A Versatile Synthesis of Novel *N,N,N'*-Trisubstituted Guanidines[1]

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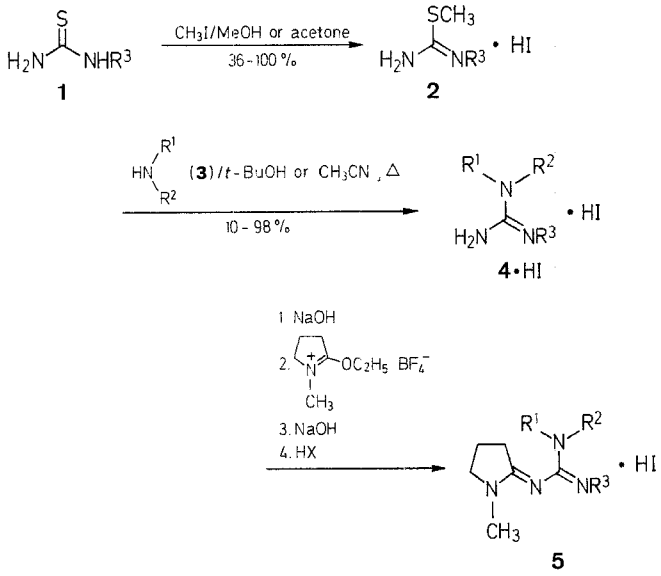
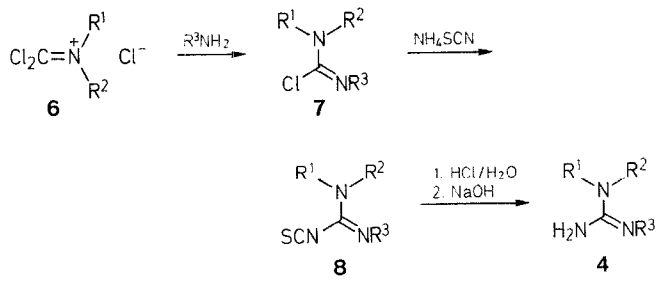
N,N,N''-Trisubstituted guanidines (most of them *N''*-aryl-*N*-azacycloalkanecarboximidamides) are prepared in generally good yields by *S*-methylation of monosubstituted thioureas with methyl iodide in methanol or acetone and reaction of the resultant methyl carbamimidothioate hydroiodides with secondary amines in boiling *tert*-butyl alcohol or acetonitrile.

In the preceding article,[3] we described modifications of procedures for obtaining monosubstituted thioureas **1** in improved yields. Thioureas **1** serve as convenient starting materials for synthesis, via methyl *N'*-substituted carbamimidothioate (isothiouronium) salts **2**, of a wide variety of novel trisubstituted guanidines **4** (Scheme **A**), which are useful as intermediates for preparation of a new class of oral hypoglycemic agents **5**.[4]



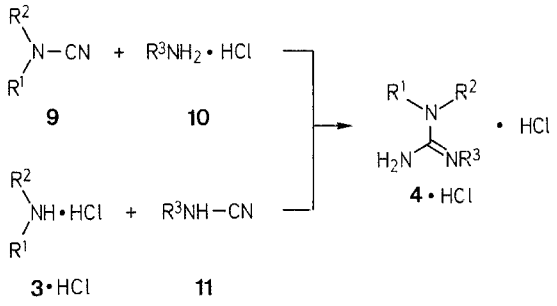
Scheme **A**

Only a few guanidines **4**, wherein R^1-N-R^2 forms a ring, have been reported; these having been prepared either by hydrochloric acid hydrolysis of carbamimidoyl isothiocyanates **8** (Scheme **B**)[5,6] or reaction of either a cyclic cyanamide **9** with an aniline hydrochloride **10** or an aromatic cyanamide **11** with an amine **3** hydrochloride (Scheme **C**).[7,8,9]



Scheme **B**

We elected to examine the synthesis of cyclic amine-containing guanidines **4** as shown in Scheme **A**. Treatment of thioureas **1** with methyl iodide in methanol or acetone gave their respective methyl carbamimidothioate (isothiouronium) salt derivatives **2** (Table 1). Reactions of **2** with various cyclic amines **3** in refluxing *tert*-butyl alcohol gave a wide variety of guanidines **4** (Table 2) in generally fair to good yields (unoptimized). Furthermore, amines **3** in which one of the groups R^1 and R^2 is a bulky cycloalkyl ring may also be successfully employed (Table 2, entries 6, 8, 48, 83, etc.) Scheme **A** accommodates phenyl substituents which range from strongly electron-withdrawing (Table 2, entries 22 and 53) to strongly electron-donating (entries 42 and 54), as well as bulky substituents on a *ortho* position (entries 35–38). In addition to the broad array of substituted phenyl moieties, R^3 may be comprised of groups such as bicyclo[2.2.1]heptan-2-yl, diphenylmethyl, 9*H*-fluoren-9-yl, 1- and 2-naphthyl, and heteroaryl (c.f. entries 88–99).



