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Some Phenylthiourea Derivatives and their Antituberculous Activity

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The limits of structural variation compatible with activity have been outlined for a new class of *in vivo* tuberculostatic compounds best described as 1-*p*-acylphenyl-3-alkylthioureas. Pursuit of these limits led to another more active group of compounds, the thiocarbanilides, whose activity was announced by others, independently, during the course of this research. These two types of thioureas have been contrasted and certain highly active new derivatives have been prepared which share structural features common to both.

In the course of our extensive screening program in tuberculosis the activity of 1-*p*-thenoylphenyl-3-methyl-2-thiourea in the experimental mouse infection was discovered. The testing of closely related compounds disclosed that activity was a property of a wide variety of *p*-acylphenylthioureas. Eventually this work led to the much more active thiocarbanilides. In the progress of this research, papers appeared announcing the activity of certain of these thiocarbanilides[1-6]; consequently this study will be restricted to the acylphenylthioureas and to some highly active new thiocarbanilides.

The complete biological data on important representatives of these thioureas are given in a corollary paper.[7] The methods employed are described in some detail there and to greater extent in previous papers.[8-10] The test results given in the tables have been abstracted from the original data and are the bare minimum needed to allow a comparison of these thioureas one with another. The *in vitro* column gives simply the tuberculostatic concentration of these compounds measured against the human virulent H37Rv strain. The entries in the *in vivo* column appraise the prolongation of survival of treated infected mice caused by administration of the compounds at the diet levels indicated. A detailed explanation of these symbols is given in the Experimental section with a synopsis of the methods used. Unless otherwise specifically noted the discussions of activity given below refer to *in vivo* data.

The second compound of Table I, 1-*p*-acetylphenyl-3-methyl-2-thiourea, is representative of the phenylalkylthioureas. The remaining compounds of Table I afford a study of the effect on *in vivo* activity of varied substitution on the nitrogen atoms of this thiourea. Highest activity is shown by derivatives with the terminal nitrogen substituted by a single short straight chain alkyl group (compounds 2, 3, 4, 6). With increase of chain length beyond butyl and generally when the chain is branched or substituted the activity falls off drastically (compounds 5, 7–18). With this particular type, entire removal of the terminal alkyl group (compound 1) lowered activity only slightly. However, with some other *p*-acylphenylthioureas this change led to loss of nearly all activity (Table II, compounds 36, 41, 52). Dialkyl substitution on the terminal nitrogen (compounds 20, 21) or substitution on each nitrogen (compound 22) lowered activity greatly except with the 3,3-dimethyl derivative (compound 19) where only moderate loss occurred.

Replacement of the terminal alkyl group by phenyl and a wide variety of substituted phenyl groups gave substantially inactive compounds (compounds 23–26, 29–31), except, of course, where *p*-alkoxyphenyl replaces the alkyl group to give the active thiocarbanilides 27 and 28.[1]

From the examples of Table II other structural requirements for activity in the phenylalkylthioureas can be noted. Activity is preserved virtually undiminished with a variety of *p*-acyl groups. Activity extends in diminished degree to derivatives in which the *p*-acyl group is replaced by the highly electronegative alkylsulfonyl and the nitro groups (compounds 81, 82, 84, 85, 103). From the inactivity of compounds with *p*-cyano, carbethoxy, carbamyl and substituted sulfamyl (compounds 89–98), it appears that electronegativity alone is not sufficient to ensure activity.

Activity is lost if the acyl group is moved to the *m*-position (compounds 34, 35, 51, 101, 102). Attempts to make derivatives containing an *o*-acyl group were unsuccessful; consequently no test of whether this substitution is compatible with activity is available. Presumably, since the *o*-methylsulfonyl and the *o*-nitro derivatives (compounds 80 and 100) were inactive, the *o*-acyl derivatives also would be inactive.

The *p*-acyl group of these active thioureas can react with a variety of ketone reagents to give derivatives which are also active. Indeed, certain of the oximes (*e.g.*, compounds 60 and 63) in some experiments appear to be more active than the parent ketones. This led us to investigate whether ring systems which themselves contain components of these ketone derivatives could re-

(1) C. F. Huebner, J. L. Marsh, R. H. Mizzoni, B. P. Mull, D. C. Schroeder, H. A. Troxell and C. R. Scholz, THIS JOURNAL, **75**, 2274 (1953).

(2) R. L. Mayer, P. C. Eisman and E. A. Konopka, *Proc. Soc. Exptl. Biol. Med.*, **82**, 769 (1953).

(3) P. C. Eisman, E. A. Konopka and R. L. Mayer, *Am. Rev. Tuberc.*, **70**, 121 (1954).

(4) E. A. Konopka, P. C. Eisman, R. L. Mayer, F. Parker, Jr., and S. L. Robbins, *ibid.*, **70**, 130 (1954).

(5) N. P. Buu-Hoï and N. D. Xuong, *Compt. rend.*, **237**, 498 (1953).

(6) N. P. Buu-Hoï, N. D. Xuong and N. H. Nam, *J. Chem. Soc.*, 1573 (1955).

(7) G. P. Youmans, A. S. Youmans and L. Doub, *Am. Rev. Tuberc.*, **77**, 301 (1958).

(8) L. Doub and G. P. Youmans, *ibid.*, **61**, 407 (1950).

(9) G. P. Youmans and A. S. Youmans, *ibid.*, **64**, 541 (1951).

(10) G. P. Youmans, L. Doub and A. S. Youmans, "The Bacteriostatic Activity of 3500 Organic Compounds for *Mycobacterium Tuberculosis* var. *hominis*," National Research Council, Washington, D. C., 1953.

TABLE I

p-ACETYLPHENYLTHIOUREAS

No.	Substitution	Reaction conditions[a] Concn.[b]	Solvent	Hours	M.p.,[c] °C.	Crystn.[a] solvent	Yield, %	Emp. formula	Nitrogen, % Found	Calcd.	*In vitro*[d] Mg %	*In vivo*[e] Rating	(Diet concn.)
					N_2 alkyl derivatives								
1	None[f,g]				214–215		55				0.3	++	(0.25)[gg]
2	Methyl[h]	80	EtOH	6	159–160	EtOH	88	$C_{10}H_{12}N_2OS$	13.33	13.45	5.0	++(+)	(0.25–1.0)
3	Ethyl[h]	10	EtOH	6	137–139	EtOH	46	$C_{11}H_{14}N_2OS$	12.87	12.60	10	++	(1.0)
4	Allyl[h]	18	EtOH	5	124–126	EtOH	65	$C_{12}H_{14}N_2OS$	12.11	11.96	5.0	++	(0.5)
5	*i*-Propyl[h]	15	EtOH	7	136–138	50% EtOH	27	$C_{12}H_{16}N_2OS$	11.92	11.83	10	±	(0.5)
6	*n*-Butyl[h]	10	EtOH[i]	6	125–127	EtOH	65	$C_{13}H_{18}N_2OS$	11.60	11.19	1.3	++	(1.0)
7	*i*-Butyl[h]	16	EtOH[j]	7	102–104	50% EtOH	34	$C_{12}H_{18}N_2OS$[k]			5.0	0	(0.5)
8	*t*-Butyl[f]	15	EtOH	0.5	158–160	EtOH	41[l]	$C_{13}H_{18}N_2OS$	11.31	11.19	10	±	(.5)
9	*n*-Hexyl[f]	10	Et_2O[m]	<0.5	118–119	75% EtOH	68	$C_{15}H_{22}N_2OS$	10.02	10.06	2.5	±	(.5)
10	*n*-Heptyl[h]	15	EtOH[n]	6	118–119	EtOH	45	$C_{16}H_{24}N_2OS$	9.51	9.59	2.5	±	(.5)
11	*n*-Octyl[f]	12	Et_2O[m]	<0.5	88–89	75% EtOH	74	$C_{17}H_{26}N_2OS$	9.29	9.14	1.3	0	(.5)
12	*n*-Decyl[f]	13	Et_2O[m]	<0.5[o]	121–122	75% EtOH	55	$C_{19}H_{30}N_2OS$	8.30	8.38	2.5	0	(.5)
13	β-Hydroxyethyl[f]	43	EtOH	<0.5[o]	172–174		96	$C_{11}H_{14}N_2O_2S$	11.56	11.76	0.3	±	(.5)
14	γ-Diethylaminopropyl, HCl[f]	35	EtOH	16	148–149	Me_2CO	44	$C_{16}H_{26}ClN_3OS$	12.26	12.22	5.0	0	(.5)
15	Carboxymethyl[f,p]				178–179		22	$C_{11}H_{12}N_2O_3S$	11.33	11.10	10	0	(.25)
16	β-Carboxyethyl[f,p]				167–168		33	$C_{12}H_{14}N_2O_3S$	10.50	10.52	10	0	(.25)
17	ω-Carboxy-*n*-amyl[f,p]				162–164	EtOH	61	$C_{15}H_{20}N_2O_3S$	9.31	9.09	2.5	0	(.5)
18	α-Carboxy-γ-methylthiopropyl[f,q]				185–187	[p]	49	$C_{14}H_{18}N_2O_3S_2$	8.41	8.58	10	0	(.5)
					DIALKYL DERIVATIVES								
19	N_2,N_2-Dimethyl[f]	25	EtOH	<0.5[q]	181–182	EtOH	83	$C_{11}H_{14}N_2OS$	12.61	12.60	10	[+	(0.5)]
20	N_2,N_2-Diethyl	28	EtOH[n]	<0.5[r]	89–90	EtOH	64	$C_{13}H_{18}N_2OS$	11.34	11.19	5	0	(.5)
21	N_2,N_2-Di-(β-hydroxyethyl)	32	EtOH	<0.5[r]	145–147	EtOH	61	$C_{13}H_{18}N_2O_3S$	9.94	9.92	1.3	±	(.5)
22	N_1-Ethyl-N_2-allyl[s]	17	EtOH	24	86–88	EtOH	28[t]	$C_{14}H_{18}N_2OS$	10.05	10.68	10	0	(.5)
					N_2 ARYL DERIVATIVES								
23	Phenyl[u]				155–157						10	±	(0.5)
24	*p*-Chlorophenyl[f]	10	EtOH	0.7	168–169	Me_2CO	69	$C_{15}H_{13}ClN_2OS$	9.28	9.19	>10	0	(.5)
25	2,6-Dihydroxyphenyl[f]	20	50% EtOH	0.5	178–180	50% EtOH	27	$C_{15}H_{14}N_2O_3S$	9.24	9.27	5	[+	(.5)]
26	*o*-Anisyl[f]	10	EtOH[n]	3	132–134	MeOH	39	$C_{16}H_{16}N_2O_2S$	8.88	9.34	10	0	(.5)
27	*p*-Anisyl[f]	20	EtOH	<0.5	177–179	75% Cel	70	$C_{16}H_{16}N_2O_2S$[v]			1.3	[+	(.5)]
28	*p*-Phenetyl				169–170						0.3	[++	(.25)]
29	*p*-Acetylphenyl[f,w]				196–198						10	0	(.5)
30	*p*-Carboxyphenyl[f]	10	EtOH	0.7	>320	[x]	71	$C_{16}H_{14}N_2O_3S$	8.94	8.92	5	0	(.5)
31	*p*-Methylsulfonylphenyl[f]	31	Diox	8	177–178	AcOH	23[y]	$C_{16}H_{16}N_2O_3S_2$	8.21	8.04	10	0	(.5)
32	α-Pyridyl[f]	23	Diox	17	195–196	EtOH	21	$C_{14}H_{13}N_3OS$	15.76	15.49	>10	0	(.5)

