573. *New* NN′-*Disubstituted Thioureas and Ureas of Biological Interest.*

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The reactivity of several classes of aromatic and heterocyclic amines towards aryl *iso*cyanates and *iso*thiocyanates has been investigated, and a large number of new *NN′*-diaryl-thioureas and -ureas and their heterocyclic analogues, most of them bearing halogen groups, have been prepared for testing as potential antiviral and antibacterial agents.

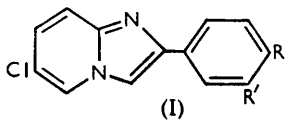
Compounds possessing notable activity *in vivo* against influenza virus have been found in the group of fluorine-containing thiocarbanilides and analogous sulphur compounds;[1] numerous *pp′*-disubstituted thiocarbanilides possess pronounced antitubercular and fungistatic activity,[2] and some are active against human leprosy.[3] A large number of new *NN′*-diarylthioureas and their pyridine analogues, most of them bearing halogen substituents (particularly fluorine), have therefore been synthesised, by condensation of primary amines with aryl *iso*thiocyanates.[4] Other substituents included alkyl, alkyloxy-, and *NN*-dialkyl groups, whose favourable influence on tuberculostatic activity is known, and *cyclo*hexyl radicals, which have not previously been investigated but now prove likewise favourable. Among the pyridine compounds, *N*-(5-chloro-2-pyridyl)-*N′*-(*p*-fluorophenyl)thiourea is a heterocyclic analogue of 4-chloro-4′-fluorothiocarbanilide, the most active antiviral compound in the series. Condensations with aryl *iso*cyanates furnished *NN′*-diarylureas, also of interest in view of the pronounced activity of certain polychlorinated carbanilides towards *Micrococcus pyogenes* var. *aureus*;[5] *N*-(5-chloro-2-pyridyl)-*N′*-3 : 4-dichlorophenylurea is a heterocyclic analogue of 3 : 4 : 4′-trichlorocarbanilide, the most active staphylostatic compound in the aromatic series.

In these condensations, the greater chemical activity of aryl *iso*cyanates than of the corresponding *iso*thiocyanates was shown by exothermic formation of ureas in the cold, whereas preparation of most of the thioureas required slight heating; also by the ready formation of ureas from complex amines such as ketones bearing nuclear amino-groups (*e.g.*, 4-amino-acetophenone and -benzophenone), methyl homologues of 2-aminopyrimidine, and 2-amino-5-nitrothiazole, all of which failed to give the corresponding thioureas under the same conditions. Similarly, sterically hindered arylamines such as *o*-trifluoromethylaniline reacted instantaneously with aryl *iso*cyanates, but sluggishly or not at all with aryl *iso*thiocyanates.[6] The new symmetrical *NN′*-diarylthioureas reported were prepared from the corresponding arylamines and carbon disulphide, by the Hugershoff method.[7]

The arylamines used in this work were characterised by various other reactions, including the formation of 2-arylamino-3-chloro-1 : 4-naphthaquinones with 2 : 3-dichloro-1 : 4-naphthaquinone,[8] of 2 : 5-diarylamino-*p*-benzoquinones with chloranil, and of 1-aryl-2 : 5-dimethylpyrroles by condensation with acetonylacetone.[9] 2-Amino-5-chloropyridine behaved like 2-aminopyridine towards ω-bromoacetophenones, readily undergoing

[1] Buu-Hoï, Gley, Xuong, and Bouffanais, *Compt. rend.*, 1954, **238**, 2582; Buu-Hoï, Gley, Bouffanais, Xuong, and Nam, *Experientia*, 1956, **12**, 73.
[2] Mayer, Eisman, and Konopka, *Proc. Soc. Exp. Biol.*, 1953, **82**, 498; Huebner, Marsh, Mizzoni, Mull, Schraeder, Troxell, and Scholz, *J. Amer. Chem. Soc.*, 1953, **75**, 2274.
[3] Buu-Hoï, *Internat. J. Leprosy*, 1954, **22**, 16; Buu-Hoï, Khuyen, and Xuong, *Bull. Acad. nat. Méd.*, 1955, **15/16**, 275; 1957, **9/10**, 1954.
[4] Cf. Buu-Hoï and Xuong, *Compt. rend.*, 1953, **237**, 498.
[5] Beaver, Roman, and Stoffel, *J. Amer. Chem. Soc.*, 1957, **79**, 1936.
[6] Buu-Hoï, Xuong, and Nam, *J.*, 1955, 1573.
[7] Hugershoff, *Ber.*, 1899, **32**, 2246.
[8] Cf. Buu-Hoï, *Bull. Soc. chim. France*, 1944, **11**, 578; Buu-Hoï, Royer, and Hubert-Habart, *Rec. Trav. chim.*, 1954, **73**, 188.
[9] Cf. Knorr, *Ber.*, 1885, **18**, 2254; Buu-Hoï, *J.*, 1949, 2882.

Tschitschibabin cyclisation [10] to give various 2-aryl-6-chloroiminazo[1,2-*a*]pyridines (I), which are of interest as potential antipurines. 4-Bromo-3-chloroaniline and 4-bromo-2-methylaniline were readily prepared from 3-chloroacetanilide and 2-methylacetanilide by means of *N*-bromosuccinimide [11] and subsequent hydrolysis; this method was also successfully applied to 3-fluoroacetanilide for the synthesis of 4-bromo-3-fluoroaniline. *N*-Chlorosuccinimide was used in a similar way for preparing 4-chloro-2-methylaniline from 2-methylacetanilide.



