6
59	4-(3-Nitroheptyl)	10^6

Alkyl esters containing nitro groups in the chain as shown in Table VII were all active in the range of 1–10 million. Approximately 20 nitroalkyl esters were prepared in which the 3,4-dichloro moiety was replaced by other groups (not listed in this paper) and, in agreement with earlier work showing the essential character of the 3,4-dichloro moiety, all were inactive.

TABLE VIII

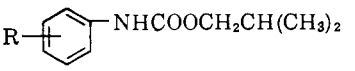


No.	R (X = O Y = S)	Activity
60	Methyl	+
61	Ethyl	10^5
62	Propyl	10^7
63	Isopropyl	10^7
64	Butyl	10^7
65	Isobutyl	10^6
66	*t*-Butyl	10^6
67	Pentyl	10^6
68	Octyl	10^6
69	Dodecyl	10^5
	R (X = S Y = O)	
70	Methyl	+
71	Ethyl	+
72	Propyl	10^6
73	Isobutyl	10^7
74	*sec*-Butyl	10^6
	R (X = S Y = S)	
75	Methyl	10^6
76	Ethyl	10^5
77	Propyl	10^6
78	Isopropyl	10^6
79	Butyl	10^6
80	Pentyl	10^5
81	Isopentyl	10^5
82	Dodecyl	+

Table VIII lists the sulfur containing esters comparing the thiol, thiono, and dithio analogs. The thiol (**60–69**) series generally are more active than their oxygen counterparts. The thiono (**70–74**) derivatives are more or less equivalent to the oxygen series. The dithio (**75–82**) derivatives are similarly equivalent but activity appears to drop off more rapidly, gradually losing effectiveness at C_5 as compared to C_8 in the oxygen series.

In previous publications[1] on carbanilides, emphasis was placed on the usual specificity of the active compounds. With carbanilides outstanding activity was obtained in only two configurations—when one phenyl ring was substituted with a 3,4-dichloro or 3-nitro group. On the other hand, the carbanilates show greater specificity in that only the 3,4-dichloro moiety imparts activity. Table IX clearly illustrates the loss in activity when the 3,4-dichloro group is replaced.

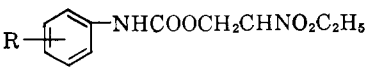
TABLE IX



No.	R	Activity
6	3,4-Dichloro	10^6
95	H	10^3
96	2-Chloro	10^3
97	3-Chloro	10^5
98	4-Chloro	+
99	2,5-Dichloro	+
100	2-Methyl	+
101	3-Methyl	+
102	4-Methyl	+
103	2-Methoxy	+
104	4-Methoxy	+
105	2-Nitro	+
106	3-Nitro	+
107	4-Nitro	10^4

The same specificity is found with the very active 2-nitrobutyl ester (**56**), Table IXA, as well as all other ester groups examined.

TABLE IXA



No.	R	Activity
56	3,4-Dichloro	10^7
83	2-Chloro	10^4
84	3-Chloro	10^5
85	4-Chloro	10^5
86	2-Nitro	10^4
87	4-Nitro	10^4

In summary, approximately 49 carbanilates have been found which are active *in vitro* against *Staphylococcus aureus* in dilutions of 1–10 million or greater. It has been shown that the ester portion of the compound can be changed considerably while retaining activity but any change in the 3,4-dichlorocarbanilic phenyl ring causes considerable to complete loss of activity.

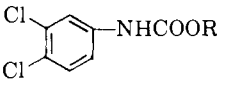
Experimental

Bacteriostatic Test Procedure.—The standard procedure used in screening the compounds against *Staphylococcus aureus* was as follows. Stock solutions are prepared by dissolving 100 mg. of the test compound in 10 ml. of acetone, alcohol, or other solvent. The stock solutions are diluted serially by pipetting 2 ml. of the stock solutions into 18 ml. of sterile nutrient agar to obtain a $1:10^3$ dilution and continuing in the same manner for dilutions up to $1:10^7$. The agar is poured into Petri dishes, allowed to harden, and spot inoculated with one drop of a cell suspension of *Straphylococcus aureus* which was prepared by suspending the growth from a 24 hr. nutrient agar slant culture in 10 ml. of distilled water. The plates are incubated at 37° for 48 hr. and examined for the presence or absence of growth. The results reported in the Tables are the minimum concentration of the test compound which will completely inhibit the growth of the bacteria. A "+" indicates that the compound is inactive at a dilution of $1:10^3$.