Scheme **C**

We have determined that one of the Scheme **A** reactants (**2** or **3**) should be in a salt form which is soluble in the reaction medium in order for these reactions to proceed at satisfactory rates. This observation was made when morpholine (2 mol) was added to methyl *N'*-phenylcarbamimidothioate hydroiodide (**2**, $R^3 = C_6H_5$; (1 mol), causing an immediate separation of morpholine hydroiodide. This precipitation effectively removed most of the soluble proton source from the reaction mixture, thereby causing a significant slowing of the reaction rate (Table 2, entries 2, 12, 25). We found that addition of ~ 1 mol of triethylamine allowed the reaction mixtures to remain homogeneous, permitted reduction of the quantity of morpholine employed, and gave satisfactory reaction rates (entries 11, 14, 19, etc.). Thus, a readily available proton source appears to be required to allow more efficient displacement and evolution of methanethiol, since an attempted reaction of **2** ($R^3 = C_6H_5$) in free base form with morpholine under the same conditions gave little or no result. In addition, we also found triethylamine to be a useful adjunct in reactions which employed expensive amines (entries 3, 6, 8, etc.). Reactions in which compounds **2** as free bases were treated with either an amine salt (entry 15) or with the amine plus added acid (1 equiv; entry 78) gave the expected products **4** in yields similar to those obtained from salts of **2** with amines.