[a] These thioureas were made without exception by the reaction of amines with isothiocyanates usually by refluxing in the indicated solvent for the indicated times. These reactants are identified for each entry by a separate footnote. Except where specified the procedure is that given in the Experimental section. The abbreviations of solvents follows *Chemical Abstracts* where possible; the following also are used: Cel = Cellosolve, Diox = dioxane, DMF = dimethylformamide, I = isoöctane. Percentage figures in the solvent columns refer to aqueous solvent mixtures. [b] The concentration is approximate only and gives the total weight of reactants per 100 ml. of solvent. [c] All melting points were determined in capillary tubes and are uncorrected. [d] Tuberculostatic end-point in mg. per 100 cc. of medium; see Experimental section. [e] Rated according to the increased survival time of animals treated at the given diet level compared to untreated controls. See Experimental section. [f] Prepared by treating *p*-acetylphenyl isothiocyanate with the amine

component. [g] H. V. George and R. F. Hunter, *J. Chem. Soc.*, 442 (1927). [gg] Compound slightly toxic at this diet level. [h] Prepared by treating *p*-aminoacetophenone with the isothiocyanate component. [i] The reaction mixture was cooled in a Dry Ice-bath for isolation. [j] The reaction solution was concentrated to small volume and precipitated with petroleum ether. [k] Calcd.: C, 62.37; H, 7.25. Found: C, 62.45; H, 6.97. [l] Crude yield 65%, m.p. 156–158°. [m] Product isolated by concentrating the reaction mixture to dryness. [n] The reaction mixture concentrated one-half and cooled to isolate product. [o] Reactants combined in solvent at *ca.* 45° and allowed to stand unheated. [p] The detailed preparation is given in the Experimental section. [q] The reactants were combined at 0°. [r] The reactants were combined at room temperature. [s] *p*-Ethylaminoacetophenone [W. D. Kumler, THIS JOURNAL, **68**, 1191 (1946)] allowed to react with allyl isothiocyanate. [t] Crude yield 37%, m.p. 83°. [u] C. V. Gheorghiu, *J. prakt. Chem.*, **130**, 49 (1931); *C. A.*, **25**, 3323 (1931). [v] Calcd.: C, 64.25; H, 5.37. Found: C, 64.08; H, 5.44. [w] Reference 21. [x] The product was purified by dissolution in dilute alkali, treating with charcoal, filtering and precipitating with dilute acetic acid. It was then crystallized from 50% aqueous dimethylformamide. [y] Crude yield 78%; m.p. 175–178°.

TABLE II

N_1-SUBSTITUTED PHENYL-N_2-ALKYLTHIOUREAS

No.	Substitution[a]	Reaction conditions[b] Concn.[c]	Solvent	Hours	M.p.,[d] °C.	Crystn.[b] solvent	Yield, %	Emp. formula	Nitrogen, % Found	Calcd.	*In vitro*[e] Mg. %	*In vivo*[f] Rating	(Diet concn.)
33	N_1-*p*-Formylphenyl-N_2-methyl	25	EtOH[g]	2	148–149	50% EtOH	[h]	$C_9H_{10}N_2OS$	14.47	14.43	5.0	0	(0.5)
34	N_1-*m*-Acetylphenyl-N_2-methyl	13	EtOH	6	120–122	EtOH	63	$C_{10}H_{12}N_2OS$[i]			>10	0	(.5)
35	N_1-*m*-Acetylphenyl-N_2-allyl	47	EtOH	7	86–87	EtOH	39	$C_{12}H_{14}N_2OS$	11.78	11.96	10	0	(.5)
36	N_1-*p*-Propionylphenyl[j]	24	EtOH	16[k]	187–189	EtOH	59	$C_{10}H_{12}N_2OS$	13.43	13.45	1.3	0	(.13)[gg]
37	N_1-*p*-Propionylphenyl-N_2-methyl	15	EtOH	6	155–157	EtOH	64	$C_{11}H_{14}N_2OS$[l]			5.0	[++	(1.0)]
38	N_1-*p*-Propionylphenyl-N_2-allyl	17	EtOH	6	137–138	EtOH	53	$C_{13}H_{16}N_2OS$	10.98	11.28	2.5	++	(0.5–1.0)
39	N_1-*p*-Propionylphenyl-N_2-*i*-propyl	15	EtOH	6	106–108	EtOH	70	$C_{13}H_{18}N_2OS$	11.17	11.19	0.6	0	(.5)
40	N_1-*p*-Propionylphenyl-N_2-butyl	15	EtOH	6	139–141	EtOH	45	$C_{14}H_{20}N_2OS$[m]			10	±	(.5)
41	N_1-*p*-Butyrylphenyl[j]	43	EtOH	16[k]	171–172	EtOH	72	$C_{11}H_{14}N_2OS$	12.60	12.60	0.2	±	(.5)
42	N_1-*p*-Butyrylphenyl-N_2-methyl	64	EtOH	17	135–137	EtOH	55	$C_{12}H_{16}N_2OS$	11.65	11.83	0.2	+++	(.5)
43	N_1-*p*-Butyrylphenyl-N_2-allyl	44	EtOH	17	148–149	EtOH	25	$C_{14}H_{18}N_2OS$	10.67	10.68	0.3	[++(+)	(.5)]
44	N_1-β-Hydroxyethyl-N_2-*p*-butyryl-phenyl	60	EtOH	1[k]	98–99	50% EtOH	72	$C_{13}H_{18}N_2O_2S$	10.47	10.52	0.08	0	(.13)
45	N_1-*p*-Valerylphenyl-N_2-methyl	42	EtOH	22	134–136	EtOH	44	$C_{13}H_{18}N_2OS$	11.11	11.19	0.02	++	(.1–0.5)
46	N_1-*p*-Caproylphenyl-N_2-methyl	14	EtOH	8	132–133	60% EtOH	63	$C_{14}H_{20}N_2OS$	10.53	10.60	0.002	+++	(.5)
47	N_1-*p*-Caprylylphenyl-N_2-methyl	42	EtOH	22	115–117	EtOH	61	$C_{16}H_{24}N_2OS$	9.40	9.58	10	+	(.1)
48	N_1-*p*-(α,α-Dicarbethoxyacetyl)-phenyl-N_2-methyl	26	EtOH	6[n]	148–149	EtOH	31	$C_{16}H_{20}N_2O_5S$	7.92	7.95	>10	±	(.25)
49	N_1-*p*-Benzoylphenyl-N_2-methyl	10	EtOH	6	161–163	EtOH	31	$C_{15}H_{14}N_2OS$	10.16	10.38	10	++	(.5–1.0)
50	N_1-*p*-Benzoylphenyl-N_2-allyl	15	EtOH	6[g]	132–134	EtOH	69	$C_{17}H_{16}N_2OS$	9.86	9.57	1.3	±	(.5)
51	N_1-*m*-(2-Thenoyl)-phenyl-N_2-methyl	20	95% EtOH	4.5	158–159	EtOH	72	$C_{13}H_{12}N_2OS_2$	10.29	10.14	2.5	0	(1.0)
52	N_1-*p*-(2-Thenoyl)-phenyl[o]				196–197	95% MeOH	54	$C_{12}H_{10}N_2OS_2$	10.66	10.68	2.5	0	(0.5)
53	N_1-*p*-(2-Thenoyl)-phenyl-N_2-methyl	16	EtOH	6	158–160	EtOH	70	$C_{13}H_{12}N_2OS_2$	9.81	10.14	0.6	+++(+)	(1.0–4.0)
54	N_1-*p*-(2-Thenoyl)-phenyl-N_2-ethyl	15	EtOH	5	160–161	95% EtOH	74	$C_{14}H_{14}N_2OS_2$	9.36	9.65	1.3	±	(1.0)
55	N_1-*p*-(2-Thenoyl)-phenyl-N_2-allyl	15	EtOH[g]	6	122–124	EtOH	61	$C_{15}H_{14}N_2OS_2$	9.00	9.34	0.6	+	(1.0)
56	N_1-*p*-(2-Thenoyl)-phenyl-N_2-butyl	8	EtOH	16	129–131	EtOH	48	$C_{16}H_{18}N_2OS_2$	8.63	8.79	0.3	+	(0.5)
57	N_1-*p*-Picolinylphenyl-N_2-methyl	10	EtOH[n]	19	165–166	Aq. MeOH	41	$C_{14}H_{13}N_3OS$	15.68	15.50	0.6	±	(.5)
58	N_1-*p*-Isonicotinyl-N_2-methyl	10	EtOH[n]	6	169–171	Aq. MeOH	42	$C_{14}H_{13}N_3OS$	15.64	15.50	0.3	±	(.5)
59	N_1-*p*-Oximidomethylphenyl-N_2-methyl[o,p]				178–179	50% EtOH	(73)[o]	$C_9H_{11}N_3OS$	19.97	20.08	2.5	0	(.25)
60	N_1-*p*-(1-Oximidoethyl)-phenyl-N_2-methyl[o,p]				189–190	50% EtOH	(54)[o]	$C_{10}H_{13}N_3OS$	19.27	18.88	0.16	+++	(.5)
61	N_1-*p*-(1-Oximidoethyl)-phenyl-N_2-ethyl[o,p]				178–180	EtOH	(37)[o]	$C_{11}H_{15}N_3OS$	17.78	17.71	5.0	[++	(.5)]

TABLE II (*Continued*)