Chemical Procedures.[2]—The compounds described in Tables

(2) Melting points were taken in capillary tubes using calibrated thermometers and are corrected.

TABLE X



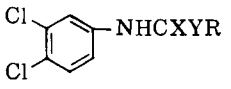
No.	R	Procedure	Yield, %	M.p. °C.	Empirical formula	Analyses, % chlorine Calcd.	Found
1	Methyl	A	94	111–112[a]	$C_8H_7Cl_2NO_2$	32.3	32.4
2	Ethyl	A	97	73–74	$C_9H_9Cl_2NO_2$	30.3	30.2
3	Propyl	A	85	73–74	$C_{10}H_{11}Cl_2NO_2$	28.6	28.5
4	Isopropyl	A	94	105–106	$C_{10}H_{11}Cl_2NO_2$	28.6	28.5
5	Butyl	A	97	76–77	$C_{11}H_{13}Cl_2NO_2$	27.0	27.6
6	Isobutyl	A	90	95–96	$C_{11}H_{13}Cl_2NO_2$	27.0	27.0
7	*sec*-Butyl	A	79	73–74	$C_{11}H_{13}Cl_2NO_2$	27.0	27.1
8	*t*-Butyl	A	96	114–115	$C_{11}H_{13}Cl_2NO_2$	27.0	27.0
9	2-Pentyl	A	99	Sirup	$C_{12}H_{15}Cl_2NO_2$	25.7	26.0
10	3-Pentyl	A	93	54–55	$C_{12}H_{15}Cl_2NO_2$	25.7	26.0
11	Hexyl	A	99	Sirup	$C_{13}H_{17}Cl_2NO_2$	24.4	24.5
12	Octyl	A	90	33–34	$C_{15}H_{21}Cl_2NO_2$	22.3	22.3
13	Decyl	A	85	Sirup	$C_{17}H_{25}Cl_2NO_2$	20.5	20.6
14	Dodecyl	A	73	47–48	$C_{19}H_{29}Cl_2NO_2$	18.9	19.0
15	2-Chloroethyl	B	97	100–101	$C_9H_8Cl_3NO_2$	39.6	39.6
16	2-Bromoethyl	A	94	105–106	$C_9H_8BrCl_2NO_2$	N, 4.4	N, 4.4
17	3-Chloropropyl	A	76	84–85	$C_{10}C_{10}Cl_3NO_2$	37.7	37.7
18	2(1-Chloropropyl)	B	83	71–72	$C_{10}H_{10}Cl_3NO_2$	37.7	37.6
19	3-Bromopropyl	B	88	75–76	$C_{10}H_{10}BrCl_2NO_2$	N, 4.2	N, 4.5
20	2(1,3-Dichloropropyl)	B	85	71–72	$C_{10}H_9Cl_4NO_2$	44.7	44.7
21	2,3-Dichloropropyl	B	53	82–83	$C_{10}H_9Cl_4NO_2$	44.7	44.5
22	4-Chlorobutyl	A	83	85–86	$C_{11}H_{12}Cl_3NO_2$	35.8	35.9
23	2-Chloroallyl	B	27	64–65	$C_{10}H_8Cl_3NO_2$	38.0	38.1
24	2,3-Dichloroallyl	A	66	53–54	$C_{10}H_7Cl_4NO_2$	45.0	45.0
25	3,3-Dichloroallyl	A	88	51–52	$C_{10}H_7Cl_4NO_2$	45.0	44.9
26	4-Chloro-2-butynyl	A	91	114–115	$C_{11}H_8Cl_3NO_2$	36.4	36.2
27	Allyl	A	93	57–58	$C_{10}H_9Cl_2NO_2$	28.8	29.1
28	Methallyl	A	72	50–51	$C_{11}H_{11}Cl_2NO_2$	27.2	27.2
29	Propynyl	B	84	79–80	$C_{10}H_7Cl_2NO_2$	29.0	29.1
30	3-Butynyl	A	88	74–75	$C_{11}H_9Cl_2NO_2$	27.5	27.6