Table 1. Methyl *N'*-Arylcarbamimidothioates **2** Prepared

Entry	R^3	mol thiourea **1**	mol CH_3I	Solvent	Time (h)	Yield[a] (%)	mp (°C)[b] (solvent)	Molecular Formula[c] or Lit. mp (°C)
1	C_6H_5	0.55	0.55	MeOH	17	94	145–147 (*i*-PrOH/Et_2O)	147[12]
2	4-FC_6H_4	0.68	0.75	MeOH	2	70	149.5–150.5 (*t*-BuOH/Et_2O)	147–150[13]
3	2-ClC_6H_4	0.82	0.90	MeOH	3	96	162.5–166 (*t*-BuOH)	154–156[14]
4	3-ClC_6H_4	0.20	0.22	MeOH	18	82	129–131 (*t*-BuOH/Et_2O)	$C_8H_9ClN_2S \cdot HI$ (200.7/328.6)
5	4-ClC_6H_4	0.47	0.51	MeOH	3	89	165–168 (*i*-PrOH/Et_2O)	163–165[15]
6	2-BrC_6H_4	0.49	0.54	MeOH	3	98	154–156 (*t*-BuOH/Et_2O)	$C_8H_9BrN_2S \cdot HI$ (245.1/373.0)
7	3-$CF_3C_6H_4$	0.054	0.10	acetone	1	92	120–122 (acetone/Et_2O)	$C_9H_9F_3N_2S \cdot HI$ (234.2/362.2)
8	4-$CF_3C_6H_4$	0.45	0.49	MeOH	18	36[d]	126–190 dec (*t*-BuOH/Et_2O)	$C_9H_9F_3N_2S \cdot HI$ (234.2/362.2)
9	2-$CH_3C_6H_4$	0.79	0.87	MeOH	2	94	128–129 (*t*-BuOH/Et_2O)	127.5–130[14]
10	3-$CH_3C_6H_4$	0.79	0.95	acetone	2	85	149–152 (acetone)	$C_9H_{12}N_2S \cdot HI$ (180.3/308.2)
11	4-$CH_3C_6H_4$	1.0	1.0	acetone	18	94[e]	129–130.5 (*i*-PrOH/Et_2O)	128–130[15]
12	2-$C_2H_5C_6H_4$	0.71	0.83	MeOH	4	90	125–128 (Et_2O)	$C_{10}H_{14}N_2S \cdot HCl$ (194.3/230.8)
13	4-$C_2H_5C_6H_4$	0.58	0.63	MeOH	1	69	110–111 (*t*-BuOH/Et_2O)	$C_{10}H_{14}N_2S \cdot HI$ (194.3/322.2)
14	2-[H_2C=$C(CH_3)$]C_6H_4	0.31	0.35	MeOH	18	100 (crude)	152–154 (*t*-BuOH/Et_2O)	$C_{11}H_{14}N_2S \cdot HI$ 206.3/334.2
15	2-(*i*-C_3H_7)C_6H_4	0.55	0.61	MeOH	18	85	107–109 (MeOH/Et_2O)	$C_{11}H_{16}N_2S \cdot HI$ (208.3/336.2)
16	4-(*i*-C_3H_7)C_6H_4	0.46	0.5	MeOH	1	73	140–142 (*t*-BuOH/Et_2O)	$C_{11}H_{16}N_2S \cdot HI$ (208.3/336.2)
17	4-(*t*-C_4H_9)C_6H_4	0.124	0.136	MeOH	3	63	185–187 (acetone/Et_2O)	$C_{12}H_{18}N_2S \cdot HI$ (222.4/350.3)
18	4-$C_4H_9C_6H_4$	0.05	0.05	acetone	18	65	77–79 (*t*-BuOH/Et_2O)	$C_{12}H_{18}N_2S \cdot HI$ (222.4/350.3)
19	4-OHC_6H_4	0.62	0.70	MeOH	3	76	174–176 (*t*-BuOH/Et_2O)	176–181[16]
20	2-$CH_3OC_6H_4$	0.38	0.42	MeOH	1	92	123–125 (*i*-PrOH/Et_2O)	125 (dec)[17]
21	3-$CH_3OC_6H_4$	0.10	0.15	acetone	10	95	119–123 (acetone/Et_2O)	$C_9H_{12}N_2OS \cdot HI$ (196.3/324.2)
22	4-$CH_3OC_6H_4$	0.77	0.92	MeOH	18	92	162–163 (MeOH/Et_2O)	164–165[18]
23	3-($C_6H_5CH_2O$)C_6H_4	0.23	0.28	MeOH	5	93	103–105 (*t*-BuOH/Et_2O)	$C_{15}H_{16}N_2OS \cdot HI$ (272.4/400.3)
24	4-($C_6H_5CH_2O$)C_6H_4	0.18	0.31	acetone	1 (reflux)	88	199–201.5 (acetone/Et_2O)	$C_{15}H_{16}N_2OS \cdot HI$ (272.4/400.3)
25	4-$CH_3SC_6H_4$	0.43	0.50	MeOH	18	91	165–167 (*t*-BuOH)	$C_9H_{12}N_2S_2 \cdot HI$ (212.3/340.3)
26	4-$NO_2C_6H_4$	0.12	0.24	MeOH	48	76	190–197 dec (*i*-PrOH)	188–190[15]
27	4-[$N(CH_3)_2$]C_6H_4	0.43	0.43	MeOH	6	85	166–168 (*t*-BuOH/Et_2O)	$C_{10}H_{15}N_3S \cdot HI$ (209.3/337.2)
28	2,3-$Cl_2C_6H_3$	0.77	0.85	MeOH	2	85	151–152 (*t*-BuOH/Et_2O)	$C_8H_8Cl_2N_2S \cdot HI$ (255.1/363.0)
29	2,6-$Cl_2C_6H_3$	0.064	0.064	acetone	2	71	184–187 (acetone/EtOAc)	170[19]
30	3,4-$Cl_2C_6H_3$	0.89	0.98	MeOH	3	73	156–158 (*t*-BuOH/Et_2O)	168–171[20]
31	2-Cl-4-$CH_3C_6H_3$	0.31	0.36	MeOH/ acetone	4	84[f]	150–152 (MeOH/Et_2O)	$C_9H_{11}ClN_2S \cdot HI$ (214.7/342.6)
32	3-Cl-2-$CH_3C_6H_3$	0.77	0.85	MeOH	18	80	158–160 (*t*-BuOH/Et_2O)	$C_9H_{11}ClN_2S \cdot HI$ (214.7/342.6)
33	3-Cl-4-$CH_3C_6H_3$	0.35	0.38	MeOH	18	88	137–140 (MeOH/*t*-BuOH/ Et_2O)	$C_9H_{11}ClN_2S \cdot HI$ (214.7/342.6)
34	4-Cl-2-$CH_3C_6H_3$	0.65	0.72	MeOH	18	100 (crude)	137–140 (MeOH/*t*-BuOH)	$C_9H_{11}ClN_2S \cdot HI$ (214.7/342.6)

