TABLE II
5H-THIAZOLO[2,3-b]QUINAZOLIN-5-ONE-DERIVATIVES (VI)

Sl. no.	2-Chloro-5-methylthiazole derivative	(VI): X[a]	Yield, %	M.p., °C.	Molecular formula	Analysis Calcd., %	Analysis Found, %
1.	4-(*p*-Bromo-phenyl)	Br	30	184–58	$C_{17}H_{11}BrN_2OS$	N, 7.54	7.7
						Br, 21.54	Br, 21.7
2.	4-Phenyl	H	43	210	$C_{17}H_{12}N_2OS$	N, 9.58	9.40
						S, 10.96	S, 11.50
3.	4-(*p*-Chloro-phenyl)	Cl	45	145	$C_{17}H_{11}ClN_2OS$	N, 8.54	8.7
						S, 9.81	S, 10.00
4.	4-(*p*-Tolyl)	CH_3	22	172	$C_{18}H_{14}N_2OS$	N, 9.15	9.25
						S, 10.45	10.60
5.	4-(4-Ethylphenyl)	C_2H_5	15	178	$C_{19}H_{16}N_2OS$	N, 8.75	8.90
						S, 10.0	10.2

[a] Recrystallized from dilute ethanol.

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The Synthesis of Halogenated Tuberculostatic Thiocarbanilides

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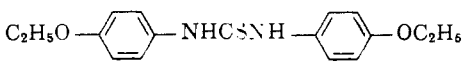
Numerous publications have shown that the class of thiocarbanilides (N,N′-diarylthioureas) bearing alkoxy groups includes very potent antimycobacterial agents.[1] Several such compounds are now in current use in human therapeutics: 4,4′-diethoxythiocarbanilide (I) and 4-butoxy-4′-dimethylaminothiocarbanilide in the treatment of leprosy,[2] and 4,4′-diisoamyloxythiocarbanilide in the treatment of tuberculosis.[3] Further,



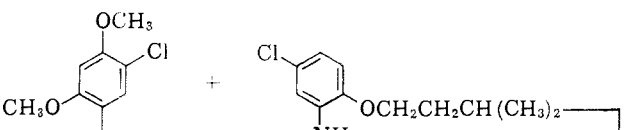
I

II

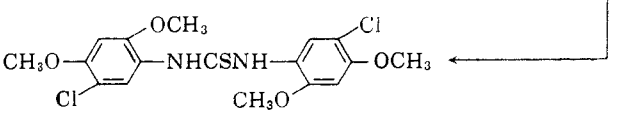
several thiocarbanilides bearing halogen substituents, such as 3,5-dichloro-4′-fluorothiocarbanilide (II), have shown considerable fungistatic properties, both experimentally and in clinical practice.[4] It was therefore logical to proceed to the synthesis of thiocarbanilides bearing at the same time halogen and alkoxy substituents, and to investigate their activity with regard both to mycobacteria and to pathogenic fungi.

The synthesis of symmetrical thiocarbanilides was effected by condensation of the appropriate halogenated mono- or dialkoxyaniline with carbon disulfide in the presence of small amounts of sulfur or potassium hydroxide (Hugershof reaction).[5] This reaction was found to be sensitive to steric hindrance, and the presence of bulky substituents *ortho* to the amino group led to yields that were distinctly lower than normally observed; the presence of nitro groups inhibited the reaction, and 2-amino-5-nitroanisole and 4-amino-3-nitroanisole failed to give condensation products under normal experimental conditions. Similar observations had already been made with the nitroanilines,[5] and with 5-nitro-2-aminothiazole.[6]

Unsymmetrical thiocarbanilides (Table I) were obtained from the reaction of the appropriate arylamine and aryl isothiocyanate; the isothiocyanates were prepared by treatment of symmetrical thiocarbanilides (Table II) with acetic anhydride (Werner reaction). The condensation of arylamines with aryl isothiocyanates was also found to be sensitive to steric hindrance; for instance, 5-chloro-2,4-dimethoxyphenyl isothiocyanate (III) reacted with 5-chloro-2-isoamyloxyaniline (IV) to give the symmetrical 5,5′-dichloro-2,4,2′,4′-tetramethoxythiocarbanilide (V), instead of



III IV



V

the expected, sterically more hindered unsymmetrical thiocarbanilide. With the same isothiocyanate, normal condensation products were obtained; however, when the reacting arylamine was not sterically hindered, as in the case of *p*-isoamyloxyaniline, or was less sterically hindered, as with 4-bromo-2-methoxy-5-

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(6) *Cf.* N. P. Buu-Hoï, N. D. Xuong, and V. T. Suu, *ibid.*, 2815 (1958).