No.	Substitution[a]	Reaction conditions[b] Concn.[c]	Solvent	Hours	M.p.,[d] °C.	Crystn.[b] solvent	Yield, %	Emp. formula	Nitrogen, % Found	Calcd.	*In vitro*[e] Mg. %	*In vivo*[f] Rating	(Diet concn.)
62	N_1-*p*-(1-Oximidoethyl)-phenyl-N_2-propyl[o,p]				167–168	60% EtOH	(75)[o]	$C_{12}H_{17}N_3OS$	16.74	16.72	2.5	[+	(.5)]
63	N_1-*p*-(1-Oximidopropyl)-phenyl-N_2-methyl[o,p]				168–169	EtOH	(65)[o]	$C_{11}H_{15}N_3OS$	17.58	17.71	5.0	[+++	(.5)]
64	N_1-*p*-(1-Oximidopropyl)-phenyl-N_2-allyl[o,p]				156–157	50% EtOH	(65)[o]	$C_{13}H_{17}N_3OS$	16.17	15.96	2.5	[++	(.5)]
65	N_1-*p*-(1-Oximidobutyl)-phenyl-N_2-methyl[o,p]				161–162	50% EtOH	(72)[o]	$C_{12}H_{17}N_3OS$	16.90	16.72	1.3	[++	(.5)]
66	N_1-*p*-(1-Oximidobutyl)-phenyl-N_2-(2-hydroxyethyl)[o,p]				166–167	EtOH	(79)[o]	$C_{13}H_{19}N_3O_2S$	15.12	14.94	2.5	0	(.13)
67	N_1-*p*-(1-Oximidoamyl)-phenyl-N_2-methyl[o,p]				167–169	EtOH	(57)[o]	$C_{13}H_{19}N_3OS$	16.02	15.84	0.3	+	(.25–0.5)
68	N_1-*p*-(1-Acetylhydrazonoethyl)-phenyl-N_2-methyl[o,p]				250–252	[q]	(74)[o]	$C_{12}H_{16}N_4OS$[r]			>10	+	(.5)
69	N_1-*p*-(1-Phenylhydrazonoethyl)-phenyl-N_2-methyl[o,p]				190–192	85% Cel	(85)[o]	$C_{16}H_{18}N_4S$	19.12	18.77	>10	0	(.5)
70	N_1-*p*-(1-Semicarbazonoethyl)-phenyl-N_2-methyl[o,p]				220–222	DMF	(68)[o]	$C_{11}H_{15}N_5OS$	26.85	26.46	5.0	±	(.5)
71	N_1-*p*-(2-Isoxazolin-3-yl)-phenyl-N_2-methyl	4	EtOH	18	176–177	EtOH–I[s]	76	$C_{11}H_{11}N_3OS$[t]			0.63	[++	(.25)]
72	N_1-*p*-2-(1-Oxopyridyl)-phenyl-N_2-methyl	7	EtOH	1	202–203	Aq. EtOH	50	$C_{13}H_{13}N_3OS$[u]			10	++	(.25)
73	N_1-*p*-α-Pyridylphenyl[j]	16	EtOH	24	184–185	EtOH	74	$C_{12}H_{11}N_3S$	18.12	18.33	0.16	++	(.13)[yy]
74	N_1-*p*-α-Pyridylphenyl-N_2-methyl	20	EtOH	6	169–171	EtOH	80	$C_{13}H_{13}N_3S$	16.91	17.25	.16	[+	(.5)]
75	N_1-β-Hydroxyethyl-N_2-*p*-α-pyridylphenyl	16	EtOH	<0.5	158–160	EtOH	87	$C_{14}H_{15}N_3OS$	15.70	15.37	.16	0	(.13)
76	N_1-N_1-Di-(β-hydroxyethyl)-N_2-*p*-α-pyridylphenyl	16	EtOH	<0.5	175–177	50% Diox	63	$C_{16}H_{19}N_3O_2S$	13.12	13.24	.3	+	(.25)
77	N_2-γ-Diethylaminopropyl-N_2-*p*-α-pyridylphenyl	16	EtOH	<0.5	122–124	[q]	74	$C_{19}H_{26}N_4S$	16.19	16.36	.16	0	(.25)
78	N_1-*p*-(α-Pyridylmethyl)-phenyl-N_2 methyl	10	EtOH[n]	10	126.5–127.5	PhH–I[s]	89	$C_{14}H_{15}N_3S$[v]			5.0	+++	(.5)
79	N-*p*-(γ-Pyridylmethyl)-phenyl-N_2-methyl	7	EtOH	6	192–193	EtOH	91	$C_{14}H_{15}N_3S$	16.14	16.33	5.0	[+++	(.5)]
80	N_1-*o*-Methylsulfonylphenyl-N_2-methyl	24	EtOH[g]	17	140–141	75% EtOH	18[w]	$C_9H_{12}N_2O_2S$	11.48	11.47	10	0	(.5)
81	N_1-*p*-Methylsulfonylphenyl[j]	33	EtOH[k]	24	200–202 (eff.)	AcOH	69	$C_8H_{10}N_2O_2S_2$	12.10	12.17	0.63	+	(.5)
82	N_1-*p*-Methylsulfonylphenyl-N_2-methyl	27	EtOH[g]	18	198–200	EtOH	43	$C_9H_{12}N_2O_2S_2$	11.49	11.47	>10	+	(.5)
83	N_1-*p*-Methylsulfonylphenyl-N_2-allyl	34	EtOH[g]	24	120–122	EtOH	34	$C_{11}H_{14}N_2O_2S_2$	10.13	10.36	10	±	(.5)
84	N_1-*p*-Ethylsulfonylphenyl-N_2-methyl	64	EtOH[g]	15	157–159	EtOH	44	$C_{10}H_{14}N_2O_2S_2$	10.74	10.85	10	[+	(.5)]
85	N_1-*p*-Ethylsulfonylphenyl-N_2-allyl	61	EtOH[g]	15	108–110	EtOH	43	$C_{12}H_{16}N_2O_2S_2$	9.79	9.85	10	[+	(.5)]

86	N_1-*p*-Propylsulfonylphenyl-N_2-methyl	36	EtOH[g]	16	139–140	EtOH	47	$C_{11}H_{16}N_2O_2S_2$	10.45	10.29	10	[+	(.5)]
87	N_1-*p*-Propylsulfonylphenyl-N_2-allyl	40	EtOH[g]	16	107–108	EtOH	22	$C_{13}H_{18}N_2O_2S_2$	9.53	9.38	10	±	(.5)
88	N_1-*p*-Butylsulfonylphenyl-N_2-methyl	71	EtOH	34	139–141	EtOH	45	$C_{12}H_{18}N_2O_2S_2$	9.69	9.79	10	0	(.5)
89	N_1-*p*-Sulfamylphenyl-N_2-methyl[z]				205–206						>10	±	(1.0)
90	N_1-*p*-(N-Dimethylsulfamyl)-phenyl-N_2-methyl, H_2O	10	EtOH	6	180–182	EtOH	32	$C_{19}H_{17}N_3O_3S_2$	14.58	14.45	>10		Not tested
91	N_1-*p*-(N-Dimethylsulfamylphenyl)-N_2-allyl[y]				184–186						5.0	±	(0.5)
92	N_1-*p*-[N-(2-Pyrimidyl)-sulfamyl-phenyl]-N_2-allyl	10	Cel	16	242–244	[q]	30	$C_{14}H_{15}N_5O_2S_2$	19.98	20.09	>10	±	(.5)
93	N_1-*p*-[N-(2-thiazolyl)-sulfamyl]-phenyl-N_2-allyl	10	EtOH	4	208–210	EtOH–DMF	20	$C_{13}H_{14}N_4O_2S_3$	15.87	15.70	10	0	(.5)
94	N_1-*p*-Carbethoxyphenyl-N_2-methyl[aa]				145–147						0.3	±	(.5)
95	N_1-*p*-Carbethoxyphenyl-N_2-allyl	53	EtOH	16	89–90	EtOH	51	$C_{13}H_{16}N_2O_2S$	10.82	10.60	0.16	±	(.5)
96	N_1-*p*-Carbamylphenyl-N_2-methyl	15	EtOH	3	185–187	H_2O	75	$C_9H_{11}H_3OS$[bb]			>10	0	(.5)
97	N_1-*p*-(N_3-Carboxymethylcarbamyl-phenyl)-N_2-allyl	20	50% EtOH[g]	16	182–184	50% EtOH	17	$C_{13}H_{15}N_3O_3S$	14.53	14.32	>10	0	(.5)
98	N_1-*p*-Cyanophenyl-N_2-methyl	20	EtOH	6	191–192	EtOH	31	$C_9H_9N_3S$[cc]			>10	0	(.5)
99	N_1-(3-Hydroxy-4-carboxyphenyl)-N_2-allyl[dd]				184–185						0.16	0	(.5)
100	N_1-Methyl-N_2-*o*-nitrophenyl	37	Diox	<0.2	109–111	$CHCl_3$	50	$C_8H_9N_3O_2S$	19.76	19.89	10	0	(.5)
101	N_1-*m*-Nitrophenyl-N_2—methyl	27	EtOH[g]	7	164–165	EtOH	53	$C_8H_9N_3O_2S$	19.71	19.89	>10	0	(.5)
102	N_1-*m*-Nitrophenyl-N_2-allyl	27	EtOH[g]	7	121–123	EtOH	49	$C_{10}H_{11}N_3O_2S$	17.95	17.71	10	0	(.5)
103	N_1-*p*-Nitrophenyl-N_2-methyl[ee]				209–211						10	+	(.5)
104	N_1-*p*-Nitrophenyl-N_2-ethyl	33	EtOH	17	159–160	EtOH	32	$C_9H_{11}N_3O_2S$	18.87	18.65	2.5	0	(.5)
105	N_1-*p*-Nitrophenyl-N_2-butyl	27	EtOH	17	113–114	EtOH	25	$C_{11}H_{15}N_3O_2S$	16.79	16.59	2.5	0	(.5)
106	N_1-(4-Nitro-2-methoxyphenyl)-N_2-methyl	27	EtOH	16	189–190	EtOH	12	$C_9H_{11}N_3O_3S$	17.70	17.42	10	0	(.5)
107	N_1-Phenyl-N_2-methyl[ff]				111–113						>10	0	(1.0)
108	N_1-*o*-Tolyl-N_2-methyl[gg]				163–164						>10	0	(0.13)
109	N_1-*o*-Tolyl-N_2-allyl[hh]				97–98						>10	0	(.13)
110	N_1-*m*-Tolyl-N_2-methyl[ii]				103–104						>10	0	(.5)
111	N_1-*m*-Tolyl-N_2-allyl	21	EtOH	17	63–65	EtOH	45	$C_{11}H_{14}N_2S$	13.58	13.58	10	0	(.5)
112	N_1-*p*-Tolyl-N_2-methyl[ff]				128–130						10	0	(.5)
113	N_1-*p*-Tolyl-N_2-allyl[kk]				95–97						0.25	0	(.5)
114	N_1-(4-*m*-Xylyl)-N_2-methyl	97	EtOH	40	152–153	EtOH	40	$C_{10}H_{14}N_2S$	14.49	14.42	>20	0	(.5)
115	N_1-Carvacryl-N_2-methyl	14	EtOH	17	126–128	EtOH	41	$C_{12}H_{19}N_2S$	12.68	12.60	10	0	(.5)
116	N_1-(2-Biphenylyl)-N_2-methyl	48	EtOH	7	155–156	EtOH	70	$C_{14}H_{14}N_2S$	11.65	11.56	10	0	(.5)
117	N_1-(2-Biphenylyl)-N_2-allyl	48	EtOH	7	95–97	EtOH	62	$C_{16}H_{16}N_2S$	10.46	10.44	5.0	0	(.5)
118	N_1-(4-Biphenylyl)-N_2-methyl[ll]				141–142						0.08	0	(.5)
119	N_1-(4-Biphenylyl)-N_2-allyl	18	EtOH	6	96–98	EtOH	58	$C_{16}H_{16}N_2S$	10.35	10.44	5.0	0	(.5)
120	N_1-β-Naphthyl-N_2-methyl[mm]				131–132						0.13	0	(.5)
121	N_1-α-Naphthyl-N_2-allyl	33	EtOH	7	108–109	EtOH	42	$C_{14}H_{14}N_2S$	10.21	11.56	0.63	0	(.5)
122	N_1-(3-Fluorenyl)-N_2-methyl	60	EtOH	0.5	185–187	EtOH	83	$C_{15}H_{14}N_2S$	11.21	11.02	0.63	±	(.5)
123	N_1-(3-Fluorenyl)-N_2-allyl	50	EtOH	0.5	170–171	EtOH	56	$C_{17}H_{16}N_2S$	10.03	9.99	5.0	0	(.5)

TABLE II (*Continued*)