Table 1. (continued)

Entry	R^3	mol thiourea **1**	mol CH_3I	Solvent	Time (h)	Yield[a] (%)	mp (°C)[b] (solvent)	Molecular Formula[c] or Lit. mp (°C)
35	5-Cl-2-$CH_3C_6H_3$	0.62	0.69	MeOH/ acetone (1:1)	3	83	173–176 (MeOH/Et_2O)	$C_9H_{11}ClN_2S \cdot HI$ (214.7/342.6)
36	2,3-$(CH_3)_2C_6H_3$	0.65	0.72	MeOH	18	82	160–162 (*t*-BuOH/Et_2O)	$C_{10}H_{14}N_2S \cdot HI$ (194.3/322.1)
37	2,4-$(CH_3)_2C_6H_3$	0.35	0.38	MeOH	18	87	124–127 (*t*-BuOH/Et_2O)	134[21]
38	2,5-$(CH_3)_2C_6H_3$	0.64	0.69	MeOH	18	91	– (MeOH/Et_2O)	146[21]
39	2,6-$(CH_3)_2C_6H_3$	0.38	0.38	acetone	18	84	156–158 (acetone/EtOAc)	164[21]
40	3,4-$(CH_3)_2C_6H_3$	0.66	0.73	MeOH	4	73	128–131 (polymorph), 144–146 (*t*-BuOH/Et_2O)	$C_{10}H_{14}N_2S \cdot HI$ (194.3/322.1)
41	3,5-$(CH_3)_2C_6H_3$	0.61	0.67	MeOH	4	81	163–164 (*t*-BuOH/Et_2O)	$C_{10}H_{14}N_2S \cdot HI$ (194.3/322.1)
42	3,4-$(CH_2)_3C_6H_3$	0.75	0.83	MeOH	18	77[f]	138–140 (*t*-BuOH/Et_2O)	$C_{11}H_{14}N_2S \cdot HI$ (206.3/334.2)
43	5-Cl-2-$CH_3OC_6H_3$	0.65	0.90	MeOH	5	84	157.5–159.5 (*t*-BuOH)	$C_9H_{11}ClN_2OS \cdot HI$ (230.7/358.6)
44	2-Cl-4-$(C_6H_5CH_2O)C_6H_3$	0.1	0.11	MeOH	18	88	126–127.5	$C_{15}H_{15}ClN_2OS$ (306.8)
45	3,4$(OCH_2O)C_6H_3$	0.45	0.49	MeOH	18	95	138–140 (MeOH/*t*-BuOH/ Et_2O)	$C_9H_{10}N_2O_2S \cdot HI$ (210.2/338.1)
46	3,4-$(OCH_3)_2C_6H_3$	0.30	1.2	MeOH	96	88	186–193 dec (*i*-PrOH)	$C_{10}H_{14}N_2O_2S \cdot HI$ (226.3/354.2)
47	2,4,5-$(CH_3)_3C_6H_2$	0.67	0.74	MeOH	18	79	174–176 (*t*-BuOH/Et_2O)	$C_{11}H_{16}N_2S \cdot HI$ (208.3/336.2)
48	2,5-$(CH_3)_2$-4-$CH_3OC_6H_2$	0.28	0.35	MeOH	72	89	127.5–129 (*t*-BuOH/Et_2O)	$C_{11}H_{16}N_2OS \cdot HI$ (224.3/352.2)
49	2-pyrimidinyl	0.63	0.95	MeOH	18 (reflux)	54	174–176 dec (EtOH)	228[22]
50	2-pyridinyl	0.34	0.35	acetone/ MeOH	4	91	136–139 (MeOH/*i*-PrOH)	$C_7H_9N_3S \cdot HI$ (167.2/295.2)
51	3-pyridinyl	0.56	0.58	acetone	1 (25°C), 0.5 (reflux)	64	98–100 (toluene)	$C_7H_9N_3S$ (167.2)
52	*exo*-bicyclo[2.2.1]-heptan-2-yl	0.2	0.24	acetone	3 (reflux)	~100 (crude)	viscous oil[f]	$C_9H_{16}N_2S \cdot HI$ (184.3/312.2)
53	1-naphthalenyl	0.2	0.2	CH_2Cl_2/ MeOH (4:1)	18	73	191–192 (*i*-PrOH)	182–183[23]
54	9*H*-fluoren-9-yl	0.15	0.19	acetone	72	97	208–210 (acetone)	$C_{15}H_{14}N_2S \cdot HI$[g] (254.3/382.3)
55	$CH(C_6H_5)_2$	0.05	0.05	MeOH	18	76	177–182 (MeOH)	178–180[24]