(I)

Tests *in vitro* against *Micrococcus pyogenes* var. *aureus* showed several polyhalogenated carbanilides and thiocarbanilides to be active in a concentration range $1 : 10^{-5}$—10^{-6}; notable activity *in vitro* and *in vivo* against *Mycobacterium tuberculosis* var. *hominis* (strain H37 Rv), as well as *in vivo* against *Mycobacterium leprae*, was shown by 4-diethylamino-4'-*iso*pentyloxythiocarbanilide.

Experimental

Preparation of 4-Bromo-3-chloroaniline.—A suspension of 3-chloroacetanilide (34 g.) and *N*-bromosuccinimide (36 g.) in dry carbon tetrachloride (300 c.c.) was refluxed for 4 hr.; after cooling, the solid precipitate was filtered off and treated with hot water to dissolve the succinimide, and the remaining 4-bromo-3-chloroacetanilide was heated with hydrochloric acid (50 c.c.) in 70% aqueous ethanol (100 c.c.) for 1 hr. After cooling and basification with ammonia, 4-bromo-3-chloroaniline (38 g.), m. p. 68° (from aqueous ethanol), was obtained. This procedure gave an amine free from isomers and by-products. 4-Bromo-2-methylaniline (36 g.), m. p. 55°, was similarly prepared from 2-methylacetanilide (30 g.) and *N*-bromosuccinimide (36 g.) in carbon tetrachloride.

4-Bromo-3-fluoroaniline.—3-Fluoroacetanilide (30 g.) and *N*-bromosuccinimide (36 g.) in carbon tetrachloride (250 c.c.) were treated as above, giving *4-bromo-3-fluoroacetanilide* (40 g.),

Substituted carbanilides.

	M. p.	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
2 : 4-Difluoro	222°	$C_{13}H_{10}ON_2F_2$	62·8	4·1	62·9	4·0
3 : 4-Difluoro	216	$C_{13}H_{10}ON_2F_2$	62·9	4·1	62·9	4·0
4-Chloro-2' : 4'-difluoro	262	$C_{13}H_9ON_2ClF_2$	55·1	3·1	55·2	3·2
4-Chloro-3' : 4'-difluoro	246	$C_{13}H_9ON_2ClF_2$	55·0	3·1	55·2	3·2
4-Bromo-3-fluoro	230	$C_{13}H_{10}ON_2BrF$	50·3	3·3	50·5	3·3
4-Bromo-3' : 5'-dichloro-3-fluoro	257	$C_{13}H_8ON_2Cl_2BrF$	41·0	2·0	41·3	2·1
4-Bromo-4'-chloro-3-fluoro	289	$C_{13}H_9ON_2ClBrF$	45·6	2·7	45·5	2·7
3 : 5 : 3'-Trichloro	233	$C_{13}H_9ON_2Cl_3$	49·3	3·2	49·5	2·9
3 : 5 : 3' : 4'-Tetrachloro	265	$C_{13}H_8ON_2Cl_4$	44·3	2·6	44·6	2·3
3 : 5 : 2' : 3'-Tetrachloro	272	$C_{13}H_8ON_2Cl_4$	44·3	2·5	44·6	2·3
4-Bromo-3 : 3' : 5'-trichloro	273	$C_{13}H_8ON_2Cl_3Br$	39·5	2·0	39·6	2·0
3 : 5-Dichloro-2' : 4'-difluoro	229	$C_{13}H_8ON_2Cl_2F_2$	49·2	2·5	49·3	2·5
3 : 5-Dichloro-3' : 4'-difluoro	232	$C_{13}H_8ON_2Cl_2F_2$	49·0	2·6	49·3	2·5
2-Trifluoromethyl	182	$C_{14}H_{11}ON_2F_3$	60·3	4·0	60·1	4·0
4-Acetyl	186	$C_{15}H_{14}O_2N_2$	71·0	5·5	70·9	5·6
4-Acetyl-4'-fluoro	218	$C_{15}H_{13}O_2N_2F$	66·0	5·0	66·2	4·8
4-Acetyl-4'-chloro	233	$C_{15}H_{13}O_2N_2Cl$	62·1	4·3	62·4	4·5
4-Acetyl-3' : 5'-dichloro	236	$C_{15}H_{12}O_2N_2Cl_2$	55·8	3·8	55·8	3·7
4-Acetyl-3' : 4'-dichloro	259	$C_{15}H_{12}O_2N_2Cl_2$	55·6	3·8	55·8	3·7
4-Benzoyl	203	$C_{20}H_{16}O_2N_2$	75·8	5·4	75·9	5·1
4-Benzoyl-4'-chloro	250	$C_{20}H_{15}O_2N_2Cl$	68·3	4·2	68·5	4·3
4-*NN*-Diethylamino	189	$C_{17}H_{21}ON_3$	72·0	7·6	72·1	7·5
4'-Diethylamino-4-fluoro	213	$C_{17}H_{20}ON_3F$	67·5	6·6	67·8	6·7
4-Chloro-4'-diethylamino	227	$C_{17}H_{20}ON_3Cl$	64·2	6·3	64·3	6·4
3 : 4-Dichloro-4'-diethylamino	177	$C_{17}H_{19}ON_3Cl_2$	57·7	5·5	58·0	5·4
3 : 5-Dichloro-4'-diethylamino	180	$C_{17}H_{19}ON_3Cl_2$	58·2	5·4	58·0	5·4
4-*NN*-Dipropylamino	155	$C_{19}H_{25}ON_3$	73·5	8·2	73·4	8·1
4-Fluoro-4'-*NN*-dipropylamino	144	$C_{19}H_{24}ON_3F$	69·6	7·6	69·4	7·4
4-Chloro-4'-*NN*-dipropylamino	169	$C_{19}H_{24}ON_3Cl$	65·7	7·2	66·0	6·9

[10] Tschitschibabin *et al.*, *Ber.*, 1925, **58**, 1704; 1926, **59**, 2048; 1931, **64**, 2842; Buu-Hoï, Jacquignon, Xuong, and Lavit, *J. Org. Chem.*, 1954, **19**, 1370.