31	1,1-Dimethyl-2-propynyl	B	91	111–112	$C_{12}H_{11}Cl_2NO_2$	26.0	26.0
32	1-Ethyl-1-methyl-2-propynyl	B	98	87–88	$C_{13}H_{13}Cl_2NO_2$	24.8	24.7
33	1-Methyl-1-hexyl-2-propynyl	B	82	60–61	$C_{17}H_{21}Cl_2NO_2$	20.7	21.0
34	1-Methyl-1-isopentyl-2-propynyl	B	67	98–99	$C_{16}H_{19}Cl_2NO_2$	21.5	21.6
35	Cyclopentyl	B	99	103–104	$C_{12}H_{13}Cl_2NO_2$	25.8	26.0
36	Cyclohexyl	A	98	118–119	$C_{13}H_{15}Cl_2NO_2$	24.6	24.7
37	Cycloheptyl	A	77	105–106	$C_{14}H_{17}Cl_2NO_2$	23.4	23.3
38	Tetrahydrofurfuryl	A	93	98–99	$C_{12}H_{13}Cl_2NO_3$	24.4	24.2
39	2-Cyclopentenyl	A	91	90–91	$C_{12}H_{11}Cl_2NO_2$	26.0	26.1
40	1-Ethynylcyclohexyl	A	98	118–119	$C_{15}H_{15}Cl_2NO_2$	22.6	22.7
41	2-Cyanoethyl	A	87	116–117	$C_{10}H_8Cl_2N_2O_2$	27.3	27.4
42	2-Thiocyanaoethyl	C	51	86–87	$C_{10}H_8Cl_2N_2O_2S$	24.4	24.5
43	2-Formamidoethyl	A	92	110–111	$C_{10}H_{10}Cl_2N_2O_3$	25.6	25.6
44	2,2,2-Trifluoroethyl	B	82	95–96	$C_9H_6F_3Cl_2NO_2$	24.6	24.7
45	2-Methoxyethyl	A	86	56–57	$C_{10}H_{11}Cl_2NO_3$	26.8	27.0
46	2-Butoxyethyl	A	99	Sirup	$C_{13}H_{17}Cl_2NO_3$	23.1	22.9
47	2-Methoxyethoxyethyl	A	92	63–64	$C_{12}H_{15}Cl_2NO_4$	23.0	23.4
48	$-CH_2(CH_2OCH_2)_3CH_2OH$	A	76	Sirup	$C_{15}H_{21}Cl_2NO_6$	18.6	18.7
49	$-CH_2(CH_2OCH_2)_4CH_2OC_{13}H_{27}$	A	99	Sirup	$C_{30}H_{51}Cl_2NO_7$	—	—
50	2-Mercaptoethyl	A	82	113–114	$C_9H_9Cl_2NO_2S$	26.6	26.7
51	2-Ethylmercaptoethyl	A	92	Sirup	$C_{11}H_{13}Cl_2NO_2S$	24.1	24.2
52	2-*t*-Butylmercaptoethyl	A	90	98–99	$C_{13}H_{17}Cl_2NO_2S$	22.0	22.3
53	2-Phenylmercaptoethyl	A	97	85–86	$C_{15}H_{13}Cl_2NO_2S$	20.7	20.7
54	2-Vinylmercaptoethyl	A	97	Sirup	$C_{11}H_{11}Cl_2NO_2S$	24.2	23.9
55	2-Diethylaminoethyl	A	99	Sirup	$C_{13}H_{18}Cl_2N_2O_2$	23.2	23.2
56	2-Nitrobutyl	A	88	121–122	$C_{11}H_{12}Cl_2N_2O_4$	23.0	23.1
57	2-Methyl-2-nitropropyl	A	98	114–115	$C_{11}H_{12}Cl_2N_2O_4$	23.0	22.9
58	4-(3-Nitroheptyl)	A	80	115–116	$C_{14}H_{18}Cl_2N_2O_4$	20.3	20.4
59	3-(2-Methyl-2-nitrohexyl)	A	99	98–99	$C_{14}H_{18}Cl_2N_2O_4$	20.3	20.2