[a] Yields are not maximized.
[b] Uncorrected, measured on a Thomas-Hoover apparatus.
[c] Satisfactory microanalyses obtained: C ±0.16, H ±0.08, N ±0.16.
[d] Extremely hygroscopic, not analyzed. Severe losses incurred during recrystallization.
[e] Overall yield from 4-methylaniline. See preceeding paper.[3]
[f] Not analyzed, see corresponding entry(ies) in Table 2.
[g] Microanalysis: calc. S 8.39, found 8.32

In a few instances, new methyl carbamimidothioate hydroiodides **2** were not analyzed, but were instead converted into guanidines **4** which were characterized by microanalyses. Guanidines **4** were generally isolated as stable, crystalline hydroiodide salts. Those **4** hydroiodides which could not be induced to crystallize were either converted to their respective free bases or to other salt forms, then purified, and characterized. During the last stages of this work, we found that reactions of **2** and **3** in boiling acetonitrile appear to proceed faster and in higher yield (Table 2, entries 39 and 40). More comparative experiments, however, are required to ascertain the validity and generality of these observations.

After this study was completed, Maryanoff et al.,[10] in connection with chemical development work associated with the synthesis of *N*-(1-methyl-2-pyrrolidinylidene)-*N'*-phenyl-4-morpholinecarboximidamide (*E*)-butenedioate (USAN linogliride fumarate), a novel oral hypoglycemic agent from these laboratories,[11] recently reported a synthesis of guanidines, viz. the guanidine of Table 2, entry 2, which obviates the evolution of the malodorous methanethiol.

***N'*-Substituted Methyl Carbamimidothioate Hydroiodides; General Procedure:**

These compounds are prepared by treating a stirring suspension of the thiourea **1** in MeOH or acetone (~1 L/mol) with an appropriate