No.	Substitution[a]	Reaction conditions[b] Concn.[c]	Solvent	Hours	M.p.[d] °C.	Crystn.[b] solvent	Yield, %	Emp. formula	Nitrogen, % Found	Calcd.	*In Vitro*[e] Mg. %	*In Vivo*[f] Rating	(Diet Conc.)
124	N_1-*o*-Hydroxyphenyl-N_2-methyl	36	EtOH	16	138–140	EtOH	28	$C_8H_{10}N_2OS$	15.32	15.38	0.3	0	(.5)
125	N_1-*m*-Hydroxyphenyl-N_2-methyl	36	EtOH	16	168–169	EtOH	42	$C_8H_{10}N_2OS$	15.33	15.38	5.0	0	(.5)
126	N_1-*m*-Hydroxyphenyl-N_2-allyl	42	EtOH	16	95–97	[q]	50	$C_{10}H_{12}N_2OS$	13.33	13.45	5.0	0	(.5)
127	N_1-*p*-Hydroxyphenyl-N_2-methyl	36	EtOH	16	197–198	EtOH	28	$C_8H_{10}N_2OS$	15.54	15.38	10	0	(.5)
128	N_1-*p*-Hydroxyphenyl-N_2-allyl	42	EtOH	16	145–147	EtOH	34	$C_{10}H_{12}N_2OS$	13.47	13.45	10	0	(.5)
129	N_1-*o*-Anisyl-N_2-methyl[nn]	28	EtOH	17	141–143	EtOH	43	$C_9H_{12}N_2OS$	14.29	14.28	>10	0	(.5)
130	N_1-*o*-Anisyl-N_2-allyl	37	EtOH	18	84–85	EtOH	53	$C_{11}H_{14}N_2OS$	12.80	12.60	>10	0	(.5)
131	N_1-*p*-Anisyl[oo]				219–221						5.0		Not tested
132	N_1-*p*-Anisyl-N_2-methyl[pp]				170–171						2.5	0	(0.5)
133	N_1-*p*-Anisyl-N_2-allyl	22	EtOH[g]	16	79–81		37	$C_{11}H_{14}N_2OS$	12.66	12.60	5.0	0	(.5)
134	N_1-*o*-Phenetyl-N_2-methyl[nn]				93–95						>10	±	(.5)
135	N_1-*o*-Phenetyl-N_2-allyl	36	EtOH[g]	17	62–63	80% EtOH	31	$C_{12}H_{16}N_2OS$	12.08	11.83	>10	0	(.5)
136	N_1-*m*-Phenetyl-N_2-methyl[nn]	26	EtOH	17	118–120	EtOH	50	$C_{10}H_{14}N_2OS$	13.33	13.32	10	0	(.5)
137	N_1-*m*-Phenetyl-N_2-allyl	24	EtOH[g]	17	73–75	EtOH	54	$C_{12}H_{16}N_2OS$	12.06	11.83	5.0	0	(.5)
138	N_1-*p*-Phenetyl[qq]				176–177						0.16	++	(1.3)[vv]
139	N_1-*p*-Phenetyl-N_2-methyl[nn]	40	EtOH	6	131–132	EtOH	54	$C_{10}H_{14}N_2OS$	13.44	13.32	0.63	0	(0.5)
140	N_1-β-Hydroxyethyl-N_2-*p*-phenetyl[rr]	40	EtOH	0.2	163–164	EtOH	70	$C_{11}H_{16}N_2O_2S$	11.64	11.66	0.08	±	(.5)
141	N_1-(5-Piperidinoamyl)-N_2-phenetyl, HCl	68	EtOH[n]	<0.2	160–161	EtOH[ss]	71	$C_{19}H_{31}ClN_3OS$	11.20	11.21	0.3	0	(.5)
142	N_1-(3-Dimethylaminopropyl)-N_2-phenetyl	56	EtOH	16[k]	135–136	[q]	86	$C_{14}H_{23}N_3OS$	14.88	14.93	0.8	0	(.2)
143	N_1-*p*-Aminophenyl-N_2-methyl	38	EtOH	17	175–177	EtOH[tt]	29	$C_8H_{11}N_3S$	23.48	23.18	>10	0	(.5)
144	N_1-*p*-Diethylaminophenyl-N_2-methyl	40	EtOH	20	114–115	EtOH	25	$C_{12}H_{19}N_3S$	17.76	17.70	5.0	0	(.5)
145	N_1-*p*-Diethylaminophenyl-N_2-allyl	40	EtOH	20	112–113	EtOH	34	$C_{14}H_{21}N_3S$	15.64	15.95	2.5	0	(.5)
146	N_1-*p*-Acetamidophenyl-N_2-methyl	10	EtOH	5	205–206	EtOH	74	$C_{10}H_{13}N_3OS$	19.06	18.87	>10	0	(.5)
147	N_1-*p*-Phenylazophenyl-N_2-methyl	27	EtOH[g]	18	178–179	EtOH	60	$C_{14}H_{14}N_4S$	20.58	20.73	10	±	(.5)
148	N_1-*p*-Phenylazophenyl-N_2-allyl[uu]				132–134						10	±	(.13)
149	N_1-*o* Chlorophenyl[oo]										10	0	(.02)[vv]
150	N_1-*o*-Chlorophenyl-N_2-methyl	27	EtOH	14	165–167	EtOH	69	$C_8H_9ClN_2S$	14.23	13.96	>10	0	(.25)
151	N_1-*o*-Chlorophenyl-N_2-allyl	30	EtOH	14	74–76	50% EtOH	60	$C_{10}H_{11}ClN_2S$	12.49	12.36	>10	+	(.5)
152	N_1-*m*-Chlorophenyl[oo]										5.0		Not tested
153	N_1-*p*-Chlorophenyl[oo]										2.5		Not tested
154	N_1-*p*-Chlorophenyl-N_2-methyl[pp]				146–147						10	0	(0.5)
155	N_1-(3,4-Dichlorophenyl)-N_2-methyl	34	EtOH	5	152–153	EtOH	44	$C_8H_8Cl_2N_2S$	12.13	11.92	0.63	0	(.5)
156	N_1-(3,4-Dichlorophenyl)-N_2-allyl	37	EtOH	5	106–108	EtOH	25	$C_{10}H_{10}Cl_2N_2S$	10.97	10.73	0.3	0	(.5)
157	N_1-(2,4-Dichlorophenyl)-N_2-methyl	34	EtOH	5	152–153	EtOH	45	$C_8H_8Cl_2N_2S$	11.92	11.92	10	0	(.13)
158	N_1-(2,4-Dichlorophenyl)-N_2-allyl	37	EtOH	5	101–103	EtOH	32	$C_{10}H_{10}Cl_2N_2S$	10.73	10.73	5.0	0	(.25)
159	N_1-(2,5-Dichlorophenyl)-N_2 allyl	37	EtOH	5	117–118	EtOH	35	$C_{10}H_{10}Cl_2N_2S$	10.72	10.73	5.0	0	(.13)
160	N_1-(2,5-Dichlorophenyl)-N_2-methyl	34	EtOH	5	176–177	EtOH	40	$C_8H_8Cl_2N_2S$	11.67	11.92	>10	0	(.25)
161	N_1-*o*-Bromophenyl-N_2-methyl	35	EtOH	4	172–174	EtOH	44	$C_8H_9BrN_2S$	11.26	11.43	>10	0	(.25)
162	N_1-*o*-Bromophenyl-N_2-ethyl	36	EtOH	4	143–145	80% EtOH	58	$C_9H_{11}BrN_2S$	10.90	10.81	>10	0	(.25)
163	N_1-*o*-Bromophenyl-N_2-allyl	39	EtOH	4	71–73	EtOH	26	$C_{10}H_{11}BrN_2S$	10.16	10.33	10	0	(.25)
164	N_1-*p*-Bromophenyl[oo]										1.25	0	(.06)[vv]

165	N-*p*-Bromophenyl-N_2-methyl[ww]	147–148	2.5	±	(.5)
166	N-*p*-Iodophenyl-N_2-methyl[xx]	174–175	1.25	0	(.5)

[a] The first named component as the amine reacted with the second component as isothiocyanate, with the exceptions noted. [b] These thioureas were made without exception by the reaction of amines with isothiocyanates usually by refluxing in the indicated solvent for the indicated times. These reactants are identified for each entry by a separate footnote. Except where specified the procedure is that given in the Experimental section. The abbreviations of solvents follows *Chemical Abstracts* where possible; the following also are used: Cel = Cellosolve, Diox = dioxane, DMF = dimethylformamide, I = isooctane. Percentage figures in the solvent columns refer to aqueous solvent mixtures. [c] The concentration is approximate only and gives the total weight of reactants per 100 ml. of solvent. [d] All melting points were determined in capillary tubes and are uncorrected. [e] Tuberculostatic end-point in mg. per 100 cc. of medium. See Experimental section. [f] Rated according to the increased survival time of animals treated at the given diet level compared to untreated controls. See Experimental section. [g] The reaction solution was concentrated to small volume and cooled for isolation. [h] Crude yield 62%, m.p. 134–137°. [i] Calcd.: C, 57.61; H, 5.81. Found: C, 57.73; H, 6.01. [j] Prepared by reaction of aromatic isothiocyanate and ammonia. [k] Reacted at room temperature. [l] Calcd.: C, 59.43; H, 6.35. Found: C, 59.71; H, 6.52. [m] Calcd.: C, 63.62; H, 7.63. Found: C, 64.03; H, 7.85. [n] Reaction solution concentrated to dryness for isolation. [o] See Experimental section for preparation. Yields in parentheses refer to reaction of parent thiourea with hydroxylamine or appropriate hydrazine. [p] See parent compound for preparation of thiourea. [q] Purified by dissolving in base (or acid), filtering and precipitating in acid (or base). [r] Calcd.: C, 54.6; H, 6.10. Found: C, 54.3; H, 5.95. [s] Isooctane added until the solution became turbid, then mixture was cooled. [t] Calcd.: C, 56.15; H, 5.57. Found: C, 56.31; H, 5.67. [u] Calcd.: C, 60.21; H, 5.05. Found: C, 60.30; H, 5.29. [v] Calcd.: C, 65.34; H, 5.88. Found: C, 65.19; H, 5.94. [w] Crude yield 50%, m.p. 130–133°. [x] J. S. Roth and E. F. Degering, THIS JOURNAL, **67**, 126 (1945). [y] K. Ganapati, *J. Indian Chem. Soc.*, **15**, 525 (1938); *C. A.*, **33**, 2496 (1939). [z] R. F. Hunter and E. R. Parken, *J. Indian Chem. Soc.*, **9**, 357 (1932); *C. A.*, **27**, 2945 (1933); these give m.p. 147–148°. [aa] Calcd.: C, 51.65; H, 5.30. Found: C, 51.66; H, 5.39. [bb] Calcd.: C, 56.78; H, 4.80. Found: C, 56.52; H, 4.74. [cc] Reference of footnote *y* gives m.p. 181°. [dd] R. F. Hunter and E. R. Parken, *J. Chem. Soc.*, 1175 (1934), give m.p. 183–184°. Our sample, calcd.: C, 45.49; H, 4.30. Found: C, 45.62; H, 4.45. [ee] W. Gebhardt, *Ber.*, **17**, 3038 (1884). [ff] R. F. Hunter and E. R. Styles, *J. Chem. Soc.*, 3024 (1928), give m.p. 161°. [gg] A. E. Dixon, *ibid.*, **67**, 559 (1895). [hh] F. B. Daines, R. D. Coghill and S. S. Tiker, *Univ. Kansas Sci. Bull.*, **24**, 25 (1936); *C. A.*, **32**, 3397 (1938). [ii] E. L. Brown and N. Campbell, *ibid.*, 1699 (1937). [jj] R. F. Hunter and J. W. T. Jones, *ibid.*, 947 (1930). [kk] G. Young and S. F. Crooks, *J. Chem. Soc.*, **89**, 71 (1906). [ll] E. J. DeBeer, J. S. Buck, W. S. Ide and A. M. Hjort, *J. Pharmacol.*, **57**, 19 (1936), give m.p. 104° for compound 129, 97° for compound 134, 111° for compound 136, 144° for compound 139. [mm] H. King and I. M. Tonkin, *J. Chem. Soc.*, 1063 (1946), give m.p. 169°. [nn] G. M. Dyson and H. J. George, *ibid.*, **125**, 1702 (1924). [oo] Stock sample. [pp] S. H. Dicke, G. S. Allen and C. P. Richter, *J. Pharmacol.*, **90**, 260 (1947); no m.p. given. [qq] The dry reaction mixture in ether was neutralized with gaseous HCl and this product was crystallized from EtOH. [rr] A three fold excess of amine was used and the acid soluble material was crystallized. [ss] Betti, *Gazz. chim. ital.*, **28I**, 244 (1898); "Beilstein," Vol. 16, p. 318. [tt] R. F. Hunter and J. W. T. Jones, *J. Chem. Soc.*, 2190 (1930). [uu] R. F. Hunter and C. Soyka, *ibid.*, **129**, 2961 (1926). [vv] Compound toxic at higher diet levels. [ww] R. F. Hunter and J. W. T. Jones, *J. Chem. Soc.*, 2190 (1930). [xx] J. A. Davis and F. B. Dains, THIS JOURNAL, **57**, 2629 (1935).

place the entire acyl group in phenylalkylthioureas to give active compounds (compounds 71–74).

The application of this analogy is illustrated by the examples

(cmpd. 60)

(cmpd. 71)

(cmpd. 74)

Activity was preserved in each of these variants.

Thus from the examples of Tables I and II there can be discerned a distinct type of active thioureas. They are 1-monophenylthioureas usually with a short alkyl group substituted in the 3-position. The phenyl group must be substituted in the *p*-position with a highly electronegative group, preferably acyl. The oxygen of the acyl group can be replaced by nitrogen either in the form of a simple ketone derivative or the nitrogen can occur in a ring system.