[a] W. Siefken, *Ann.*, **562**, 75 (1946), gives m.p. 111–112°.

X–XII were prepared following one of the procedures A to F as noted. 3,4-Dichlorophenyl iso- and isothiocyanates were prepared as described previously.[1] Other isocyanates, alcohols and mercaptans were commercially available and used without further purification. Solvents, alcohols, and mercaptans were dried to prevent reaction of the isocyanates and water to form symmetrical carbanilides.

A. Methyl 3,4-Dichloro Carbanilate (1).—A solution was readily obtained on adding 18.8 g. (0.1 mole) of 3,4-dichlorophenyl isocyanate to 32.0 g. (1.0 mole) of anhydrous methanol.

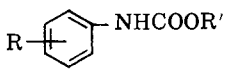
TABLE XI



No.	R	X	Y	Procedure	Yield, %	M.p., °C.	Empirical formula	Analyses, % chlorine Calcd.	Found
60	Methyl	O	S	D	75	137–138	$C_8H_7Cl_2NOS$	30.0	30.1
61	Ethyl	O	S	D	89	86–87	$C_9H_9Cl_2NOS$	28.3	28.5
62	Propyl	O	S	D	70	81–82	$C_{10}H_{11}Cl_2NOS$	26.8	27.0
63	Isopropyl	O	S	D	90	91–92	$C_{10}H_{11}Cl_2NOS$	26.8	27.1
64	Butyl	O	S	D	97	69–71	$C_{11}H_{13}Cl_2NOS$	25.4	25.7
65	Isobutyl	O	S	D	93	136–137	$C_{11}H_{13}Cl_2NOS$	25.4	25.7
66	*t*-Butyl	O	S	D	87	88–89	$C_{11}H_{13}Cl_2NOS$	25.4	25.3
67	Pentyl	O	S	D	96	58–59	$C_{12}H_{15}Cl_2NOS$	24.2	24.3
68	Octyl	O	S	D	78	63–64	$C_{15}H_{21}Cl_2NOS$	21.2	20.8
69	Dodecyl	O	S	D	81	60–61	$C_{19}H_{29}Cl_2NOS$	18.1	18.2
70	Methyl	S	O	E	99	143–144	$C_8H_7Cl_2NOS$	30.0	30.0
71	Ethyl	S	O	E	94	125–126[a]	$C_9H_9Cl_2NOS$	28.3	28.4
72	Propyl	S	O	E	92	66–67	$C_{10}H_{11}Cl_2NOS$	26.8	26.8
73	Isobutyl	S	O	E	81	70–71	$C_{11}H_{13}Cl_2NOS$	25.4	25.8
74	*sec*-Butyl	S	O	E	48	58–59	$C_{11}H_{13}Cl_2NOS$	25.4	25.5
75	Methyl	S	S	F	86	132–133	$C_8H_7Cl_2NS_2$	28.1	28.4
76	Ethyl	S	S	F	82	122–123	$C_9H_9Cl_2NS_2$	27.0	26.7
77	Propyl	S	S	F	98	78–79	$C_{10}H_{11}Cl_2NS_2$	25.1	24.9
78	Isopropyl	S	S	F	74	80–81	$C_{10}H_{11}Cl_2NS_2$	25.1	25.5
79	Butyl	S	S	F	95	73–74	$C_{11}H_{13}Cl_2NS_2$	24.1	23.9
80	Pentyl	S	S	F	92	61–62	$C_{12}H_{15}Cl_2NS_2$	23.0	23.2
81	Isopentyl	S	S	F	83	39–40	$C_{12}H_{15}Cl_2NS_2$	23.0	23.2
82	Dodecyl	S	S	F	93	75–76	$C_{19}H_{29}Cl_2NS_2$	17.4	17.7

[a] D. W. Brown and G. M. Dyson, *J. Chem. Soc.*, 178 (1934), gives m.p. 125°.