[11] Buu-Hoï, *Rev. Trav. chim.*, 1954, **73**, 197.

Ureas derived from nitrogen heterocycles.

	M. p.	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
(a) N-(5-*Chloro*-2-*pyridyl*)*ureas.*						
N'-Phenyl	214°	$C_{12}H_{10}ON_3Cl$	57·9	4·0	58·2	4·1
N'-*p*-Chlorophenyl	236	$C_{12}H_9ON_3Cl_2$	51·0	3·3	51·1	3·2
N'-*p*-Fluorophenyl	216	$C_{12}H_9ON_3FCl$	54·0	3·2	54·3	3·4
N'-(3 : 4-Dichlorophenyl)	277	$C_{12}H_8ON_3Cl_3$	45·5	2·8	45·5	2·6
N'-(3 : 5-Dichlorophenyl)	284	$C_{12}H_8ON_3Cl_3$	45·5	2·7	45·5	2·6
(b) N-(5-*Nitro*-2-*pyridyl*)*ureas.*						
N'-Phenyl	238	$C_{12}H_{10}O_3N_4$	56·0	4·2	55·9	3·9
N'-*p*-Chlorophenyl	285	$C_{12}H_9O_3N_4Cl$	49·0	3·0	49·3	3·1
N'-*p*-Fluorophenyl	283	$C_{12}H_9O_3N_4F$	52·0	3·5	52·2	3·3
N'-(3 : 4-Dichlorophenyl)	291	$C_{12}H_8O_3N_4Cl_2$	44·0	2·5	44·1	2·5
N'-(3 : 5-Dichlorophenyl)	268	$C_{12}H_8O_3N_4Cl_2$	43·8	2·7	44·1	2·5
(c) N-(5-*Nitro*-2-*thiazolyl*)*ureas*						
N'-Phenyl	259	$C_{10}H_8O_3N_4S$	45·2	3·0	45·5	3·1
N'-*p*-Chlorophenyl	284	$C_{10}H_7O_3N_4ClS$	40·0	2·6	40·2	2·4
N'-*p*-Fluorophenyl	254	$C_{10}H_7O_3N_4FS$	42·5	2·5	42·6	2·5
N'-(3 : 4-Dichlorophenyl)	296	$C_{10}H_6O_3N_4Cl_2S$	35·8	1·9	36·1	1·8
(d) N-2-*Pyrimidyl*ureas.						
N'-*p*-Chlorophenyl	238	$C_{11}H_9ON_4Cl$	53·0	3·9	53·2	3·7
N'-*p*-Fluorophenyl	234	$C_{11}H_9ON_4F$	56·6	4·0	56·9	3·9
N'-(3 : 4-Dichlorophenyl)	253	$C_{11}H_8ON_4Cl_2$	46·4	3·0	46·7	2·8
N'-(3 : 5-Dichlorophenyl)	275	$C_{11}H_8ON_4Cl_2$	46·5	2·8	46·7	2·8
(e) N-(4 : 6-*Dimethyl*-2-*pyrimidyl*)*ureas.*						
N'-*p*-Fluorophenyl	212	$C_{13}H_{13}ON_4F$	59·8	4·9	60·1	5·0
N'-*p*-Chlorophenyl	216	$C_{13}H_{13}ON_4Cl$	56·3	4·9	56·5	4·7
N'-(3 : 4-Dichlorophenyl)	232	$C_{13}H_{12}ON_4Cl_2$	50·1	3·9	50·2	3·9
N'-(3 : 5-Dichlorophenyl)	236	$C_{13}H_{12}ON_4Cl_2$	50·0	4·1	50·2	3·9
(f) N-(2 : 4-*Dimethyl*-6-*pyrimidyl*)*ureas.*						
N'-*p*-Chlorophenyl	249	$C_{13}H_{13}ON_4Cl$	56·2	4·5	56·5	4·7
N'-(3 : 4-Dichlorophenyl)	251	$C_{13}H_{12}ON_4Cl_2$	50·0	4·0	50·2	3·9
N'-(3 : 5-Dichlorophenyl)	267	$C_{13}H_{12}ON_4Cl_2$	49·9	4·0	50·2	3·9