Table 2. Guanidines **4** Prepared

Entry	R^3	mol **2**	HNR^1R^2	mol HNR^1R^2	mol $N(C_2H_5)_3$	Reflux Time (h)	HX	Yield[a,h] (%)	mp (°C)[b] (Solvent)	Molecular Formula[i]
1	C_6H_5	0.17	pyrrolidine	0.34	–	18	HI	75	180–182 (*t*-BuOH)	$C_{11}H_{15}N_3 \cdot HI$ (189.3/317.2)
2	C_6H_5	0.30	morpholine	0.60	–	24	HI	63	175–177 (acetone)	$C_{11}H_{15}N_3O \cdot HI$ (205.3/333.2)
3	C_6H_5	0.05	tetrahydro-1,4-thiazine	0.055	0.05	17	HBr	44	203–205 (*i*-PrOH/acetone)	$C_{11}H_{15}N_3S \cdot HBr$ (221.3/302.2)
4	C_6H_5	0.40	piperidine	0.8	–	24	HNO_3	36	139–141 (*i*-PrOH/EtOH)	$C_{12}H_{17}N_3 \cdot HNO_3$ (203.3/266.3)
5	C_6H_5	0.05	1-methylpiperazine	0.10	–	22	HI	27	221–222 (*i*-PrOH)	$C_{12}H_{18}N_4 \cdot HI$ (218.3/346.2)
6	C_6H_5	0.10	$HN(CH_3)$ *c*-C_5H_9	0.13	0.10	11	HI	64	154–157 (*t*-BuOH/Et_2O)	$C_{13}H_{19}N_3 \cdot HI$ (217.3/345.2)
7	C_6H_5	0.05	2,6-dimethylpiperazine	0.12	–	18	HI	10	266 (dec) (*t*-BuOH)	$C_{13}H_{20}N_4 \cdot 2HI$ (232.3/488.2)
8	C_6H_5	0.1	H_2N(*c*-C_7H_{13})	0.125	0.075	18	–	46	132.5–134 (Et_2O/hexane)	$C_{14}H_{21}N_3$ (231.3)
9	4-FC_6H_4	0.25	morpholine	0.28	0.28	4	HI	71	202–204[j] (*i*-PrOH/Et_2O)	$C_{11}H_{14}FN_3O \cdot HI$ (223.2/351.2)
10	2-ClC_6H_4	0.1	pyrrolidine	0.2	–	17	HI	79	134–135 (*t*-BuOH/Et_2O)	$C_{11}H_{14}ClN_3 \cdot HI$ (223.7/351.6)
11	2-ClC_6H_4	0.05	morpholine	0.08	0.05	72	–	93 (crude)	88–91 (–)	$C_{11}H_{14}ClN_3O$[k] (239.7)
12	3-ClC_6H_4	0.2	morpholine	0.4	–	24	–	53	144–145.5 (EtOH/H_2O)	$C_{11}H_{14}ClN_3O$ (239.7)
13	4-ClC_6H_4	0.6	$HN(CH_3)_2$	large excess	–	72 (25°C)	HI	79	173–175 (*t*-BuOH/Et_2O)	$C_9H_{12}ClN_3 \cdot HI \cdot 1/4H_2O$[l] (197.7/325.6/334.6)
14	4-ClC_6H_4	0.39	morpholine	0.44	0.43	48	HI	62	209–211 (*t*-BuOH/Et_2O)	$C_{11}H_{14}ClN_3O \cdot HI$ (239.7/367.6)
15	4-ClC_6H_4	0.07 (base)	tetrahydro-1,4-thiazine · HCl	0.084	0.084	6	CH_3SO_3H	60	200–205 (*i*-PrOH/Et_2O)	$C_{11}H_{14}ClN_3S \cdot CH_3SO_3H$ (255.8/351.9)
16	4-ClC_6H_4	0.06	$HN(C_2H_5)_2$	0.072	0.063	17	–	100 (crude)	oil	$C_{11}H_{16}ClN_3$[m] (225.7)
17	4-ClC_6H_4	0.05	piperidine	0.1	–	4	–	50	96–98 (Et_2O)	$C_{12}H_{16}ClN_3$ (237.7)
18	2-BrC_6H_4	0.23	pyrrolidine	0.49	–	17	HI	53	172.5–174.5 (*t*-BuOH/Et_2O)	$C_{11}H_{14}BrN_3 \cdot HI$ (268.2/396.1)