TABLE XII



No.	R	R′	Procedure	Yield, %	M.p., °C	Empirical formula	Analyses, % chlorine Calcd.	Found
83	2-Chloro	2-Nitrobutyl	A	40	98–99	$C_{11}H_{13}ClN_2O_4$	13.0	13.2
84	3-Chloro	2-Nitrobutyl	A	72	97–98	$C_{11}H_{13}ClN_2O_4$	13.0	13.2
85	4-Chloro	2-Nitrobutyl	A	29	96–97	$C_{11}H_{13}ClN_2O_4$	13.0	13.1
86	2-Nitro	2-Nitrobutyl	A	88	Sirup	$C_{11}H_{13}N_3O_6$	N, 14.8	N, 14.8
87	4-Nitro	2-Nitrobutyl	A	52	98–99	$C_{11}H_{13}N_3O_6$	N, 14.8	N, 14.4
88	3,4-Dichloro	2-Chlorophenyl	B	71	150–151	$C_{13}H_8Cl_3NO_2$	33.6	33.6
89	3,4-Dichloro	3-Chlorophenyl	B	70	112–113	$C_{13}H_8Cl_3NO_2$	33.6	33.9
90	3,4-Dichloro	4-Chlorophenyl	B	88	150–151[a]	$C_{13}H_8Cl_3NO_2$	33.6	33.8
91	3,4-Dichloro	3,4-Dichlorophenyl	B	91	148–149[a]	$C_{13}H_7Cl_4NO_2$	40.1	40.2
92	3,4-Dichloro	4-Chloro-3-methylphenyl	B	69	147–148	$C_{14}H_{10}Cl_3NO_2$	32.1	32.4
93	3,4-Dichloro	4-Chloro-3,5-dimethylphenyl	B	80	173–174	$C_{15}H_{12}Cl_3NO_2$	30.9	31.0
94	3,4-Dichloro	2,4,5-Trichloro	B	70	166–167	$C_{13}H_6Cl_5NO_2$	46.0	46.0
95	H	Isobutyl	A	97	86–87[b]	$C_{11}H_{15}NO_2$	N, 7.2	N, 7.2
96	2-Chloro	Isobutyl	A	99	Sirup	$C_{11}H_{14}ClNO_2$	15.6	15.5
97	3-Chloro	Isobutyl	A	99	Sirup	$C_{11}H_{14}ClNO_2$	15.6	15.8
98	4-Chloro	Isobutyl	A	82	75–76	$C_{11}H_{14}ClNO_2$	15.6	15.6
99	2,5-Dichloro	Isobutyl	A	97	40–41	$C_{11}H_{13}Cl_2NO_2$	27.1	27.0
100	2-Methyl	Isobutyl	A	42	50–51[c]	$C_{12}H_{17}NO_2$	N, 6.7	N, 7.1
101	3-Methyl	Isobutyl	A	95	Sirup	$C_{12}H_{17}NO_2$	N, 6.7	N, 7.0
102	4-Methyl	Isobutyl	A	47	45–46	$C_{12}H_{17}NO_2$	N, 6.7	N, 7.1
103	2-Methoxy	Isobutyl	A	88	Sirup	$C_{12}H_{17}NO_3$	N, 6.2	N, 6.4
104	4-Methoxy	Isobutyl	A	80	69–70[d]	$C_{12}H_{17}NO_3$	N, 6.2	N, 6.3
105	2-Nitro	Isobutyl	A	93	Sirup[e]	$C_{11}H_{14}N_2O_4$	N, 11.7	N, 11.7
106	3-Nitro	Isobutyl	A	80	88–89	$C_{11}H_{14}N_2O_4$	N, 11.7	N, 11.6
107	4-Nitro	Isobutyl	A	90	68–69[e]	$C_{11}H_{14}N_2O_4$	N, 11.7	N, 11.7