TABLE I

DERIVATIVES OF UNSYMMETRICAL THIOCARBANILIDES

Substituents	M.p., °C.	Formula	Analysis			
			Calcd.		Found	
			C	H	C	H
4-Fluoro-5′-chloro-2′-methoxy	178	$C_{14}H_{12}ClFN_2OS$	54.1	3.9	54.2	3.9
4-Fluoro-3′-chloro-4′-methoxy	160	$C_{14}H_{12}ClFN_2OS$	54.1	3.9	54.1	4.0
4-Fluoro-5′-chloro-2′,4′-dimethoxy	183	$C_{15}H_{14}ClFN_2O_2S$	52.9	4.1	53.0	4.1
4-Fluoro-2′-chloro-4′-ethoxy	140	$C_{15}H_{14}ClFN_2OS$	55.5	4.3	55.4	4.3
4-Fluoro-5′-chloro-2′-isobutoxy	140	$C_{17}H_{18}ClFN_2OS$	57.7	5.1	58.0	5.2
4-Fluoro-2′-chloro-4′-isoamyloxy	141	$C_{18}H_{20}ClFN_2OS$	58.9	5.5	59.0	5.5
4-Fluoro-2′-bromo-5′-methoxy	144	$C_{14}H_{12}BrFN_2OS$	47.3	3.4	47.0	3.5
4-Fluoro-3′-bromo-4′-methoxy	136	$C_{14}H_{12}BrFN_2OS$	47.3	3.4	47.3	3.5
4-Fluoro-4′-bromo-3′-methoxy	136	$C_{14}H_{12}BrFN_2OS$	47.3	3.4	47.4	3.3
4-Fluoro-4′-bromo-2′-methoxy-5′-methyl	155	$C_{15}H_{14}BrFN_2OS$	48.8	3.8	48.8	3.8
4,4′-Difluoro-3-methoxy	138	$C_{14}H_{12}F_2N_2OS$	57.1	4.1	57.5	4.1
4-Fluoro-3-methoxy-4′-isoamyloxy	115	$C_{19}H_{23}FN_2O_2S$	63.0	6.4	62.7	6.3
3,4′-Difluoro-4-methoxy	160	$C_{14}H_{12}F_2N_2OS$	57.1	4.1	57.0	4.3
3-Fluoro-4′-isoamyloxy-4-methoxy	127	$C_{19}H_{23}FN_2O_2S$	63.0	6.4	63.0	6.4
3-Fluoro-4,4′-dimethoxy	183	$C_{15}H_{15}FN_2O_2S$	58.8	4.9	59.1	5.0
3-Fluoro-2′-ethoxy-4-methoxy	138	$C_{16}H_{17}FN_2O_2S$	60.0	5.4	60.0	5.4
3-Fluoro-4′-chloro-4,2′-dimethoxy-5′-methyl	154	$C_{16}H_{16}ClFN_2O_2S$	54.2	4.5	54.2	4.6
3-Fluoro-5′-chloro-4,2′-dimethoxy	151	$C_{15}H_{15}ClFN_2O_2S$	52.9	4.1	52.5	4.2
5-Chloro-2,4′-dimethoxy	177	$C_{15}H_{15}ClN_2O_2S$	55.8	4.7	55.9	4.6
5-Chloro-2,2′,5′-trimethoxy	127	$C_{16}H_{17}ClN_2O_2S$	54.5	4.9	54.2	5.0
5,3′-Dichloro-2,4′-dimethoxy	157	$C_{15}H_{14}Cl_2N_2O_2S$	50.5	4.0	50.3	3.9
5-Chloro-4′-ethoxy-2-methoxy	185	$C_{16}H_{17}ClN_2O_2S$	57.0	5.1	57.1	5.1