N-*Aryl*-N'-*pyridylthioureas.*

	M. p.	Formula	Found N (%)	Reqd. N (%)
N-*p*-Fluorophenyl-*N'*-3-pyridyl	190°	$C_{12}H_{10}N_3FS$	16·9	17·0
N-*p*-Chlorophenyl-*N'*-3-pyridyl	198	$C_{12}H_{10}N_3ClS$	15·6	15·9
N-*p*-Bromophenyl-*N'*-3-pyridyl	220	$C_{12}H_{10}N_3BrS$	13·6	13·6
N-*p*-Tolyl-*N'*-3-pyridyl	175	$C_{13}H_{13}N_3S$	17·2	17·3
N-(2 : 4-Xylyl)-*N'*-3-pyridyl	172	$C_{14}H_{15}N_3S$	16·0	16·3
N-*p*-Methoxyphenyl-*N'*-3-pyridyl	201	$C_{13}H_{13}ON_3S$	16·0	16·2
N-*p*-Ethoxyphenyl-*N'*-3-pyridyl	178	$C_{14}H_{15}ON_3S$	15·3	15·4
N-*p*-*iso*Pentyloxyphenyl-*N'*-3-pyridyl	136	$C_{17}H_{21}ON_3S$	13·3	13·3
N-*p*-Fluorophenyl-*N'*-(4-methyl-2-pyridyl)	182	$C_{13}H_{12}N_3FS$	16·0	16·1
N-*p*-Chlorophenyl-*N'*-(4-methyl-2-pyridyl)	216	$C_{13}H_{12}N_3ClS$	14·9	15·1
N-*p*-Bromophenyl-*N'*-(4-methyl-2-pyridyl)	222	$C_{13}H_{12}N_3BrS$	12·9	13·0
N-*p*-Fluorophenyl-*N'*-(5-methyl-2-pyridyl)	202	$C_{13}H_{12}N_3FS$	15·8	16·1
N-*p*-Chlorophenyl-*N'*-(5-methyl-2-pyridyl)	212	$C_{13}H_{12}N_3ClS$	15·0	15·1
N-*p*-Bromophenyl-*N'*-(5-methyl-2-pyridyl)	219	$C_{13}H_{12}N_3BrS$	12·9	13·0
N-*p*-Tolyl-*N'*-(5-methyl-2-pyridyl)	182	$C_{14}H_{15}N_3S$	16·5	16·3
N-(2 : 4-Xylyl)-*N'*-(5-methyl-2-pyridyl)	200	$C_{15}H_{17}N_3S$	15·2	15·5
N-*p*-Methoxyphenyl-*N'*-(5-methyl-2-pyridyl)	214	$C_{14}H_{15}ON_3S$	15·2	15·4
N-*p*-Ethoxyphenyl-*N'*-(5-methyl-2-pyridyl)	190	$C_{15}H_{17}ON_3S$	14·5	14·6
N-*p*-*iso*Pentyloxyphenyl-*N'*-(5-methyl-2-pyridyl)	132	$C_{18}H_{23}ON_3S$	12·8	12·8
N-*p*-Fluorophenyl-*N'*-(5-chloro-2-pyridyl)	198	$C_{12}H_9N_3ClFS$	14·6	14·9
N-*p*-Chlorophenyl-*N'*-(5-chloro-2-pyridyl)	230	$C_{12}H_9N_3Cl_2S$	14·0	14·1
N-*p*-Bromophenyl-*N'*-(5-chloro-2-pyridyl)	238	$C_{12}H_9N_3ClBrS$	12·0	12·3
N-Phenyl-*N'*-(5-chloro-2-pyridyl)	195	$C_{12}H_{10}N_3ClS$	16·0	15·9
N-*p*-Tolyl-*N'*-(5-chloro-2-pyridyl)	194	$C_{13}H_{12}N_3ClS$	14·9	15·1
N-*p*-Ethylphenyl-*N'*-(5-chloro-2-pyridyl)	173	$C_{14}H_{14}N_3ClS$	14·3	14·4
N-*p*-Methoxyphenyl-*N'*-(5-chloro-2-pyridyl)	226	$C_{13}H_{12}ON_3ClS$	14·0	14·3
N-*p*-Ethoxyphenyl-*N'*-(5-chloro-2-pyridyl)	181	$C_{14}H_{14}ON_3ClS$	13·6	13·7
N-*p*-*iso*Pentyloxyphenyl-*N'*-(5-chloro-2-pyridyl)	151	$C_{17}H_{20}ON_3ClS$	11·9	12·0

Thiocarbanilides.