[a] Reported previously; see ref. 1. [b] A. Michael and P. H. Cobb, *Ann.*, **363**, 84 (1908), give m.p. 86°. [c] E. Mylius, *Ber.*, **5**, 972 (1872), reports compound as an oil. [d] O. Brunner and R. Wohrl, *Monatsh.*, **63**, 374 (1933), gives m.p. 71°. [e] S. E. Swartz, *Am. Chem. J.*, **19**, 319 (1897), gives m.p.'s of 13 and 62°, respectively.

The reaction was exothermic and allowed to continue without cooling. Sufficient heat was generated to bring the solution to reflux. After standing 1 hr., the product crystallized in fine white needles, yield 94.5%. It was later found more convenient to allow the isocyanate and alcohol to react in equimolar quantities, giving a sirup which crystallized on cooling. Secondary alcohols invariably suffered partial dehydration, the liberated water combining to form the symmetrical carbanilide. In these cases, the solid material was taken up in boiling heptane or methanol, filtered hot to remove the insoluble carbanilide, recovering the product from the filtrate.

B. 2-Chloroethyl 3,4-Dichlorocarbanilate (15).—A solution

of 18.8 g. (0.1 mole) of 3,4-dichlorophenyl isocyanate and 8.1 g. (0.1 mole) of ethylene chlorohydrin was charged into a stoppered erlenmeyer flask and held at 80° for 6 hr. On cooling, the sirup crystallized. Recrystallization from heptane gave small colorless granules, yield 97.5%.

C. 2-Thiocyanoethyl 3,4-Dichlorocarbanilate (42).—A solution of 44.0 g. (0.14 mole) of 2-bromoethyl 3,4-dichlorocarbanilate and 14.5 g. (0.15 mole) potassium thiocyanate in 100 ml. of acetone was refluxed for 16 hr. Acetone was distilled while adding 100 ml. of water dropwise during the distillation. On cooling, the product solidified and was removed by filtration. Recrystallization from chlorobenzene gave fine white granules, yield 51.8%.

D. Propyl 3,4-Dichlorothiolcarbanilate (62).—A solution of 18.8 g. (0.1 mole) of 3,4-dichlorophenylisocyanate and 7.6 g. (0.1 mole of propyl mercaptan in 150 ml. of heptane was stirred at 50° using 3 drops of triethylamine as catalyst. The product began to separate at once. After standing 1 hr., it was filtered. Recrystallization from dilute methanol gave fine white needles, yield 70.8%.

E. Propyl 3,4-Dichlorothionocarbanilate (72).—The method is essentially procedure B using equimolar amounts of 3,4-dichlorophenyl isothiocyanate and propanol. Fine colorless needles crystallized from heptane, yield 92.2%.

F. Propyl 3,4-Dichlorodithiocarbanilate (77).—Same as procedure D using equimolar amounts of 3,4-dichlorophenyl isothiocyanate and propyl mercaptan. Fine colorless needles crystallized from heptane, yield 93.7%.

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

The Synthesis of Some New Sulfonylureas

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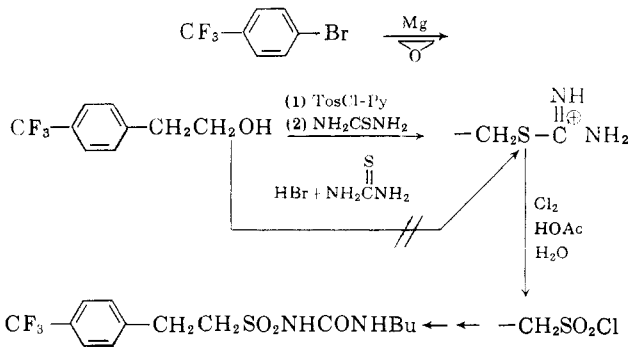
The synthesis of some new sulfonylureas is described. Two compounds have been found whose high hypoglycemic activity is surprising in view of what has previously been known regarding structure–activity relationships in this area.