5-Chloro-2′-ethoxy-2-methoxy	148	$C_{16}H_{17}ClN_2O_2S$	57.0	5.1	56.8	5.3
5-Chloro-4′-butoxy-2-methoxy	150	$C_{18}H_{21}ClN_2O_2S$	59.3	5.8	59.4	5.8
5-Chloro-4′-isoamyloxy-2-methoxy	135	$C_{19}H_{23}ClN_2O_2S$	60.2	6.1	60.5	6.1
5,3′-Dichloro-2-methoxy-2′-methyl	164	$C_{15}H_{14}Cl_2N_2OS$	52.8	4.1	52.9	4.1
5,4′-Dichloro-2-methoxy	167	$C_{14}H_{12}Cl_2N_2OS$	51.4	3.7	51.4	3.7
5,2′,5′-Trichloro-2-methoxy	173	$C_{14}H_{11}Cl_3N_2OS$	46.5	3.1	46.3	3.1
3-Chloro-4,4′-dimethoxy	182	$C_{15}H_{15}ClN_2O_2S$	55.8	4.7	55.4	4.7
3-Chloro-4,2′,5′-trimethoxy	116	$C_{16}H_{17}ClN_2O_3S$	54.5	4.9	54.7	4.9
3-Chloro-4′-isoamyloxy-4-methoxy	114	$C_{19}H_{23}ClN_2O_2S$	60.2	6.1	60.5	5.9
3-Chloro-4′-butoxy-4-methoxy	109	$C_{18}H_{21}ClN_2O_2S$	59.3	5.8	59.7	6.0
3,4′-Dichloro-4-methoxy	161	$C_{14}H_{12}Cl_2N_2OS$	51.4	3.7	51.4	3.6
3,3′-Dichloro-4-methoxy	138	$C_{14}H_{12}Cl_2N_2OS$	51.4	3.7	51.2	3.7
4-Chloro-2,4′-dimethoxy-5-methyl	157	$C_{16}H_{17}ClN_2O_2S$	58.8	4.9	58.4	5.0
4-Chloro-2,2′,5′-trimethoxy-5-methyl	139	$C_{17}H_{19}ClN_2O_3S$	55.7	5.2	55.3	5.0
4,5′-Dichloro-2,2′-dimethoxy-5-methyl	178	$C_{16}H_{16}Cl_2N_2O_2S$	51.8	4.4	52.0	4.1
4,3′-Dichloro-2,4′-dimethoxy-5-methyl	173	$C_{16}H_{16}Cl_2N_2O_2S$	51.8	4.4	52.0	4.5
4,3′-Dichloro-2-methoxy-5,2′-dimethyl	151	$C_{16}H_{16}Cl_2N_2OS$	54.1	4.5	54.0	4.4
4,4′-Dichloro-2-methoxy-5-methyl	150	$C_{15}H_{14}Cl_2N_2OS$	52.8	4.1	52.7	4.0
5-Chloro-2,4,4′-trimethoxy	190	$C_{16}H_{17}ClN_2O_3S$	54.5	4.9	54.4	4.8
5,5′-Dichloro-2,4,2′-trimethoxy	211	$C_{16}H_{16}Cl_2N_2O_3S$	49.6	4.2	49.5	4.1
5,3′-Dichloro-2,4,4′-trimethoxy	180	$C_{16}H_{16}Cl_2N_2O_3S$	49.6	4.2	49.4	4.1
5-Chloro-4′-ethoxy-2,4-dimethoxy	134	$C_{17}H_{19}ClN_2O_3S$	55.6	5.2	55.5	5.3
5-Chloro-4′-isoamyloxy-2,4-dimethoxy	189	$C_{20}H_{25}ClN_2O_3S$	58.7	6.2	58.9	6.2