A few exceptions to this pattern occur in the examples of Tables I and II, in addition to the alkoxythiocarbanilides already mentioned. 1-*p*-Phenetylthiourea (compound 138) is active possibly because it too is related to the alkoxythiocarbanilides. However, if this is true, it is evident from the lack of activity of the several 1-*p*-phenetyl-3-alkylthioureas (compounds 139–142) that there is no smooth continuity of active structures between this *p*-phenetylthiourea and the thiocarbanilide counterpart. Whether 1-*p*-(α-pyridylmethyl)-phenyl-3-methylthiourea and 1-*p*-(γ-pyridylmethyl)-phenyl-3-methylthiourea (compounds 78 and 79) are an extension of the acylphenylthioureas or represent a new type of active thiourea is of course uncertain. Questions of this sort must await an answer in the elucidation of the mechanism of action of these compounds. With the *p*-acylphenylthioureas, as noted by Huebner, *et al.*, for the thiocarbanilides,[1] replacement of the thiourea sulfur by a variety of moieties leads to complete loss of *in vivo* activity. This data is included in the Experimental section on a *p*-acetylphenyl substituted urea, guanidine, pseudothiourea, pseudourea and, in addition, 1-*p*-pyridyl-3-*p*-ethoxycarbanilide.

The structural characteristics of the active alkoxythiocarbanilides have been developed and published by others independently.[1–5,8] The present study of thiocarbanilides will be restricted largely to those compounds which contain *para* in one ring a group characteristic of the active acylphenylthioureas and *para* in the other ring an alkoxy group. These compounds are listed in Table III. Such thiocarbanilides with simple acyl groups showed activity at the highest diet levels which is roughly comparable to that shown by the acylphenylalkylthioureas (compounds 167–173).

TABLE III: 4,4′-SUBSTITUTED THIOCARBANILIDES

No.	Substitution[a]	Reaction conditions[b] Concn.[c]	Solvent	Hours	M.p.,[d] °C.	Crystn.[b] solvent	Yield, %	Emp. formula	Nitrogen, % Found	Calcd.	*In vitro*[e] Mg. %	Rating	*In vivo*[f] (Diet concn.)
167	4-*n*-Butoxy-4′-acetyl	68	EtOH	0.3	165–166	EtOH	51	$C_{19}H_{22}N_2O_2S$	8.03	8.18	0.04	[++	(0.5)]
168	4-Ethoxy-4′-propionyl	65	EtOH	.3	186–187	Cel	41[g]	$C_{18}N_{20}N_2O_2S$	8.43	8.53	.16	+++	(.13)[z]
169	4-Butyryl-4′-ethoxy	34	EtOH	.3	173–175	EtOH	22[h,i]	$C_{19}H_{22}N_2O_2S$	8.30	8.18	.16	[+(+)	(.5)]
170	4-Butyryl-4′-*n*-butoxy	74	EtOH	2	175–176	*j*	12[k]	$C_{21}H_{26}N_2O_2S$	7.83	7.56	.16	[+	(.5)]
171	4-Ethoxy-4′-thenoyl	40	Diox	14	156–157	EtOH	*l*	$C_{20}H_{18}N_2O_2S_2$	7.33	7.17	.04	[++	(.5)]
172	4-Propylsulfonyl-4′-ethoxy	70	EtOH	3	165–167	EtOH	26	$C_{18}H_{22}N_2O_3S_2$	7.48	7.40	.08	[++	(.5)]
173	4-Butylsulfonyl-4′-ethoxy	36	EtOH	3	153–156	EtOH	23	$C_{19}H_{24}N_2O_3S_2$	7.31	7.14	.08	[++	(.25)]
174	4,4′-Diethoxy[m]				172–173						1.25	[++	(.1)]
175	4-Phenyl-4′-ethoxy				205–207[n]						0.04	++	(.5)
176	4-α-Pyridyl-4′-ethoxy	22	EtOH	0.7	164–165	EtOH	51[o]	$C_{20}H_{19}N_3OS$	12.28	12.03	.04	++++	(.13)
												+	(.03)
177	4-α-Pyridyl-4′-*i*-propoxy	18	EtOH	0.5	139–141	EtOH	51	$C_{21}H_{21}N_3OS$	11.86	11.56	.08	+++	(.125)
												+	(.03)
178	4-α-Pyridyl-4′-*n*-butoxy	19	EtOH	1	151–152	EtOH	54[p]	$C_{22}H_{23}N_3OS$	11.16	11.13	.02	+++	(.03–0.25)
												++	(.008)
179	4-α-Pyridyl-4′-*i*-butoxy	19	EtOH	1	149–150	EtOH	59	$C_{22}H_{23}N_3OS$	11.35	11.13	.08	+++	(.03–0.13)
												±	(.004)
180	4-*sec*-Butoxy-4′-α-pyridyl	13	MeOH	<0.1	131–133	80% MeOH	60	$C_{23}H_{23}N_3OS$	11.34	11.13	.16	++(+)	(.03)
												0	(.008)
181	4-α-Pyridyl-4′-*n*-amoxy	20	EtOH	0.5	136–137	75% EtOH	40[q]	$C_{23}H_{25}N_3OS$	10.53	10.73	.08	+++	(.03–0.13)
												0	(.008)
182	4-α-Pyridyl-4′-*i*-amoxy	20	EtOH	0.05	127–128	75% EtOH	59	$C_{23}H_{25}N_3OS$	10.71	10.73	.08	++	(.03–0.13)
												0	(.008)
183	4-β-Pyridyl-4′-ethoxy	10	EtOH	1	189–191	EtOH	43	$C_{20}H_{19}N_3OS$	11.87	12.03	.04	+++	(.03–0.25)
												+	(.008–0.016)
184	4-β-Pyridyl-4′-*n*-propoxy	11	EtOH	1	179–180	EtOH	38	$C_{21}H_{21}N_3OS$	11.69	11.56	.16	+++	(.25)
												0	(.004)
185	4-β-Pyridyl-4′-*n*-butoxy	11	EtOH	2	171–172	EtOH	21	$C_{22}H_{23}N_3OS$	11.16	11.13	..	++	(.13)
												0	(.004)
186	4-β-Pyridyl-4′-*n*-amoxy	12	EtOH	2.5	159–160	EtOH	19	$C_{23}H_{25}N_3OS$	10.54	10.73	.08	+++	(.01)
												±	(.015)
187	4-γ-Pyridyl-4′-ethoxy	10	EtOH	0.3	186–187	EtOH	39[r]	$C_{20}H_{19}N_3OS$	12.19	12.03	.04	+++	(.25)
												++	(.03)
188	4-γ-Pyridyl-4′-*n*-butoxy	8	[s]	1	157–158	EtOH	30	$C_{22}H_{23}N_3OS$	11.32	11.13	.02	+++	(.25)
												++	(.016)
189	4-Acetyl-4′-α-pyridyl	10	EtOH	<0.2	173–175	Cel	53[t]	$C_{20}H_{17}N_3OS$	11.99	12.10	.63	++++	(.5)
												+	(.06–0.12)
190	4-α-Pyridyl-4′-dimethylamino	35	EtOH	2	144–146	75% Diox	48	$C_{20}H_{20}N_4S$	16.20	16.08	.08	+	(.03–0.13)
191	4,4′-Di-α-pyridyl[u]	[u]	[u]	[u]	193–194	80% EtOH	[u]	$C_{23}H_{18}N_4S$	14.79	14.65	.31	+	(.1)
192	4-(γ-Pyridylmethyl)-4′-*n*-butoxy	27	MeOH	18[v]	105	[w]	77[x]	$C_{23}H_{25}N_3OS$[y]			.02	++	(.1)

[a] The first named component as the amine reacted with the second component as the isothiocyanate. [b] These compounds were made, with the exception of no. 191, by the reaction of amines with isothiocyanates usually by refluxing in the indicated solvent for the indicated times. These reactants are identified for each entry by a separate footnote. Except where specified the procedure is that given in the Experimental section. The abbreviations of solvents followed *Chemical Abstracts* where possible; the following also are

used: Cel = Cellosolve, Diox = dioxane, DMF = dimethylformamide, I = isoöctane. Percentage figures in the solvent columns refer to aqueous solvent mixtures. [c] The concentration is approximate only and gives the total weight of reactants per 100 ml. of solvent. [d] All melting points were determined in capillary tubes and are uncorrected. [e] Tuberculostatic end-point in mg. per 100 cc. of medium. See Experimental section. [f] Rated according to the increased survival time of animals treated at the given diet level compared to untreated controls. See Experimental section. [g] Crude yield 74%, m.p. 184–185°. [h] The reaction solution was concentrated to small volume and cooled for isolation. [i] Crude yield 44%, m.p. 174–176°. [j] The product was crystallized from a mixture 3 parts EtOH–2 parts Cellosolve. [k] Crude yield 34%, m.p. 168–170°. [l] Crude yield 47%, m.p. 151–153°. [m] See reference 1 of paper. [n] R. Q. Brewster and A. M. H. Horner, *Trans. Kansas Acad. Sci.*, **40**, 101 (1937); *C. A.*, **33**, 5374[8] (1939), m.p. 198°. [o] Crude yield 84%, m.p. 157–159°. [p] Crude yield 74%, m.p. 150–152°. [q] Crude yield 72%, m.p. 136–137°. [r] Crude yield 81%, m.p. 181–183° [s] 1–1 EtOH–benzene. [t] Crude yield 83%, m.p. 172–174°. [u] Preparation described in Experimental section. [v] Reaction mixture was held at room temperature. [w] Crystallized from acetone–isoöctane mixture at low temperatures to avoid dismutation. [x] Crude yield 97%, m.p. 104–106°. [y] Calcd.: C, 70.56; H, 6.39. Found: C, 70.59; H, 6.47. [z] Compound toxic at higher diet levels.

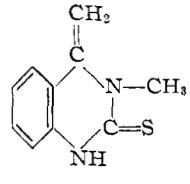
Thiocarbanilides of this type with a *p*-pyridyl substitution (compounds 176–188) show somewhat greater activity at the high diet levels than do the phenylalkylthioureas. However, they differ strikingly in that they exhibit substantial activity even at very low doses, and in this respect they resemble the thiocarbanilides reported by Huebner, *et al.*[1] Some of these compounds (notably 178 and 179) show distinct protective effects at diet levels as low as 0.004–0.008% (8–16 mg./kg./day). The three compounds, 189, 190 and 191 at the end of Table III illustrate that with the *p*-pyridyl thiocarbanilides a *p*-alkoxy group is not necessary for qualitative activity.

It is interesting to compare quantitatively the *in vivo* activity of the better *p*-acylphenylthioureas with that of the variously substituted thiocarbanilides. At very low doses the thiocarbanilides are much more active and increase the median survival time in mice to about the same extent as do comparable doses of streptomycin or isoniazid.[7] At somewhat higher doses the increase in survival shown by the thiocarbanilides approaches a maximum of *ca.* 25–40 days, compared to untreated controls, which is not surpassed even when the dosage is increased 20–50 times. Although the acylphenylalkylthioureas at roughly ten times the dose only begin to show minimal activity, they nevertheless at highest doses give prolongation of survival nearly equal to that shown by the best thiocarbanilides. This same maximum increase is also roughly that reached by PAS (*p*-aminosalicylic acid) at its highest tolerated doses.[9] The better acylphenylthioureas are roughly twice as active as PAS while the thiocarbanilides often are more than ten to twenty times as active as PAS based on the lowest doses needed to reach this common minimum dose response plateau. These thioureas and thiocarbanilides are thus comparable to PAS rather than to streptomycin or isoniazid which latter drugs at the higher doses give much greater prolongation of survival time (increases of 60 to 120 days are usual). These thiocarbanilides therefore are indicated as a substitute for PAS in its combination with either streptomycin or isoniazid in the treatment of tuberculosis. Extrapolation of the results in mice to this application in humans would lead one to expect that less than 1 g. of one of the pyridylalkoxythiocarbanilides could substitute for the 10–12 g. per day of PAS used at the present time.