	M. p.	Formula	Found N (%)	Reqd. N (%)
4-Bromo-3 : 4'-difluoro	185°	$C_{13}H_9N_2BrF_2S$	8·1	8·2
4 : 4'-Dibromo-3-fluoro	213	$C_{13}H_9N_2Br_2FS$	7·1	6·9
3 : 4-Dichloro-4'-fluoro	135	$C_{13}H_9N_2Cl_2FS$	8·6	8·9
3 : 5-Dichloro-4'-fluoro	176	$C_{13}H_9N_2Cl_2FS$	8·8	8·9
3 : 4 : 4'-Trichloro	160	$C_{13}H_9N_2Cl_3S$	8·2	8·4
4-Bromo-3' : 4'-dichloro	172	$C_{13}H_9N_2Cl_2BrS$	7·3	7·4
2 : 3-Dichloro-4'-fluoro	161	$C_{13}H_9N_2Cl_2FS$	9·1	8·9
2 : 3 : 4'-Trichloro	199	$C_{13}H_9N_2Cl_3S$	8·1	8·4
4-Bromo-2' : 3'-dichloro	201	$C_{13}H_9N_2Cl_2BrS$	7·6	7·4
2-Bromo-4'-fluoro	188	$C_{13}H_{10}N_2BrFS$	8·6	8·6
2-Bromo-4'-chloro	198	$C_{13}H_{10}N_2ClBrS$	8·0	8·2
2 : 4'-Dibromo	202	$C_{13}H_{10}N_2Br_2S$	7·0	7·3
2-Bromo-4'-methoxy	181	$C_{14}H_{13}ON_2BrS$	8·1	8·3
2-Bromo-4'-ethoxy	190	$C_{15}H_{15}ON_2BrS$	8·2	8·0
2-Bromo-4'-ethyl	185	$C_{15}H_{15}N_2BrS$	8·1	8·4
2-Bromo-4'-methyl	193	$C_{14}H_{13}N_2BrS$	8·8	8·7
2-Bromo-2' : 4'-dimethyl	170	$C_{15}H_{15}N_2BrS$	8·5	8·4
3-Bromo-4'-fluoro	128	$C_{13}H_{10}N_2BrFS$	8·6	8·6
3-Bromo-4'-chloro	133	$C_{13}H_{10}N_2ClBrS$	8·4	8·2
3 : 4'-Dibromo	162	$C_{13}H_{10}N_2Br_2S$	7·0	7·3
3-Bromo-4'-methyl	135	$C_{14}H_{13}N_2BrS$	8·5	8·7
3-Bromo-2' : 4'-dimethyl	133	$C_{15}H_{15}N_2BrS$	8·2	8·4
3-Bromo-4'-ethoxy	129	$C_{15}H_{15}ON_2BrS$	7·8	8·0
3-Bromo-4'-*iso*pentyloxy	119	$C_{18}H_{21}ON_2BrS$	7·0	7·1
4-Fluoro-4'-iodo	167	$C_{13}H_{10}N_2FIS$	7·2	7·5
4-Chloro-4'-iodo	213	$C_{13}H_{10}N_2ClIS$	7·2	7·2
4-Bromo-4'-iodo	224	$C_{13}H_{10}N_2BrIS$	6·6	6·5
4-Bromo-4'-ethoxy	197	$C_{15}H_{15}ON_2BrS$	8·1	8·0
4-Bromo-4'-*iso*pentyloxy	192	$C_{18}H_{21}ON_2BrS$	7·1	7·1
3 : 4-Difluoro	148	$C_{13}H_{10}N_2F_2S$	10·6	10·6
3 : 4 : 4'-Trifluoro	162	$C_{13}H_9N_2F_3S$	10·0	9·9
4-Chloro-3' : 4'-difluoro	164	$C_{13}H_9N_2ClF_2S$	9·1	9·4
4-Bromo-3' : 4'-difluoro	178	$C_{13}H_9N_2BrF_2S$	8·2	8·2
4-Ethyl-3' : 4'-difluoro	136	$C_{15}H_{14}N_2F_2S$	9·5	9·6
3 : 4-Difluoro-2' : 4'-dimethyl	151	$C_{15}H_{14}N_2F_2S$	9·5	9·6
4-Ethoxy-3' : 4'-difluoro	163	$C_{15}H_{14}ON_2F_2S$	9·0	9·1
3 : 4-Difluoro-4'-*iso*pentyloxy	146	$C_{18}H_{20}ON_2F_2S$	7·8	8·0
2 : 4-Difluoro	136	$C_{13}H_{10}N_2F_2S$	10·3	10·6
2 : 4 : 4'-Trifluoro	176	$C_{13}H_9N_2F_3S$	9·7	9·9
4-Bromo-2' : 4'-difluoro	190	$C_{13}H_9N_2BrF_2S$	8·0	8·2
4-Ethyl-2' : 4'-difluoro	155	$C_{15}H_{14}N_2F_2S$	9·3	9·6
2 : 4-Difluoro-2' : 4'-dimethyl	149	$C_{15}H_{14}N_2F_2S$	9·8	9·6
4-Ethoxy-2' : 4'-difluoro	148	$C_{15}H_{14}ON_2F_2S$	9·0	9·1
2 : 4-Difluoro-4'-*iso*pentyloxy	132	$C_{18}H_{20}ON_2F_2S$	7·9	8·0
4-Bromo-3-chloro-4'-fluoro	178	$C_{13}H_9N_2ClBrFS$	7·5	7·8
4-Bromo-3' : 4'-dichloro	187	$C_{13}H_9N_2Cl_2BrS$	7·5	7·4
4 : 4'-Dibromo-3-chloro	191	$C_{13}H_9N_2ClBr_2S$	6·4	6·7
4 : 4'-Dibromo-3 : 3'-dichloro [a]	216	$C_{13}H_8N_2Cl_2Br_2S$	6·0	6·2
4-Chloro-4'-fluoro-2-methyl	117	$C_{14}H_{12}N_2ClFS$	9·2	9·5
4 : 4'-Dichloro-2-methyl	150	$C_{14}H_{12}N_2Cl_2S$	8·8	9·0
4-Bromo-4'-chloro-2'-methyl	167	$C_{14}H_{12}N_2ClBrS$	7·6	7·9
4 : 4'-Dibromo-2-methyl	185	$C_{14}H_{12}N_2Br_2S$	6·9	7·0
4-Bromo-4'-chloro-2-methyl	172	$C_{14}H_{12}N_2ClBrS$	7·7	7·9
4-*NN*-Diethylamino-4'-fluoro	148	$C_{17}H_{20}N_3FS$	13·4	13·2
4-Chloro-4'-*NN*-diethylamino	173	$C_{17}H_{20}N_3ClS$	12·5	12·6
4-Bromo-4'-*NN*-diethylamino	199	$C_{17}H_{20}N_3BrS$	11·0	11·1
4-*NN*-Dipropylamino-4'-fluoro	141	$C_{19}H_{24}N_3FS$	12·0	12·2
4-*NN*-Dipropylamino-4'-chloro	167	$C_{19}H_{24}N_3ClS$	11·3	11·6
4-Bromo-4'-*NN*-dipropylamino	172	$C_{19}H_{24}N_3BrS$	10·1	10·3
4-Chloro-4'-*NN*-diethylamino-2'-methyl	190	$C_{18}H_{22}N_3ClS$	12·0	12·1
2-Ethyl-4'-fluoro	120	$C_{15}H_{15}N_2FS$	10·0	10·2
4-Chloro-2'-ethyl	139	$C_{15}H_{15}N_2ClS$	9·3	9·6
2 : 4'-Diethyl	125	$C_{17}H_{20}N_2S$	9·5	9·8
4-Ethoxy-2'-ethyl	160	$C_{17}H_{20}ON_2S$	9·2	9·3
4-Chloro-4'-*cyclo*hexyl	229	$C_{19}H_{21}N_2ClS$	8·0	8·2
4-*cyclo*Hexyl	185	$C_{19}H_{22}N_2S$	8·9	9·0
4-*cyclo*Hexyl-2'-methoxy	176	$C_{20}H_{24}ON_2S$	8·3	8·2
4-*cyclo*Hexyl-4'-methyl	176	$C_{20}H_{24}N_2S$	8·3	8·6
4-Ethyl-4'-*cyclo*hexyl	151	$C_{21}H_{26}N_2S$	8·5	8·3