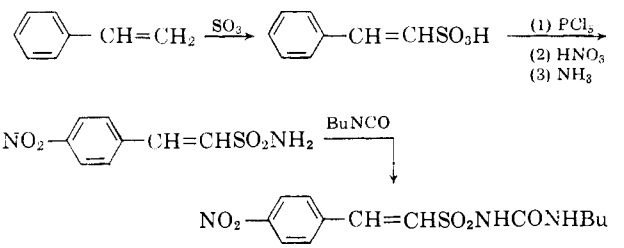
Although certain sulfonylureas have proven to be clinically useful oral antidiabetic agents,[1] recent reports describing the high rate of development of resistance to these[2] prompted us to search for related agents which might be active in such patients. Toward this end, we have synthesized some new sulfonylureas. Table I lists the sulfonylureas prepared.

The starting benzyl- and phenethylsulfonyl chlorides were prepared by reaction of the corresponding benzyl- and phenethyl halides with thiourea,[3] followed by chlorination of the resulting thiuronium salts in aqueous acetic acid.[3] 2-(*p*-Trifluoromethylphenyl)-ethanol was not converted to the thiuronium salt on heating with concentrated hydrobromic acid and thiourea.[4] The tosylate, however, reacted readily.

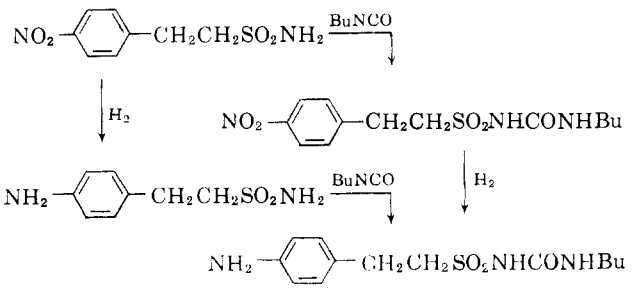


The sulfonamides were prepared by reaction of the sulfonyl chlorides with anhydrous ammonia. Table II lists the new sulfonamides.

In the synthesis of the styrene sulfonamides, the procedure of Bordwell[5] was employed.



The sulfonylureas were prepared by the reaction of the sulfonamide with butyl isocyanate in aqueous acetone containing one equivalent of base; the use of organic bases in nonaqueous systems gave poorer yields. The amino-substituted sulfonylurea was prepared both by reaction of the isocyanate with the aminosulfonamide and by reduction of the nitrosulfonylurea. The products were identical.



The 4-cyano-, carboxy-, carboxamido-, carbethoxy-, and acetamidophenethylsulfonylureas were most con-

(1) Particularly 1-*n*-butyl-3-(4-tolylsulfonyl)-urea (tolbutamide) and 1-(4-chlorobenzenesulfonyl)-3-*n*-propylurea (chlorpropamide).

(2) D. E. DeLawter and J. M. Moss, *J. Am. Med. Assoc.*, **181**, 89 (1962); R. A. Camerini-Davalos and A. Marble, *ibid.*, **181**, 176 (1962); Editorial, *ibid.*, **181**, 131 (1962).

(3) General procedure of T. B. Johnson and J. M. Sprague, *J. Am. Chem. Soc.*, **58**, 1348 (1936). We found that in the preparation of the sulfonyl chlorides, the use of aqueous acetic acid as solvent gave better yields and more consistent results than the aqueous system recommended by these authors.

(4) General procedure of D. F. Lee, B. Saville, and B. R. Trego, *Chem. Ind.* (London), **27**, 868 (1960).

(5) F. G. Bordwell, C. M. Suter, J. M. Hebert, and C. S. Rondestvelt, *J. Am. Chem. Soc.*, **68**, 139, 1778 (1946).