5-Chloro-4′-butoxy-2,4-dimethoxy	167	$C_{19}H_{23}ClN_2O_3S$	57.8	5.9	58.0	6.0
5,4′-Dichloro-2,4-dimethoxy	211	$C_{15}H_{14}Cl_2N_2O_2S$	50.5	4.0	50.3	4.0
2,5′-Dichloro-4-ethoxy-2′,4′-dimethoxy	166	$C_{17}H_{18}Cl_2N_2O_3S$	50.9	5.0	50.8	5.0
2-Chloro-4,4′-diethoxy	133	$C_{17}H_{19}ClN_2O_2S$	58.2	5.5	58.3	5.4
2-Chloro-4,2′-diethoxy	139	$C_{17}H_{19}ClN_2O_2S$	58.2	5.5	58.0	5.5
5,5′-Dichloro-2-ethoxy-2′,4′-dimethoxy	181	$C_{17}H_{18}Cl_2N_2O_3S$	50.9	5.0	50.9	4.9
5-Chloro-2,4′-diethoxy	185	$C_{17}H_{19}ClN_2O_2S$	58.2	5.5	58.3	5.4
5-Chloro-4′-ethoxy-2-isobutoxy	161	$C_{19}H_{23}ClN_2O_2S$	60.2	6.1	60.0	6.0
5-Chloro-2-isobutoxy-4′-isoamyloxy	146	$C_{22}H_{29}ClN_2O_2S$	62.8	6.9	62.7	6.9
2,5′-Dichloro-4-isoamyloxy-2′,4′-dimethoxy	175	$C_{20}H_{24}Cl_2N_2O_3S$	54.2	5.5	53.9	5.4
2-Chloro-4′-ethoxy-4-isoamyloxy	123	$C_{20}H_{25}ClN_2O_2S$	61.1	6.4	61.3	6.3
2-Chloro-2′-ethoxy-4-isoamyloxy	138	$C_{20}H_{25}ClN_2O_2S$	61.1	6.4	61.1	6.4
2-Chloro-4,4′-diisoamyloxy	113	$C_{23}H_{31}ClN_2O_2S$	63.5	7.2	63.7	7.2
5-Chloro-2,4′-diisoamyloxy	144	$C_{23}H_{31}ClN_2O_2S$	63.5	7.2	63.8	7.0
3-Chloro-4,2′-dimethoxy-5-methyl	133	$C_{16}H_{17}ClN_2O_2S$	57.0	5.1	57.1	5.1
5′-Chloro-4-dodecyloxy-2′,4′-dimethoxy	113	$C_{27}H_{39}ClN_2O_3S$	63.9	7.8	64.0	8.0
5′-Chloro-2′,4′-dimethoxy-4-tetradecyloxy	107	$C_{29}H_{43}ClN_2O_3S$	65.1	8.1	65.0	8.1
5′-Chloro-2′-methoxy-4-tetradecyloxy	111	$C_{28}H_{41}ClN_2O_2S$	66.6	8.2	66.4	8.1
5′-Chloro-4-allyloxy-2′,4′-dimethoxy	155	$C_{18}H_{19}ClN_2O_3S$	57.1	5.1	57.2	5.1
5′-Chloro-4-allyloxy-2′-methoxy	160	$C_{17}H_{17}ClN_2O_2S$	58.5	4.9	58.5	5.0
3′-Chloro-4-allyloxy-4′-methoxy	135	$C_{17}H_{17}ClN_2O_2S$	58.5	4.9	58.4	4.9
5′-Chloro-4-benzyloxy-2′,4′-dimethoxy	160	$C_{22}H_{21}ClN_2O_3S$	61.6	4.9	61.3	5.0