The *in vitro* activity of the thiocarbanilides of Table III correlates well with their *in vivo* activity in that all of these very active compounds are highly inhibitory *in vitro*. However, with the phenylalkylthioureas of Tables I and II the correlation is not nearly as good. The *in vitro* data recorded in the tables refer to determinations in a simple medium. It is worth noting that contrary to our earlier expectations when serum is added to the medium the inhibitory concentrations obtained with these thioureas and thiocarbanilides correlate much more poorly with *in vivo* activity.[10]

With exception of compound 191 all of the new thioureas reported in the tables were made by reaction, usually in alcohol, of the appropriate amine and isothiocyanate. Prolonged refluxing generally was employed when aliphatic isothiocyanates were treated with weak aromatic amines; with the aromatic isothiocyanates the reaction time could be shortened drastically. With some of the latter, especially the *p*-acylphenylisothiocyanates, the reaction with even weak amines often was highly exothermic. Where alcohol was used as solvent doubtless urethan formation occurred in some instances with consequent loss in yield. For example, in an early attempt to prepare compound 100, employing *o*-nitrophenyl isothiocyanate with methylamine in alcohol, only the urethan[11] was isolated. Another important cause of decreased yield where prolonged refluxing is needed could be the dismutation of the thiourea originally produced. This dismutation may be surprisingly facile with some thiocarbanilides. Indeed, the first attempt to prepare *p*-(γ-pyridylmethyl)-*p'*-butoxythiocarbanilide (compound 192) failed entirely. The product actually isolated was bis-*p*-butoxy thiocarbanilide.[1] In this first trial the reactants were refluxed in alcohol for five hours and the product crystallized from hot alcohol. When the reaction and crystallization were conducted at room temperature this dismutation was prevented and a 77% yield of expected product was obtained.

When methyl isothiocyanate was allowed to react with *o*-aminoacetophenone the expected thiourea was not formed. Instead, a product was isolated which appears to be derived from the thiourea by loss of one molecule of water. On the basis of its analysis and spectrum this product has been assigned the provisional structure



The aliphatic isothiocyanates used to prepare the compounds of Tables I and II, when not commercially available, were made by the action of

(11) G. M. Dyson and D. W. Browne, *J. Chem. Soc.*, 3285 (1931).

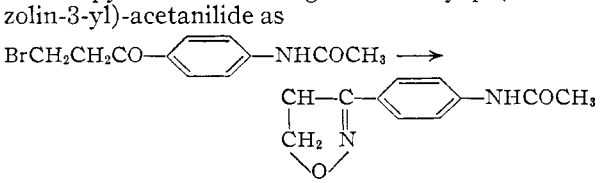
lead acetate on the corresponding sodium dithiocarbamates following closely the procedure of Delepine.[12] The aromatic isothiocyanates were made either by a modification of the foregoing procedure or by reaction of the amine salts with thiophosgene.[13] The thiophosgene was used directly[14] or indirectly by reaction *in situ* of trichloromethanesulfenyl chloride with stannous chloride.[15] In our adaptation of this last modification the laborious steam distillation was avoided and the product was extracted in equally good yield directly from the reaction mixture by ether.

The ureas, pseudothioureas, pseudoureas and guanidines used to evaluate the effect of the thiourea sulfur atom on activity were prepared by standard methods. Particularly facile was the route through *p*-acetylphenyl methyl carbodiimide which is an easily prepared crystalline compound. Also standard and described by typical conditions in the Experimental section are the preparations of the oximes, hydrazones and semicarbazones of the active acylphenylthioureas.

The majority of the acylanilines needed in the preparation of these thioureas were prepared by reaction of acid chlorides with acetanilide in nitrobenzene solution following principally the procedure of Kunckell.[16]

α-*p*-Nitrophenylpyridine needed for the amino compound was prepared by nitration of α-phenylpyridine and separation from isomers.[17] The corresponding β- and γ-isomers were prepared from the nitro compounds resulting by the action of *p*-nitrobenzene diazonium chloride on pyridine by the method of Haworth.[18,19]

Oximation of *p*-acetamino-β-bromopropiophenone in pyridine solution gave directly *p*-(2-isoxazolin-3-yl)-acetanilide as



This product on hydrolysis gave the amine which was allowed to react with methyl isothiocyanate to give the thiourea (compound 71). The structure of this compound is assumed on the basis of its analysis and ultraviolet spectrum.

Experimental

All melting points uncorrected.

Biological Test Methods.—The *in vitro* tuberculostatic concentration is judged to be that lowest concentration of the compound which in a simple synthetic medium at 37° prevents the growth of the human virulent H37Rv strain of tubercle bacillus for fourteen days. In the test, beginning with 10 mg. % (10 mg. per 100 ml.), each succeeding concentration is formed from the next higher by the addition of an equal volume of plain medium. Thus the test levels run 10, 5, 2.5, 1.25, 0.625, 0.312, etc. To save space, these numbers as they appear in the tables have been rounded off to the smallest number which will indicate its position in this serial dilution set. In general, our experience indicates that the end point for any given compound is reproducible only to within one place in this dilution set.

For *in vivo* testing each compound was administered in the diet to mice infected with the H37Rv strain. An increase in the median survival time of treated animals compared with infected controls was taken as a measure of the antituberculous activity of the compound. This activity expressed in days increase in survival time is coded in the table as: 0 = <2 days, ± = 2 to <5 days, + = 5 to <11 days, ++ = 11 to <21 days, +++ = 21 to <31 days, ++++ = 31 to <41 days.

Each entry in the *in vivo* column of the tables consists of two parts. The first part under "rating" is the evaluation symbol corresponding to the maximum survival obtained. The second entry, in parentheses under "diet concn.," lists the diet level(s) (in per cent.) giving this result. When a single figure occurs in the diet column it refers to the highest non-toxic diet level used. When a single figure occurs but the entire activity entry is enclosed in brackets, this signifies that the evaluation rests upon only one experiment. Comparison with other compounds in these instances is limited since it is not known how variation in dose would affect activity. With the remaining active compounds the two figures following the evaluation symbols refer, respectively, to the lowest and highest diet concentrations which cover the entire range where the given evaluation holds.

The diet levels in these experiments usually represent a serial dilution set whose individual concentrations are related as described above for the *in vitro* tests. These numbers have been rounded off and each occurs in the tables as the smallest number which indicates its relative position.

At the risk of being superficial this summary of the biological methods and their interpretation has been held to the barest minimum consistent with following the structure–activity argument of this paper. The reader is urged to consult the companion paper of this series[7] and previous papers for a fuller grasp of this subject.[8-10]

Type Reaction of Isothiocyanates with Amines.—The amine and the isothiocyanate used for each compound is indicated in the tables. In Table I this is signified by a footnote for each entry. In Tables II and III the portion of the name corresponding to the amine is placed first while that corresponding to the isothiocyanate is placed second for each compound.

The amine and isothiocyanate, generally in equimolar ratio, usually were refluxed in a solvent for one to several hours. The particular solvent and number of hours are entered for each compound in the "solvent" and "hours" column, respectively. The approximate total weight of reactants per 100 ml. of solvent is given in the "concentration" column. Generally the product was filtered off after the reaction mixture was cooled in an ice-bath to *ca.* 5°. The crude product was crystallized to constant melting point from the designated solvent. The indicated yields were calculated from this final crystallized product and are often much lower than the crude yields because of purification losses. Departures from this scheme are given by appropriate footnotes. Compound 191, bis-*p*-α-pyridylthiocarbanilide, was made by the method given separately below. Also given separately below are the four thioureas 15, 16, 17 and 18 whose preparations depart widely from the type reaction.

1-*p*-Acetylphenyl-3-carboxymethyl-2-thiourea (No. 15).—To 4.23 g. of glycine (0.056 mole) in 10 ml. of water was added 5.7 ml. of 10 *N* sodium hydroxide followed by 10.0 g. of *p*-acetylphenyl isothiocyanate (0.056 mole) dissolved in 30 ml. of abs. alcohol. This mixture was warmed under reflux on a steam-bath for one hour and then chilled overnight. The reaction mixture was acidified with 4.8 ml. of concd. hydrochloric acid (0.057 mole) dissolved in 100 ml. of water. The product was filtered off (m.p. 178–181°) and purified three times in succession by dissolving it in dilute aqueous potassium bicarbonate, adding charcoal (Darco G60), filtering, and reprecipitating from the filtrate with hydrochloric acid. This gave a white product, m.p. 178–179° dec., yield 3.1 g. (22%).

1-*p*-Acetylphenyl-3-β-carboxyethyl-2-thioureas (No. 16).—β-Alanine and *p*-acetylphenyl isothiocyanate in the same

(12) M. M. Delepine, *Compt. rend.*, **144**, 1126 (1907).

(13) F. B. Dains, R. Q. Brewster and C. P. Olander, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 447.

(14) F. Arndt and B. Rosenau, *Ber.*, **60**, 1255 (1917).

(15) J. M. Connolly and G. M. Dyson, *J. Chem. Soc.*, 681 (1935).

(16) F. Kunckell, *Ber.*, **33**, 2642 (1900).

(17) R. Forsyth and F. L. Pyman, *J. Chem. Soc.*, 2912 (1926).

(18) J. W. Haworth, I. M. Heilbron and D. H. Hey, *ibid.*, 349 (1940).

(19) Mr. Theodore Sulkowski of the Parke, Davis and Co. Product Development Department prepared the β- and γ-compounds for this work. We are glad to acknowledge our indebtedness to him for this contribution.

molar quantities were treated as the preceding glycine derivative. The crude product melted at 160–164° (efferv.) and after two precipitations from bicarbonate solution with acid as above gave a white solid, m.p. 167–168° dec., yield 4.9 g. (33%).

1-*p*-Acetylphenyl-3-ω-carboxyamyl-2-thiourea (No. 17).—As in the preceding examples, ε-aminocaproic acid and *p*-acetylphenyl isothiocyanate in 0.033-mole quantities were allowed to react. The isolation was done similarly except that the reaction mixture was concentrated to half-volume and cooled in an ice-bath before acidification. The crude product (m.p. 162–164°) was recrystallized from alcohol to give a light yellow solid, m.p. 162–164°, yield 6.2 g. (61%).

1-*p*-Acetylphenyl-3-α-carboxy-γ-methylthiopropyl-2-thiourea (No. 18).—To 14.9 g. of methionine (0.1 mole) dissolved in 25 ml. of water by the addition of 10 ml. of 10 *N* sodium hydroxide was added 17.7 g. of *p*-acetylphenyl isothiocyanate followed by 50 ml. of absolute alcohol. This mixture was refluxed for 1 hour and chilled for 20 days. The brown solid which had separated (presumably the sodium salt) was collected by filtration and was treated with 300 ml. of 3 *N* hydrochloric acid followed by a water wash. This product was purified twice by dissolution and precipitation as in the glycine example above, m.p. 185–187°, yield 16.0 g. (49%).

***p,p'*-Bis-α-pyridylthiocarbanilide (No. 192).**—2-*p*-Aminophenylpyridine (17.0 g., 0.1 mole), 0.9 g. of potassium ethyl xanthate (0.006 mole) and 7.6 g. of carbon disulfide (0.1 mole) in 60 ml. of absolute alcohol were refluxed for two hours. The yellow solid was filtered off, washed with water and dried yielding 12.0 g. (63%) of crude product, m.p. 188–190°. On crystallization from aqueous ethanol and drying at 85° at 20 mm. the purified product was obtained, m.p. 193–194°.

Anal. Calcd. for $C_{23}H_{18}N_4S$: N, 14.65. Found: N, 14.79.