Thiocarbanilides (contd.).

	M. p.	Formula	Found N (%)	Reqd. N (%)
4-Ethoxy-4′-*cyclo*hexyl	170°	$C_{21}H_{26}ON_2S$	7·8	7·9
4-*cyclo*Hexyl-4′-*iso*pentyloxy	155	$C_{24}H_{32}ON_2S$	7·0	7·1
4-Fluoro-4′-*cyclo*hexyl	163	$C_{19}H_{21}N_2FS$	8·2	8·5
4-Fluoro-3′ : 4′-dimethyl	164	$C_{15}H_{15}N_2FS$	10·0	10·2
4-Chloro-3′ : 4′-dimethyl	168	$C_{15}H_{15}N_2ClS$	9·5	9·6
4-Bromo-3′ : 4′-dimethyl	172	$C_{15}H_{15}N_2BrS$	8·3	8·4
3 : 4 : 4′-Trimethyl	108	$C_{16}H_{18}N_2S$	10·1	10·4
2 : 4 : 3′ : 4′-Tetramethyl	128	$C_{17}H_{20}N_2S$	10·1	9·9
4-Methoxy-3′ : 4′-dimethyl	120	$C_{16}H_{18}ON_2S$	9·9	9·8
3 : 4-Dimethyl-4′-*iso*pentyloxy	105	$C_{20}H_{26}ON_2S$	8·0	8·2
4-Fluoro-2′ : 5′-dimethyl	147	$C_{15}H_{15}N_2FS$	10·0	10·2
4-Chloro-2′ : 5′-dimethyl	160	$C_{15}H_{15}N_2ClS$	9·4	9·6
4-Bromo-2′ : 5′-dimethyl	178	$C_{15}H_{15}N_2BrS$	8·3	8·4
2 : 4 : 2′ : 5′-Tetramethyl	133	$C_{17}H_{20}N_2S$	9·6	9·9
4-Methoxy-2′ : 5′-dimethyl	126	$C_{16}H_{18}ON_2S$	9·6	9·8
4-Ethoxy-2′ : 5′-dimethyl	119	$C_{17}H_{20}ON_2S$	9·5	9·3
4-Fluoro-2′ : 4′ : 5′-trimethyl	156	$C_{16}H_{17}N_2FS$	9·4	9·7
4-Chloro-2′ : 4′ : 5′-trimethyl	175	$C_{16}H_{17}N_2ClS$	9·0	9·1
4-Ethyl-2′-methyl-5′-propyl	116	$C_{19}H_{24}N_2S$	8·9	9·0
4-Ethoxy-2′-methyl-5′-propyl	93	$C_{19}H_{24}ON_2S$	8·4	8·5
4-Methoxy-2′-methyl-5′-propyl	113	$C_{18}H_{22}ON_2S$	8·6	8·9
5-Butyl-2-ethyl-4-fluoro	95	$C_{19}H_{23}N_2FS$	8·1	8·4
5-Butyl-4′-ethoxy-2-ethyl	122	$C_{21}H_{28}ON_2S$	8·0	7·9
5-Butyl-2-ethyl-4′-methoxy	110	$C_{20}H_{26}ON_2S$	8·0	8·2
4-Acetamido	198	$C_{15}H_{15}ON_3S$	14·8	14·7
4-Acetamido-4′-methyl	224	$C_{16}H_{17}ON_3S$	14·2	14·0
4-Acetamido-2′ : 4′-dimethyl	184	$C_{17}H_{19}ON_3S$	13·1	13·4
4-Acetamido-4′-ethyl	199	$C_{17}H_{19}ON_3S$	13·2	13·4
4-Acetamido-4′-fluoro	220	$C_{15}H_{14}ON_3FS$	13·6	13·9
4-Acetamido-4′-bromo	229	$C_{15}H_{14}ON_3BrS$	11·4	11·5
4-Acetamido-4′-methoxy	216	$C_{16}H_{17}O_2N_3S$	13·5	13·3
4-Acetamido-4′-ethoxy	215	$C_{17}H_{19}O_2N_3S$	12·6	12·8
4-Acetamido-4′-*iso*pentyloxy	188	$C_{20}H_{25}O_2N_3S$	11·0	11·3
4 : 4′-Bis-(*NN*-diethylamino)	173	$C_{21}H_{30}N_4S$	15·0	15·1
4-*NN*-Diethylamino-4′-ethyl	147	$C_{19}H_{25}N_3S$	12·5	12·8
4-*NN*-Diethylamino-2′ : 4′-dimethyl	146	$C_{19}H_{25}N_3S$	12·6	12·8
4-*NN*-Diethylamino-4-ethoxy	153	$C_{19}H_{25}ON_3S$	12·1	12·2
4-*NN*-Diethylamino-4′-*iso*pentyloxy	132	$C_{22}H_{31}ON_3S$	10·6	10·9
4-*NN*-Dipropylamino-4′-ethyl	148	$C_{21}H_{29}N_3S$	11·8	11·8
4-*NN*-Diethylamino-2 : 4′-dimethyl	171	$C_{19}H_{25}N_3S$	13·1	12·9
4-*NN*-Diethylamino-2 : 3′-dimethyl	136	$C_{19}H_{25}N_3S$	13·0	12·9
4-*NN*-Diethylamino-4′-methoxy-2-methyl	165	$C_{19}H_{25}ON_3S$	12·1	12·3
4-*NN*-Diethylamino-2′-methoxy-2-methyl	151	$C_{19}H_{25}ON_3S$	12·0	12·3
4-*NN*-Diethylamino-2 : 2′ : 4′-trimethyl	168	$C_{20}H_{27}N_3S$	12·5	12·3