TABLE I (*continued*)

Substituents	M.p., °C.	Formula	Analysis Calcd. C	Calcd. H	Found C	Found H
5′-Chloro-4-benzyloxy-2′-methoxy	176	$C_{21}H_{19}ClN_2O_2S$	63.2	4.8	63.3	4.8
3′-Chloro-4-benzyloxy-4′-methoxy	160	$C_{21}H_{19}ClN_2O_2S$	63.2	4.8	63.0	4.8
3′-Chloro-4-hydroxy-4′-methoxy	186	$C_{14}H_{13}ClN_2O_2S$	54.5	4.2	54.4	4.3
3′-Chloro-3-hydroxy-4′-methoxy	185	$C_{14}H_{13}ClN_2O_2S$	54.5	4.2	54.4	4.2
2-Bromo-4′-ethoxy-5-methoxy	164	$C_{16}H_{17}BrN_2O_2S$	50.4	4.5	50.4	4.0
2-Bromo-4′-isoamyloxy-5-methoxy	128	$C_{19}H_{23}BrN_2O_2S$	53.9	5.5	54.0	5.5
3-Bromo-4,4′-dimethoxy	180	$C_{15}H_{15}BrN_2O_2S$	49.1	4.1	49.0	4.2
3-Bromo-5′-chloro-4,2′-dimethoxy	156	$C_{15}H_{14}BrClN_2O_2S$	44.8	3.5	44.7	3.5
3-Bromo-4′-ethoxy-4-methoxy	143	$C_{16}H_{17}BrN_2O_2S$	50.4	4.5	49.9	4.5
3-Bromo-2′-ethoxy-4-methoxy	144	$C_{16}H_{17}BrN_2O_2S$	50.4	4.5	49.9	4.4
3-Bromo-4′-isoamyloxy-4-methoxy	115	$C_{19}H_{23}BrN_2O_2S$	53.9	5.5	53.8	5.4
4-Bromo-3,4′-dimethoxy	141	$C_{15}H_{15}BrN_2O_2S$	49.1	4.1	48.9	4.1
4-Bromo-5′-chloro-3,2′-dimethoxy	165	$C_{15}H_{14}BrClN_2O_2S$	44.8	3.5	44.9	3.6
4-Bromo-4′-ethoxy-3-methoxy	143	$C_{16}H_{17}BrN_2O_2S$	50.4	4.5	50.8	4.5
4-Bromo-2′-ethoxy-3-methoxy	142	$C_{16}H_{17}BrN_2O_2S$	50.4	4.5	50.1	4.5
4-Bromo-4′-isoamyloxy-3-methoxy	135	$C_{19}H_{23}BrN_2O_2S$	53.9	5.5	53.8	5.5
4-Bromo-4′-chloro-3,2′-dimethoxy-5′-methyl	162	$C_{16}H_{16}BrClN_2O_2S$	46.2	3.9	46.5	3.9
4-Bromo-5′-chloro-2,2′-dimethoxy-5-methyl	181	$C_{16}H_{16}BrClN_2O_2S$	46.2	3.9	46.2	3.9
4-Bromo-5′-chloro-2,2′,4′-trimethoxy-5-methyl	195	$C_{17}H_{18}BrClN_2O_3S$	45.8	4.0	46.0	4.0
4-Bromo-4′-ethoxy-2-methoxy-5-methyl	150	$C_{17}H_{19}BrN_2O_2S$	51.7	4.8	51.6	4.8
4-Bromo-4′-isoamyloxy-2-methoxy-5-methyl	152	$C_{20}H_{25}BrN_2O_2S$	54.9	5.8	55.0	5.8
4-Bromo-4′-chloro-2,2′-dimethoxy-5,5′-dimethyl	162	$C_{17}H_{18}BrClN_2O_2S$	47.5	4.2	47.6	4.3
5-Bromo-5′-chloro-2′-methoxy	172	$C_{14}H_{12}BrClN_2OS$	45.2	3.3	45.5	3.2
4-Bromo-4′-chloro-2′-methoxy-5′-methyl	150	$C_{15}H_{14}BrClN_2OS$	46.7	3.7	46.8	3.8
4-Bromo-3′-chloro-4′-methoxy	166	$C_{14}H_{12}BrClN_2OS$	45.2	3.3	45.6	3.2
3-Bromo-3′-chloro-4′-methoxy	154	$C_{14}H_{12}BrClN_2OS$	45.2	3.3	45.3	3.2
4-Iodo-5′-chloro-2′-methoxy	169	$C_{14}H_{12}ClIN_2OS$	40.2	2.9	39.9	2.8
4-Iodo-3′-chloro-4′-methoxy	160	$C_{14}H_{12}ClIN_2OS$	40.2	2.9	39.9	2.8
4-Iodo-4′-chloro-2′-methoxy-5′-methyl	156	$C_{15}H_{14}ClIN_2OS$	41.6	3.3	41.8	3.2
4-Iodo-5′-chloro-2′,4′-dimethoxy	177	$C_{15}H_{14}ClIN_2O_2S$	40.1	3.1	40.0	3.2