19	2-BrC_6H_4	0.01	morpholine	0.012	0.2	17	HI	58	194–196 (MeOH/acetone)	$C_{11}H_{14}BrN_3O \cdot HI$ (284.2/412.1)
20	3-$CF_3C_6H_4$	0.08	morpholine	0.088	0.088	6	HI	76	194–196 (*i*-PrOH/Et_2O)	$C_{12}H_{14}F_3N_3O \cdot HI$[n] (273.3/401.2)
21	3-$CF_3C_6H_4$	0.1	$HN(CH_3)$ *c*-C_5H_9	0.13	0.1	7	fumaric acid	60	154–156 dec. (*i*-PrOH/Et_2O)	$C_{14}H_{18}F_3N_3 \cdot 1 1/2C_4H_4O_4$ (285.3/401.4)
22	4-$CF_3C_6H_4$	0.14	morpholine	0.15	0.15	17	–	38	118–120 (toluene/hexane)	$C_{12}H_{14}F_3N_3O$ (273.3/401.2)
23	2-$CH_3C_6H_4$	0.1	pyrrolidine	0.2	–	17	HI	75	151.5–153 (*t*-BuOH/Et_2O)	$C_{12}H_{17}N_3 \cdot HI$ (203.3/331.2)
24	2-$CH_3C_6H_4$	0.13	morpholine	0.13	0.2	18	HI	70	169–171 (*t*-BuOH/Et_2O)	$C_{12}H_{17}N_3O \cdot HI$ (219.3/347.2)
25	3-$CH_3C_6H_4$	0.12	morpholine	0.24	–	18	HI	78	168–191 dec (*i*-PrOH)	$C_{12}H_{17}N_3O \cdot HI \cdot 1/4H_2O$ (219.3/347.2/351.7)
26	3-$CH_3C_6H_4$	0.05	tetrahydro-1,4-thiazine	0.05	0.05	18	–	43	110–111 (Et_2O/hexane)	$C_{12}H_{17}N_3S$
27	3-$CH_3C_6H_4$	0.095	$HN(CH_3)$ *c*-C_5H_9	0.1	0.1	24	*N*-cyclohexylsulfamic acid	58	170–172 (*i*-PrOH/acetone)	$C_{14}H_{21}N_3 \cdot C_6H_{13}NO_3S$ (231.4/410.6)
28	4-$CH_3C_6H_4$	0.05	$HN(CH_3)_2$	large excess	–	17 (25°C)	HI	96	162.5–164 (*t*-BuOH/Et_2O)	$C_{10}H_{15}N_3 \cdot HI$ (177.2/305.2)
29	4-$CH_3C_6H_4$	0.2	pyrrolidine	0.4	–	18	HI	62	168–169 (acetone/Et_2O)	$C_{12}H_{17}N_3 \cdot HI$ (203.3/331.2)
30	4-$CH_3C_6H_4$	0.2	morpholine	0.4	–	18	HI	95	197–204 (*i*-PrOH/Et_2O)	$C_{12}H_{17}N_3O \cdot HI \cdot 1/4H_2O$ (219.3/347.2/351.7)
31	4-$CH_3C_6H_4$	0.05	tetrahydro-1,4-thiazine	0.06	0.05	18	–	58°	119–120 (Et_2O)	$C_{12}H_{17}N_3S$ (235.3)
32	2-$C_2H_5C_6H_4$	0.173	pyrrolidine	0.37	–	18	HCl	98	196–197 (MeOH/Et_2O)	$C_{13}H_{19}N_3 \cdot HCl$ (217.3/253.8)
33	2-$C_2H_5C_6H_4$	0.087	morpholine	0.14	0.1	72	HI	65	210–212 (MeOH/Et_2O)	$C_{13}H_{19}N_3O \cdot HI$ (233.3/361.2)
34	4-$C_2H_5C_6H_4$	0.093	morpholine	0.10	0.19	5	HI	82	175–177 (*t*-BuOH/Et_2O)	$C_{13}H_{19}N_3O \cdot HI$ (233.3/361.2)
35	2-[H_2C=C(CH_3)]C_6H_4	0.16	pyrrolidine	0.17	0.3	18	HI	78	171.5–173 (EtOH/Et_2O)	$C_{14}H_{19}N_3 \cdot HI$ (229.3/357.2)
36	2-[H_2C=C(CH_3)]C_6H_4	0.15	morpholine	0.15	0.3	18	HI	78	179–181 (EtOH/Et_2O)	$C_{14}H_{19}N_3O \cdot HI$ (245.3/373.2)