Oximes in Table II (Nos. 59, 60, 61, 62, 63, 64, 65, 66 and 67).—The parent thioureas were refluxed 0.5 to 1 hour in approximately 50% aqueous alcohol with a slight excess of hydroxylamine hydrochloride (buffered with excess sodium acetate). The product was filtered off after strongly cooling the reaction mixture (except the reaction mixture of 59 was diluted first with water). The crude product was crystallized (or purified) as described in Table II; the yields cited refer to the purified products. The weight of carbonyl compound per 100 cc. of original reaction solvent for each case follows with the compound number listed first and followed by the concentration: 59, 14; 60, 10; 61, 10; 62, 35; 63, 50; 64, 29; 65, 29; 66, 50; 67, 17.

Hydrazones in Table II (Nos. 68, 69 and 70).—These derivatives were prepared by the method used for the oximes. In each case the carbonyl compound reacted at the concentration of 10 g. per 100 cc. of solvent. For 68, free acetylhydrazine was employed, the solvent was absolute alcohol and the reflux time was one hour. For 69, phenylhydrazine hydrochloride plus sodium acetate was used in 50% aqueous alcohol and the reflux time was *ca.* 10 minutes. For 70, semicarbazide hydrochloride plus sodium acetate in 75% aqueous alcohol was used and the reflux time was *ca.* 5 minutes.

Aliphatic Isothiocyanates.—Methyl, ethyl, allyl, butyl and heptyl isothiocyanates were obtained from commercial sources. Propyl and isobutyl isothiocyanates were made by the action of lead acetate on the sodium dithiocarbamates closely following the procedure of Delepine.[12] Isopropyl isothiocyanate was prepared by a similar procedure.

Aromatic Isothiocyanates *via* Thiophosgene or Congeners.—*o*-Nitrophenyl isothiocyanate was prepared by the direct action of thiophosgene on *o*-nitroaniline.[14] *p*-Acetylphenyl- and *p*-ethoxyphenyl isothiocyanates were prepared by a modification of this method whereby thiophosgene is formed *in situ* by the action of stannous chloride on trichloromethanesulfenyl chloride.[15] However, the product was isolated by extracting the reaction product with ether instead of distilling it out with steam. This is illustrated in the following procedure for making *p*-propionylphenyl isothiocyanate.

A solution of 29.9 g. of *p*-aminopropiophenone (0.2 mole) in 535 ml. of 11.7 *N* hydrochloric acid and 1040 ml. of water was treated with 166.9 g. of stannous chloride dihydrate (0.74 mole). The resulting solution was strongly stirred (mechanically) as 80 g. of trichloromethanesulfenyl chloride (47.3 ml., 0.43 mole) was added dropwise. After stirring at room temperature for 16 hours the entire reaction mixture was extracted repeatedly with ether. Evaporation of the combined ether extracts gave a yellow solid, m.p. 60–62°. Crystallization of this material from isoöctane yielded 22.0 g., 58%, of *p*-propionylphenyl isothiocyanate, m.p. 64–65°.

Anal. Calcd. for $C_{10}H_9NOS$: N, 7.33. Found: N, 7.35.

p-Butyrylphenyl isothiocyanate was prepared similarly using *p*-aminobutyrophenone, yield 35%, m.p. 37°. *p*-Methylsulfonylaniline in this procedure gave *p*-methylsulfonyl isothiocyanate, m.p. 136–137°, in 26% yield after numerous ether extractions because of the slight solubility of the product in ether. The identity of both of these isothiocyanates was established by preparation of analyzed derivatives (nos. 41, 44 and 81).

Aromatic Isothiocyanates *via* Dithiocarbamates.—Adapting closely the usual conditions for treating carbon disulfide with amines and desulfurizing the product with lead salts (lead acetate was substituted for the nitrate)[13] the following phenyl isothiocyanates were prepared from the proper amines: *p*-*n*-propoxy, *p*-*n*-butoxy, *p*-isobutoxy, *p*-isoamyloxy,[20] *p*-amyloxy (65% yield, b.p. 203–205° (25 mm.) Calcd. for $C_{12}H_{15}NO_5$: C, 65.12; H, 6.83. Found: C, 65.16; H, 7.11), *p*-isopropoxy (75% yield, b.p. 170–172° (26 mm.). Calcd. for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74. Found: C, 62.29; H, 6.06) and *p*-α-pyridyl (29% yield, m.p. 50–51°. Calcd. for $C_{12}H_8N_2S$: N, 13.20. Found: N, 12.88, 12.72).

The following procedure for the preparation of *p*-dimethylaminophenyl isothiocyanate is a distinct improvement (65% yield compared to 13%) over the published directions.[13]

Add 20 ml. of 10*N* sodium hydroxide (0.2 mole) to a solution of 34.5 g. (0.2 mole) of *p*-aminodimethylaniline hydrochloride in 150 ml. of water. This was then added slowly to a cooled (<10°) and mechanically stirred mixture of 19 g. of carbon disulfide (0.25 mole) and 22 ml. of 10 *N* sodium hydroxide. The mixture was stirred for one hour without further cooling and 300 ml. of water was added. The reaction was treated with 76 g. of lead acetate trihydrate (0.2 mole) in 300 ml. of water. After standing for one hour the mixture was heated at 70° for 20 minutes. The lead sulfide precipitate was filtered off from the cooled reaction mixture and suspended in water (*ca.* 10% suspension). The solution was adjusted approximately to *p*H 8 with 10 *N* sodium hydroxide. This basic suspension was extracted successively three times with ether using a combination of filtration and decantation to separate the ether. The combined ether extracts were washed with water and dried with magnesium sulfate. Evaporation of the ether gave 25.5 g. of yellow solid, m.p. 69–71°. Crystallization of this material from isoöctane gave 23.0 g. (65%) of product, m.p. 69–71°.[21]

1-*p*-Acetylphenyl-3-methylcarbodiimide.—Desulfurization of 1-*p*-acetylphenyl-3-methyl-2-thiourea with yellow mercuric oxide in refluxing benzene in a close adaptation of the method of Weith[22] gave a 79% yield of product, m.p. 59–61°.

Anal. Calcd. for $C_{10}H_{10}N_2O$: N, 16.02. Found: N, 16.27.

1-*p*-Acetylphenyl-2-ethyl-3-methylguanidine.—The above carbodiimide reacted with aqueous ethylamine to give the product, m.p. 116–117° (from benzene).

Anal. Calcd. for $C_{12}H_{17}N_3O$: N, 19.20. Found: N, 18.73; activity, *in vitro*, >10 mg. %; *in vivo*, inactive at 0.5%.

1-*p*-Acetylphenyl-2-butyl-3-methyl-2-pseudothiourea.—The above carbodiimide, refluxed in benzene for 5 hours with butyl mercaptan gave the product, purified by dissolution in acid and precipitation with alkali, yield 52%, m.p. 49–52°.

Anal. Calcd. for $C_{14}H_{20}N_2OS$: N, 10.60. Found: N, 10.50; activity, *in vitro*, 5.0 mg. %; *in vivo*, inactive at 0.5%.

1-*p*-Acetylphenyl-2-ethyl-3-methyl-2-pseudourea.—The above carbodiimide (8.7 g., 0.05 mole) was treated below 5° with an excess of sodium ethoxide (from 1.3 g. of sodium) in ethanol (50 ml.) and the solution allowed to stand at room temperature overnight. Solid carbon dioxide was added to the alcoholic solution which was then poured into 4 volumes of water. The resulting solid was extracted into ether and

(20) C. F. Huebner and C. R. Scholz, U. S. Patent 2,686,806.

(21) G. M. Dyson, H. J. George and R. F. Hunter, *J. Chem. Soc.*, 442 (1927).

(22) W. Weith, *Ber.*, **7**, 10 (1874).

the ether solution dried with magnesium sulfate. Evaporation of the ether left 8.4 g. of product, m.p. 110–112° (76% yield). This solid was crystallized from ethanol, m.p. 113–115°.

Anal. Calcd. for $C_{12}H_{16}N_2O_2$: N, 12.75. Found: N, 12.92; activity, *in vitro*, >10 mg. %; *in vivo*, inactive at 0.5%.

N-*p*-Acetylphenylcarbamyl Chloride.—*p*-Aminoacetophenone was substituted for *p*-nitroaniline in the reaction with phosgene after the procedure of Shriner, Horne and Cox for *p*-nitrophenyl isocyanate.[23] At the stage where approximately two-thirds of the ethyl acetate had been removed the orange-yellow carbamyl chloride precipitated. The product was filtered off and dried *in vacuo* over phosphorus pentoxide. No attempt was made to recrystallize this highly unstable substance; it melted at 107–108° and contained 7.73% N, calcd. for C_9H_8ClNO, 7.09%. This product was used without purification in the following reaction.

1-*p*-Acetylphenyl-3-methylurea.—The above carbamyl chloride in ether solution was allowed to react with an excess of 40% aqueous methylamine. The pale yellow solid which formed was collected and crystallized twice in succession from dioxane, m.p. 182–184°.

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: N, 14.58. Found: N, 14.33 (av.); activity, *in vitro*, 5.0 mg. %; *in vivo*, inactive at 0.5%.

***p*-Ethoxy-*p'*-α-pyridylcarbanilide.**—*p*-Ethoxyphenyl isocyanate and α-*p*-aminophenylpyridine were combined in a warm benzene solution; yield of product 83% after crystallization from Cellosolve, m.p. 229–230°.

Anal. Calcd. for $C_{20}H_{19}N_3O_2$: N, 12.60. Found: N, 12.49; activity, *in vitro*, 0.3 mg. %; *in vivo*, inactive at 0.5%.

Substituted Aniline Intermediates.—*p*-Aminoacetophenone, *p*-aminopropiophenone and *p*-aminobenzophenone were commercial samples. *p*-Aminobutyrophenone,[16] *p*-aminovalerophenone,[24] *p*-aminocaprophenone[24] and *p*-aminocaprylophenone,[25] were prepared by adaptation of the procedure of Kunckell.[16] Both *p*-[26] and *m*-thenoylaniline were prepared by reduction of the nitro compounds which in turn were obtained by this same procedure applied to the respective nitrobenzoyl chlorides and thiophene. *m*-Thenoylaniline, m.p. 104–105°, crystallized from ethanol, was identified by conversion to the analyzed thiourea, compound 51.

p-Isonicotinylaniline and *p*-picolinylaniline were prepared by oxidation of the *p*-nitrobenzylpyridines to the ketones, followed by reduction of the nitro compounds to amines.[27,28]

p-Methyl-, *p*-ethyl-, *p*-propyl- and *p*-butylsulfonylanilines[29] were prepared by treating sodium *p*-acetamidophenyl sulfinate with the proper halide[30] and hydrolyzing the resulting sulfone to the free amine with 3 *N* hydrochloric acid.

p-Propoxy-,[31] *p*-isopropoxy-,[32] *p*-butoxy-, *p*-isobutoxy- and *p*-isoamoxyanilines[33] were prepared by the method of Büchi, *et al.*,[32] substituting a 20-hour hydrolysis in aqueous alcoholic dilute sodium hydroxide for the acid hydrolysis. *p*-*n*-Amoxyaniline also was prepared by this method, b.p. 174–176° (26 mm.), $n^{28}D$ 1.5271.

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.82. Found: C, 73.49; H, 9.74; N, 7.80.

The isomeric *p*-aminophenylpyridines were obtained by reducing the corresponding *p*-nitrophenylpyridines which, in turn, were obtained by treating diazotized *p*-nitroaniline with pyridine.[18] The separation of the isomeric α- and β-*p*-nitropyridines from the mixture was successful following the method of Forsyth and Pyman.[17,19] However, attempts to obtain the γ-isomer from the remaining isomer mixture by this method failed. When the remaining isomer mixture was reduced to the mixed *p*-aminophenylpyridines the γ-isomer, which is rather insoluble in ethanol, could be easily separated by crystallization of the mixture from this solvent.