TABLE II

DERIVATIVES OF SYMMETRICAL THIOCARBANILIDES

Substituents	M.p., °C.	Formula	Analysis Calcd. C	Calcd. H	Found C	Found H
5,5′-Dichloro-2,2′-dimethoxy	190	$C_{15}H_{14}Cl_2N_2O_2S$	50.5	4.0	50.5	3.8
3,3′-Dichloro-4,4′-dimethoxy	194	$C_{15}H_{14}Cl_2N_2O_2S$	50.5	4.0	50.4	3.9
4,4′-Dichloro-2,2′-dimethoxy-5,5′-dimethyl	163	$C_{17}H_{18}Cl_2N_2O_2S$	53.0	4.7	52.7	4.8
2,2′-Dichloro-4,4′-diethoxy	165	$C_{17}H_{18}Cl_2N_2O_2S$	53.0	4.7	53.0	4.6
2,2′-Dichloro-4,4′-diisoamyloxy	132	$C_{23}H_{30}Cl_2N_2O_2S$	58.8	6.4	58.9	6.5
5,5′-Dichloro-2,4,2′,4′-tetramethoxy	235	$C_{17}H_{18}Cl_2N_2O_4S$	48.9	4.3	48.7	4.5

methylaniline. This strong influence of steric factors on the course of the reaction is reminiscent of the previously reported difficulties in preparing thiocarbanilides from *o*-trifluoromethylaniline.[7] This type of condensation was found to be catalyzed by strong bases.

The halogenated alkoxyanilines necessary for the present research were prepared by various methods.

(1) Reduction of the corresponding halogenonitro compounds by means of hydrazine hydrate in the presence of Raney nickel,[8] a method that has the advantage over the more routine procedures, of avoiding the sometimes observed elimination of the halogen[9]; for example, the reduction of 2-bromo-4-nitroanisole and 4-bromo-3-nitroanisole with hydrochloric acid and tin occurred with considerable loss of the halogen, whereas hydrazine hydrate and Raney nickel afforded the required amines in 80% yield.

(7) See ref. 5 a.

(8) *Cf.* R. Moore and A. Furst, *J. Org. Chem.*, **23**, 1504 (1958).

(9) 6-Bromo-2-nitroanisole can, however, be easily reduced by iron and hydrochloric acid: S. L. Chien and R. Adams, *J. Am. Chem. Soc.*, **56**, 1786 (1934).

(2) Halogenation of alkoxyacetanilides with chloro- or bromosuccinimide, the halogen entering the *para* position when free, or otherwise the *ortho* position[10]; the halogenated alkoxyacetanilides thus obtained were hydrolyzed with dilute hydrochloric acid. As with the first method, the results were better both in purity and in yields than with the more conventional halogenation techniques.

(3) Alkylation of halogenated hydroxyacetanilides by means of the appropriate alkyl halide in ethanol and in the presence of potassium hydroxide, the reaction product being subsequently hydrolyzed by hydrochloric acid when the alkyl radical was saturated or by alkali when it was ethylenic.

Along with the thiocarbanilides, some halogenated N,N′-diarylthioureas derived from naphthylamines are also reported in this work.

In *in vitro* tests on cultures of *Mycobacterium tuberculosis* var. *hominis* (strain H_{37} Rv), cultivated in Youmans medium, all the thiocarbanilides described

(10) N. P. Buu-Hoï, *Rec. trav. chim.*, **73**, 197 (1954).

here showed growth-inhibiting activity in concentrations of 100 μ./ml. Some were extremely active (5μ/ml.), especially 2-chloro-4,4′-diethoxycarbanilide and 2-chloro-4,4′-diisoamyloxythiocarbanilide, which are halogenated derivatives of 4,4′-diethoxy- and 4,4′-diisoamyloxythiocarbanilide, two drugs already in use against tuberculosis and leprosy. Compounds with alkyloxy groups in the *meta* position were considerably less active than those bearing these groups in *para* and *ortho* positions; it is also interesting that more chlorinated thiocarbanilides showed significant tuberculostatic activity than brominated ones. A more detailed account of this bacteriological study will be published elsewhere, in collaboration with Prof. J. Jadin (Antwerp, Belgium). Antifungal tests are under way.