[a] Prepared from 4-bromo-3-chloroaniline (2 mol.), carbon disulphide (1 mol.), and sulphur in boiling ethanol; recrystallisation from ethanol–benzene.

forming needles, m. p. 152°, from methanol (Found: C, 41·4; H, 3·1. C_8H_7ONBrF requires C, 41·4; H, 3·0%). Deacetylation with hydrochloric acid yielded 4-*bromo*-3-*fluoroaniline*, crystallising as leaflets, m. p. 72—73°, from water (Found: C, 37·6; H, 2·8. C_6H_5NBrF requires C, 37·9; H, 2·7%). This amine (2 mol.) was characterised by condensation with chloranil (1 mol.) in boiling ethanol, to give 3 : 6-*di*-(4-*bromo*-3-*fluoroanilino*)-2 : 5-*dichloro*-1 : 4-*benzoquinone*, brown-violet needles, m. p. >320°, from xylene (Found: C, 38·9; H, 1·7. $C_{18}H_8O_2N_2Cl_2Br_2F_2$ requires C, 39·1; H, 1·5%).

Chlorination of 2-Methylacetanilide.—A suspension of 2-methylacetanilide (45 g.) and *N*-chlorosuccinimide (35 g.) in carbon tetrachloride (300 c.c.) was refluxed for 4 hr., and the resulting 4-chloro-2-methylacetanilide was deacetylated in the usual way, giving 4-chloro-2-methylaniline (28 g.), b. p. 189—192°/40 mm., m. p. 30°.

Preparation of NN′-*Disubstituted Ureas* (*see Table*).—These compounds were obtained, mostly in almost theoretical yield, by adding a benzene solution of the aryl *iso*cyanate (1 mol.) to the amine (1 mol.) in an appropriate solvent (benzene, xylene, or anhydrous dioxan) at room temperature; the product was recrystallised from an anhydrous solvent. Sterically hindered amines reacted anomalously: with *o*-trifluoromethylaniline, phenyl *iso*cyanate gave

the expected unsymmetrical urea, but *p*-chlorophenyl *iso*cyanate gave 4 : 4'-dichlorocarbanilide, needles, m. p. 318°, from ethanol (Found: N, 9·9. Calc. for $C_{13}H_{10}ON_2Cl_2$: N, 10·0%). With the exception of ureas derived from 2-amino-5-nitrothiazole, which were yellow to orange-yellow, all the ureas were colourless.

N-*Phenyl*-N'-(5 : 6 : 7 : 8-*tetrahydro*-1-*naphthyl*)*urea* had m. p. 205° (Found: C, 76·8; H, 6·8. $C_{17}H_{18}ON_2$ requires C, 76·7; H, 6·8%), and the 4-*chloro*-5 : 6 : 7 : 8-*tetrahydro*-1-*naphthyl analogue* has m. p. 258° (Found: C, 67·8; H, 5·8. $C_{17}H_{17}ON_2Cl$ requires C, 68·0; H, 5·7%).

Preparation of NN'-*Disubstituted Thioureas*.—These were obtained, in lower yields than for the ureas, by treating the appropriate amine (1 mol.) in warm ethanol with the aryl *iso*thiocyanate (1 mol.); in most cases, the product solidified and recrystallised from ethanol, benzene, or toluene. Reaction was much slower and required slight heating at 60° when the amine and/or the *iso*thiocyanate was *ortho*-substituted. N-p-*Fluoro*-, m. p. 139° (Found: N, 9·1. $C_{17}H_{17}N_2FS$ requires N, 9·3%), N-p-*chloro*-, m. p. 192° (Found: N, 8·6. $C_{17}H_{17}N_2ClS$ requires LN, 7·8%), and N-p-*bromo*-*phenyl*-N'-(5 : 6 : 7 : 8-*tetrahydro*-1-*naphthyl*)*thiourea*, m. p. 196° (Found: N, 7·5. $C_{17}H_{17}N_2BrS$ requires N, 7·8%), were prepared.