α-*p*-Aminobenzoyl Diethyl Malonate.—Crude α-*p*-nitrobenzoyl diethyl malonate was reduced in alcohol solution with hydrogen using Adams catalyst. The product, after dissolution in acid, filtration from insoluble material and reprecipitation with alkali, was crystallized from ethanol, m.p. 94–96°.

Anal. Calcd. for $C_{14}H_{17}NO_5$: N, 5.02. Found: N, 5.08.

The requisite α-*p*-nitrobenzoyl diethyl malonate[34] was obtained using the Walker and Hauser[35] procedure but employing chlorobenzene as the solvent as suggested by Long and Troutman.[36] The crude nitro compound present after removal of the chlorobenzene was dissolved in ether and washed with dilute potassium bicarbonate and then with water. The oil remaining after removal of the ether was dissolved in alcohol and treated with charcoal. This filtered solution was used in the above reduction. The yield of amino product from crude nitro compound was *ca.* 36%.

4-Acetamido-β-bromopropiophenone.—To 135 g. (0.792 mole) of β-bromopropionyl chloride[37] (b.p. 53.5–57° (8–9 mm.)) and 46.1 g. (0.34 mole) of finely ground acetanilide in 500 ml. of carbon disulfide which was stirred vigorously mechanically was added, as reaction permitted (*ca.* 2.5 hr.), 147 g. (1.1 moles) of anhydrous aluminum chloride. The mixture was stirred under reflux for 3 hours and then *ca.* 16 hours at room temperature. The aluminum chloride layer was separated and decomposed in approximately 4 l. of cracked ice containing 300 ml. of concd. hydrochloric acid. The solid was collected, washed with cold water and dried over phosphorus pentoxide *in vacuo* for 3 days. This gave 80.3 g. of crude product (87%); subsequent runs gave as high as 98% yield at this stage. Purification of this unstable compound proved difficult; the following procedure gave the best results of several methods tried. The finely ground crude product thoroughly mixed with 10 g. of activated charcoal was extracted in a Soxhlet apparatus with boiling benzene. Concentration and cooling of the benzene extract gave successive crops totaling 64.2 g. (69.7% based on acetanilide), m.p. 139–143°. A sample was crystallized twice successively from benzene, m.p. 141–142°, λ_{max} 287.5 mμ, E^1_1 780 in chloroform (compare λ 283.5, E^1_1 1155 for 4-acetamidoacetophenone).

Anal. Calcd. for $C_{11}H_{12}BrNO_2$: N, 5.19. Found: N, 5.34.

***p*-(2-Isoxazolin-3-yl)-acetanilide.**—A mixture of 54 g. (0.2 mole) of 4-acetamido-β-bromopropiophenone and 13.3 g. (0.22 mole) of hydroxylamine hydrochloride in 400 ml. of dry pyridine, after stirring for 4 hours, was refluxed for 2 hours. The pyridine was removed under reduced pressure on the steam-bath and the red-brown residue was extracted with water which left a dark yellow crystalline solid. The aqueous extract was made strongly basic with sodium hydroxide and the separated solid collected by filtration, washed with water and combined with the preceding solid. The crude product was dried *in vacuo* at 60°, yield 15.1 g. This product was extracted four times with successive 100-ml. portions of chloroform. The combined extracts were treated with activated charcoal and filtered. The filtrate was concentrated for successive crops of product and the combined acceptable crops were recrystallized from benzene; yield 12.4 g. (30.4%), m.p. 205.5–207.5°, λ_{max} 285.5, E^1_1 1125 in chloroform.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.82; H, 5.90; N, 13.80.

***p*-(2-Isoxazolin-3-yl)-aniline.**—*p*-(2-Isoxazolin-3-yl)-acetanilide (33 g.) was refluxed in 1.5 l. of 2 *N* hydrochloric acid

(23) R. L. Shriner, W. H. Horne and R. F. B. Cox, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 453.

(24) N. Sugimoto, J. Iwao and H. Kakemi, *J. Pharm. Soc. Japan*, **71**, 1161 (1951); *C. A.*, **46**, 5011*f* (1952).

(25) Made by method of Kunckell except that a 4-hour reflux in equal parts glacial acetic acid and 6 *N* hydrochloric acid was used for hydrolysis. This product, m.p. 100–102°, was used without further characterization to prepare the thiourea.[16]

(26) F. Marschall, U. S. Patent 2,651,640, Sept. 8, 1953.

(27) E. Koenigs, H. Mensching and P. Kirsch, *Ber.*, **59B**, 1717 (1926).

(28) A. E. Tschitschibabin, B. M. Kuindshi and S. W. Benewolenskaja, *ibid.*, **58B**, 1580 (1925).

(29) W. R. Waldron and E. E. Reid, THIS JOURNAL, **45**, 2406 (1923).

(30) H. Gilman and A. Lindblad, *ibid.*, **68**, 982 (1946).

(31) L. Spiegel and S. Sabbath, *Ber.*, **34**, 1938 (1901), give m.p. of hydrochloride salt, our free base gave b.p. 153–155° (26 mm.).

(32) J. Büchi, G. Lauener, L. Ragaz, H. Böniger and R. Lieberherr, *Helv. Chim. Acta*, **34**, 282 (1951).

(33) G. Gutekunst and H. Gray, *ibid.*, **44**, 1743 (1922).

(34) C. L. Jackson and F. C. Whitmore, *ibid.*, **37**, 1930 (1915).

(35) H. G. Walker and C. R. Hauser, *ibid.*, **68**, 1387 (1946).

(36) L. M. Long and H. D. Troutman, *ibid.*, **71**, 2472 (1949).

(37) Prepared in 85% yield from 2-bromopropionic acid with thionyl chloride rather than with phosphorus trichloride as described by C. S. Hamilton and C. L. Simpson, *ibid.*, **51**, 3158 (1929).

for 0.5 hour and the solution, after cooling and filtering, was made basic to phenolphthalein with 10 *N* sodium hydroxide. The crude product resulting was crystallized twice from isooctane (with charcoal decoloration); yield 20.0 g., m.p. 190.5–191.5°, λ_{max} 295 mμ, E^1_1 1184 in ethanol.

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.28. Found: C, 66.67; H, 6.29; N, 17.23, 17.32.

3,4-Dihydro-3-methyl-4-methylene-2,1(H)quinazolinethione (Provisional Identification).—A solution of 10 g. of *o*-aminoacetophenone[38] (0.074 mole) and 5.4 g. of methyl isothiocyanate (0.074 mole) in 40 ml. of ethanol was refluxed 3 hours. The product, which began separating after approximately 1.5 hours, was collected and dried. A yield of 7.7 g. (50%) of crude product, m.p. 215–218°, was obtained. A sample for analysis, obtained by crystallization successively from ethanol, 1-1 ethanol-Cellosolve and ethanol, melted at 223–225°.

(38) N. J. Leonard and S. N. Boyd, Jr., *J. Org. Chem.*, **11**, 409 (1946).

Anal. Calcd. for $C_{10}H_{19}N_2S$: C, 63.12; H, 5.30; N, 14.73; S, 16.85. Found: C, 62.79, 62.74; H, 5.51, 5.54; N, 14.78; S, 16.62, 16.66.

The infrared spectrum (KBr disk) exhibits a band at 6.05 μ characteristic of a carbon–carbon double bond and a bond at 3.09 μ for a N–H band. In the ultraviolet the compound absorbs in three regions: λ_{max} 279 mμ, E^1_1 1344; λ_{max} 240 mμ, E^1_1 663; λ_{max} 215, E_1' 338 in ethanol.

Acknowledgment.—We wish to thank Mr. Charles Childs and co-workers for the microanalyses; Mr. Bruce Scott, Dr. J. M. Vandenbelt and co-workers for the ultraviolet and infrared determinations; and Mr. Richard Kavanaugh for technical help in the performance of the *in vivo* tests.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

Amine Oxides. Cyclic Quaternary Salts and their Decomposition[1]

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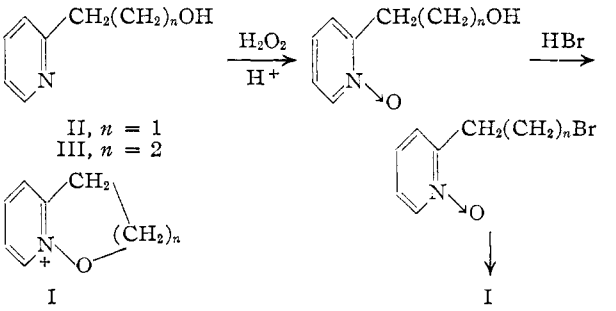
The synthesis of 2,3-dihydro-4H-oxazino[2,3-a]pyridinium bromide (IV) and its alkaline decomposition to 2-vinylpyridine and formaldehyde is described. The preparation of 2,3-dihydroisoxazolo[2,3-a]pyridinium bromide (VI) also is given but its alkaline decomposition yields products of unknown structure. The quaternization of 2-(β-bromoethyl)-pyridine results in dimerization and the product has structure XI rather than the simple azobicycloöctane structure previously assigned by Löffler.

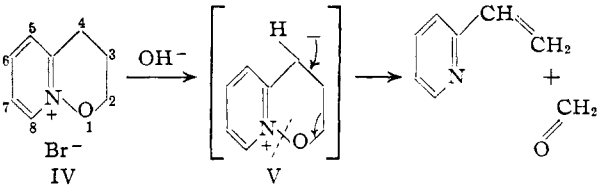
Since the time of Meisenheimer's experiments on quaternary salts of amine oxides,[3] it has been known that the decomposition of such salts would yield aldehydes. Although the yield of aldehyde obtained from such decompositions usually is poor, recent work has demonstrated that under the proper circumstances the yield of aldehydes may be quite high and the reaction may have general usefulness in preparative work.[4] A possible extension of this method would be the introduction of a carbonyl function into the side chain of simple pyridine derivatives. With this in mind we undertook to synthesize and study the properties of some simple cyclic quaternary salts of pyridine-N-oxide as shown by I.

The synthesis of the simple salts corresponding to I, where *n* was 1 and 2, followed in a straightforward fashion. As shown below, the commercially available alcohols 2-(β-hydroxyethyl)-pyridine (II) and 2-(γ-hydroxypropyl)-pyridine (III) were oxidized to the corresponding N-oxides, these were converted to the bromides with hydrobromic acid, and the bromides readily cyclized to the desired quaternary salts.

In support of the assigned structures it was found that catalytic hydrogenation of 2,3-dihydro-4H-oxazino[2,3-a]pyridinium bromide (IV) over Adams catalyst gave the crystalline hydrobromide of 3-(2′-piperidyl)-propan-1-ol. This was identical in all respects with an authentic sample prepared by the hydrogenation of III. Likewise, catalytic hydrogenation of 2,3-dihydroisoxazolo[2,3-a]pyridinium bromide (VI) gave the hydrobromide of 2-(2′-piperidyl)-ethanol, identical in all respects with a sample prepared by the hydrogenation of II.



When these cyclic salts were treated with alkali, reaction occurred readily, but the products were not the expected pyridine aldehydes. Instead, the aqueous alkaline decomposition of IV gave 2-vinylpyridine in 85% yield. If it is presumed that the first stage is the removal of a proton at the 4-position to give V, it becomes understandable how the formation of 2-vinylpyridine could readily occur with accompanying elimination of formaldehyde. When the aqueous solution from the reaction was steam distilled, formaldehyde was isolated from the distillate as its dimedon derivative.



(1) This investigation was aided by a grant from the National Science Foundation.

(2) Union Carbide and Carbon Predoctoral Fellow, 1955–1956.

(3) J. Meisenheimer, *Ann.*, **397**, 273 (1913).

(4) W. Feely, W. L. Lehn and V. Boekelheide, *J. Org. Chem.*, **22**, 1135 (1957).