Experimental

All melting points are corrected and were taken on a Maquenne block.

Preparation of Halogenated Alkoxyanilines. Method 1.—A typical example is the preparation of 4-bromo-3-methoxyaniline by reduction of 2-bromo-5-nitroanisole. A well stirred solution of 23.2 g. (0.1 mole) of this nitro compound and 12.5 g. (0.25 mole) of 90% hydrazine hydrate in 250 ml. of 95% ethanol was heated on the water bath, and 4 g. of freshly prepared Raney nickel W_2 was added in minute portions to avoid a too vigorous reaction; the refluxing was continued until the initial yellow color of the solution had disappeared. The nickel was then filtered off, the filtrate concentrated and diluted with water, and the reduction product taken up in chloroform. The chloroform solution was washed with water and dried over caustic soda, the solvent removed, and the residue vacuum-fractionated. **4-Bromo-3-methoxyaniline,** m.p. 93°, was obtained in 80% yield (lit.,[11] m.p. 90.1°). Similar good results were obtained in the reduction of 2-bromo-4-nitro- and 4-bromo-3-nitroanisole.

Method 2.—The preparation of 2-chloro-4-isoamyloxyaniline is typical of this procedure. A mixture of 33 g. of finely powdered 4-isoamyloxyacetanilide and 20 g. of N-chlorosuccinimide in 300 ml. of dry carbon tetrachloride was refluxed for 10 hr. on the water bath. After cooling, the succinimide was filtered off, the filtrate washed repeatedly with warm water and dried over sodium sulfate, the solvent was distilled, and the residue recrystallized from 50% ethanol. Yield, 20 g. of **2-chloro-4-isoamyloxyacetanilide,** m.p. 93–94°.

Anal. Calcd. for $C_{13}H_{18}ClNO_2$: C, 61.1; H, 7.0. Found: C, 61.0; H, 7.3.

A well stirred mixture of 76 g. of this amide, 80 ml. of concentrated hydrochloric acid, and 320 ml. of water was refluxed until the solid dissolved; after cooling, it was made basic with 30% aqueous sodium hydroxide, the reaction product taken up in benzene, the benzene solution washed with water and dried over caustic soda, the solvent removed, and the residue vacuum-fractionated. Yield, 47 g. of colorless oily **2-chloro-4-isoamyloxyaniline,** b.p. 173–174° (15 mm.), $n^{23}D$ 1.5470.

Anal. Calcd. for $C_{11}H_{16}ClNO$: C, 61.8; H, 7.5. Found: C, 61.7; H, 7.5.

For characterization purposes, this amine (5.3 g.) was condensed with hexane-2,5-dione (5.7 g.) by refluxing the mixture for 30 min. Vacuum-fractionation yielded 2.5 g. of **1-(2-chloro-4-isoamyloxyphenyl)-2,5-dimethylpyrrole,** a pale yellow oil, b.p. 191–192° (15 mm.), $n^{20}D$ 1.5518.

Anal. Calcd. for $C_{17}H_{22}ClNO$: C, 69.9; H, 7.6. Found: C, 69.6; H, 7.5.

A similar pyrrole cyclization, effected with 2-chloro-4-ethoxyaniline, afforded **1-(2-chloro-4-ethoxyphenyl)-2,5-dimethylpyrrole,** a pale yellow oil, b.p. 167–168° (15 mm.), $n^{24}D$ 1.5735.

Anal. Calcd. for $C_{14}H_{16}ClNO$: C, 67.3; H, 6.1. Found: C, 67.4; H, 6.1.

(11) A. S. Fry and B. S. Farqhar, *Rec. trav. chim.*, **57**, 1223 (1938).