Miscellaneous Unsymmetrical Ureas (*cf. Table*).—N-(1-*Acetyl*-7-*naphthyl*)-N'-p-*chlorophenyl*-*urea*, prepared from 7-amino-1-acetonaphthone,[12] formed needles, m. p. 242°, from benzene (Found: C, 67·3; H, 4·6. $C_{19}H_{15}O_2N_2Cl$ requires C, 67·4; H, 4·5%); N-p-*chlorophenyl*-N'-(2-*phenanthridinyl*)*urea*, obtained from 2-aminophenanthridine, formed needles, m. p. 280°, from benzene (Found: N, 11·8. $C_{20}H_{14}ON_3Cl$ requires N, 12·1%); N-(3 : 4-*dichlorophenyl*)-N'-6-*quinolylurea*, prepared from 6-aminoquinoline, crystallised as needles, m. p. 288°, from ethanol–benzene (Found: N, 12·5. $C_{16}H_{11}ON_3Cl_2$ requires N, 12·7%).

Substituted 2-*Chloro*-1 : 4-*naphthaquinones*.—These (see Table) were prepared by refluxing for 2 hr. an ethanolic solution of equimolar amounts of 2 : 3-dichloro-1 : 4-naphthaquinone and the appropriate arylamine in the presence of sodium acetate; the precipitate obtained on cooling was collected, washed with water, and recrystallised from ethanol or ethanol–benzene.

3-*Substituted* 2-*chloro*-1 : 4-*naphthaquinones*.

			Found (%)		Reqd. (%)	
3-Substituent [a]	M. p.	Formula	C	H	C	H
4-Bromo-3-chloroanilino	255°	$C_{16}H_8O_2NCl_2Br$	48·1	2·2	48·4	2·0
4-Chloro-2-methylanilino	213	$C_{17}H_{11}O_2NCl_2$	61·2	3·5	61·4	3·3
4-Bromo-2-methylanilino	218	$C_{17}H_{11}O_2NClBr$	54·2	2·6	54·2	2·9
3 : 5-Dichloroanilino	269	$C_{16}H_8O_2NCl_3$	54·3	2·3	54·5	2·3
2 : 4-Difluoroanilino	198	$C_{16}H_8O_2NClF_2$	60·0	2·7	60·1	2·5
3 : 4-Difluoroanilino	199	$C_{16}H_8O_2NClF_2$	59·8	2·7	60·1	2·5
p-*NN*-Diethylaminoanilino	159	$C_{20}H_{19}O_2N_2Cl$	68·0	5·7	67·8	5·4
p-*NN*-Dipropylaminoanilino	118	$C_{22}H_{23}O_2N_2Cl$	69·1	6·2	69·0	6·1

[a] Except for the last two compounds which were deep brown-violet, these quinones were deep red leaflets or prisms.

1-*Aryl*-2 : 5-*dimethylpyrroles*.—These compounds (see Table), synthesised for characterisation of some arylamines, were prepared by refluxing for a few hours the appropriate amine with acetonylacetone in slight excess, the product being distilled *in vacuo* and recrystallised from ligroin (b. p. 100—130°).

1-*Substituted* 2 : 5-*dimethylpyrroles*.

				Found (%)	Reqd. (%)
1-Substituent	B. p./mm.	M. p.	Formula	N	N
p-Diethylaminophenyl	181°/17	85°	$C_{16}H_{22}N_2$	11·5	11·6
p-Dipropylaminophenyl	208°/18	57	$C_{18}H_{26}N_2$	10·1	10·4
3 : 4-Difluorophenyl	155°/30	57	$C_{12}H_{11}NF_2$	7·0	6·8
4-Bromo-3-chlorophenyl	181°/18	58	$C_{12}H_{11}NBrCl$	5·0	4·9

6-*Chloro*-2-p-*chlorophenyliminazo*[1,2-a]*pyridine* (I; R = Cl, R' = H).—A solution of ω-bromo-4-chloroacetophenone (2·3 g.) and 2-amino-5-chloropyridine (1·3 g.) in ethanol (20 c.c.) was refluxed for 6 hr.; the precipitate obtained on cooling recrystallised from ethanol as needles (1·5 g.), m. p. 209° (Found: N, 10·9. $C_{13}H_8N_2Cl_2$ requires N, 10·6%). Similarly were prepared the 2-p-*bromophenyl*-6-*chloro*-, needles, m. p. 221° (from ethanol) (Found:

[12] Leonard and Hyson, *J. Amer. Chem. Soc.*, 1949, **71**, 1392.

N, 9·3. $C_{13}H_8N_2ClBr$ requires N, 9·1%), 6-*chloro*-2-p-*fluorophenyl*-, m. p. 199° (from ethanol) (Found: N, 11·7. $C_{13}H_8N_2ClF$ requires N, 11·4%), and 2-(3-*bromo*-4-*methoxyphenyl*)-6-*chloro*-*compound*, yellowish needles, m. p. 194° (from ethanol) (Found: N, 8·5. $C_{14}H_{10}ON_2ClBr$ requires N, 8·3%).

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