By Method 3.—Example: Preparation of 5-chloro-2-isobutoxyaniline. A solution of 27.9 g. (0.15 mole) of 2-acetamino-4-chlorophenol (m.p. 185°; lit., 182°) and 50.5 g. (0.2 mole) of isobutyl iodide in 400 ml. of ethanol mixed with 400 ml. of isobutyl alcohol was refluxed for 8 hr. with 11.2 g. (0.2 mole) of potassium hydroxide (dissolved in a minimum of water); the solvents were vacuum-distilled, and the crude solid 5-chloro-2-isobutoxyacetanilide was hydrolyzed with boiling 20% hydrochloric acid (100 ml.) in the usual way. After complete dissolution the reaction product was made basic with sodium hydroxide, was taken up in benzene and then vacuum-distilled. Yield, 75% of **5-chloro-2-isobutoxyaniline,** a colorless oil, b.p. 175–176° (20 mm.), $n^{24}D$ 1.5510.

Anal. Calcd. for $C_{10}H_{14}ClNO$: N, 7.0. Found: N, 6.9.

5-Chloro-2-isoamyloxyaniline, similarly prepared, was a colorless oil, b.p. 180–182° (14 mm.), $n^{23}D$ 1.5390.

Anal. Calcd. for $C_{11}H_{16}ClNO$: N, 6.6. Found: N, 6.8.

Preparation of Symmetrical Thiocarbanilides.—To a solution of 1 mole of the amine and 0.5 g. of potassium hydroxide in 500 ml. of ethanol, 2 moles of carbon disulfide was added with stirring, and the mixture gently refluxed for 24 hr. (potassium hydroxide can be replaced by sulfur); ethanol was added where necessary to ensure complete solution of the thiocarbanilide formed. The hot solution was then filtered, and the residue formed on cooling recrystallized from methanol or ethanol, or a mixture of ethanol and dimethylformamide in the case of substances melting above 200°. Yields ranged from 40 to 85%.

Preparation of Unsymmetrical Thiocarbanilides.—A solution of equimolar quantities of the amine and the appropriate aryl isothiocyanate in a minimum of ethanol was heated at 50–60° for a few min. when steric hindrance was not present, or for longer (several hr.) when the reaction was sluggish. The solid formed on cooling was recrystallized as above. Yields ranged from 30 to 95%; in some cases, the addition of traces of potassium hydroxide increased the yields.

Preparation of Aryl Isothiocyanates.—A mixture of 1 mole of the symmetrical thiocarbanilide and 2 moles of acetic anhydride was refluxed for 10 min. and the reaction product vacuum-fractionated; the isothiocyanate was redistilled and, when solid, recrystallized rapidly from ethanol. The following new aryl isothiocyanates were thus obtained in 80–90% yields:

5-Chloro-2-methoxyphenyl isothiocyanate, colorless needles, m.p. 57°.

Anal. Calcd. for C_8H_6ClNOS: C, 48.1; H, 3.0. Found: C, 48.3; H, 3.0.

4-Chloro-2-methoxy-5-methylphenyl isothiocyanate, m.p. 56°.

Anal. Calcd. for C_9H_8ClNOS: C, 50.6; H, 3.8. Found: C, 50.8; H, 3.8.

5-Chloro-2,4-dimethoxphenyl isothiocyanate, m.p. 80°.

Anal. Calcd. for $C_9H_8ClNO_2S$: C, 47.1; H, 3.5. Found: C, 47.0; H, 3.6.

N-1-Naphthyl-N′-(3-chloro-4-methoxyphenyl)thiourea.—This was prepared in 95% yield from 3-chloro-4-methoxyphenyl isothiocyanate and 1-naphthylamine: colorless needles, m.p. 174° (from ethanol and dimethylformamide).

Anal. Calcd. for $C_{18}H_{15}ClN_2OS$: C, 63.1; H, 4.4. Found: C, 62.8; H, 4.4.

N-(5,6,7,8-Tetrahydro-1-naphthyl)-N′-(3-chloro-4-methoxyphenyl)thiourea, m.p. 163° (from methanol).

Anal. Calcd. for $C_{18}H_{19}ClN_2OS$: C, 62.3; H, 5.5. Found: C, 62.1; H, 5.4.

Example of Abnormal Reaction between Isothiocyanates and Arylamines.—Equimolar amounts of the isothiocyanate III and the amine IV, when heated in ethanol in the usual way, yielded 5,5′-dichloro-2,4,2′,4′-tetramethoxythiocarbanilide, m.p. and mixture m.p. 235°.

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