Table 2. (continued)

Entry	R^3	mol **2**	HNR^1R^2	mol HNR^1R^2	mol $N(C_2H_5)_3$	Reflux Time (h)	HX	Yield[a,h] (%)	mp (°C)[b] (Solvent)	Molecular Formula[i]
37	2-(*i*-C_3H_7)C_6H_4	0.23	pyrrolidine	0.28	0.46	18	HI	81	164.5–166.5 (EtOH/Et_2O)	$C_{14}H_{21}N_3$ · HI (231.3/359.3)
38	2-(*i*-C_3H_7)C_6H_4	0.23	morpholine	0.25	0.46	18	HI	87	158–160 (EtOH/Et_2O)	$C_{14}H_{21}N_3O$ · HI (247.3/375.3)
39	4-(*i*-C_3H_7)C_6H_4	0.06	morpholine	0.065	0.12	4	HI	93[p]	185–189 (*t*-BuOH/Et_2O)	$C_{14}H_{21}N_3O$ · HI (247.3/375.3)
40	4-(*t*-C_4H_9)C_6H_4	0.07	morpholine	0.08	0.14	6	HI	81[p]	212–213 (*t*-BuOH/Et_2O)	$C_{15}H_{23}N_3O$ · HI (261.4/389.3)
41	4-(*n*-C_4H_9)C_6H_4	0.1	$HN(C_2H_5)_2$	0.2	–	2	fumaric acid	92	100–102 (*i*-PrOH/Et_2O)	$C_{15}H_{25}N_3$ · 1/8 (*E*)-$C_4H_4O_4$ (247.4/378.0)
42	4-OHC_6H_4	0.2	pyrrolidine	0.4	–	4	HI	77	214–216 (dec) (*t*-BuOH/Et_2O)	$C_{11}H_{15}N_3O$ · HI (205.3/333.2)
43	2-$CH_3OC_6H_4$	0.08	pyrrolidine	0.16	–	5	HI	84	124–125.5 (*t*-BuOH/Et_2O)	$C_{12}H_{17}N_3O$ · HI (219.3/347.2)
44	3-$CH_3OC_6H_4$	0.05	tetrahydro-1,4-thiazine	0.06	0.05	18	HI	76	189–192 (*t*-BuOH/*i*-PrOH/Et_2O)	$C_{12}H_{17}N_3OS$ · HI (251.3/279.3)
45	3-$CH_3OC_6H_4$	0.09	piperidine	0.18	–	24	fumaric acid	55	189–190 (dec) (*i*-PrOH)	$C_{13}H_{19}N_3O$ · 1/2$C_4H_4O_4$ (233.3/301.3)
46	3-$CH_3OC_6H_4$	0.05	$HN(CH_3)$ *c*-C_5H_9	0.12	0.1	18	–	67	93–95 (Et_2O/pentane)	$C_{14}H_{21}N_3O$ (247.3)
47	4-$CH_3OC_6H_4$	0.09	pyrrolidine	0.18	–	7	HI	93	185–188 (*t*-BuOH/Et_2O)	$C_{12}H_{17}N_3O$ · HI (219.3/347.2)
48	4-$CH_3OC_6H_4$	0.1	H_2NCH_2 *c*-C_6H_{11}	0.2	–	6	–	48	137–138 (EtOH/Et_2O)	$C_{15}H_{23}N_3O$ (261.4)
49	4-$CH_3OC_6H_4$	0.1	$HN(CH_3)$ *c*-C_6H_{11}	0.2	–	18	–	40	120–122 (EtOH/Et_2O)	$C_{15}H_{23}N_3O$[q] (261.4)
50	3-($C_6H_5CH_2O$)C_6H_4	0.125	pyrrolidine	0.25	–	16	HI	92	157–158 (acetone)	$C_{18}H_{21}N_3O$ · HI · C_3H_6O (295.4/423.3/481.4)
51	4-($C_6H_5CH_2O$)C_6H_4	0.17	pyrrolidine	0.36	–	3	TsOH	70	187–190 (MeOH/acetone/Et_2O)	$C_{18}H_{21}N_3O$ · $C_7H_8O_3S$ (295.4/467.6)
52	4-$CH_3SC_6H_4$	0.2	morpholine	0.22	0.22	28	HI	61	176–178 (*t*-BuOH)	$C_{12}H_{17}N_3OS$ · HI (251.3/379.3)
53	4-$NO_2C_6H_4$	0.04	pyrrolidine	0.08	–	2	HI	85	240–242 (dec) (MeOH)	$C_{11}H_{14}N_4O_2$ · HI (234.2/362.2)
54	4-[$N(CH_3)_2$]C_6H_4	0.12	piperidine	0.24	–	12	HCl	73	205–207 (*i*-PrOH)	$C_{14}H_{22}N_4$ · HCl (246.4/282.8)
55	2,3-$Cl_2C_6H_3$	0.3	morpholine	0.33	0.33	48	HI	38	204–205 (EtOH)	$C_{11}H_{13}Cl_2N_3O$ · HI (274.2/402.1)
56	2,6-$Cl_2C_6H_3$	0.04	pyrrolidine	0.08	–	96	HCl	86	292–295 (MeOH/*i*-PrOH)	$C_{11}H_{13}Cl_2N_3$ · HCl (258.2/294.6)
57	3,4-$Cl_2C_6H_3$	0.08	pyrrolidine	0.16	–	5	HI	77	252–254 (dec) (acetone/MeOH)	$C_{11}H_{13}Cl_2N_3$ · HI (258.1/386.1)
58	3,4-$Cl_2C_6H_3$	0.25	morpholine	0.28	0.28	5	HI	72	243–245 (*i*-PrOH)	$C_{11}H_{13}Cl_2N_3O$ · HI (274.1/402.1)
59	2-Cl-4-$CH_3C_6H_3$	0.12	pyrrolidine	0.25	–	18	HI	97	162–166 (*i*-PrOH/Et_2O)	$C_{12}H_{16}ClN_3$ · HI (237.7/365.6)
60	2-Cl-4-$CH_3C_6H_3$	0.06	morpholine	0.10	0.07	68	HI	84	214–217 (MeOH/Et_2O)	$C_{12}H_{16}ClN_3O$ · HI (253.7/381.6)
61	3-Cl-2-$CH_3C_6H_3$	0.25	morpholine	0.28	0.28	72	HI	90	168–172 (*i*-PrOH/Et_2O)	$C_{12}H_{16}ClN_3O$ · HI (253.7/381.6)
62	3-Cl-4-$CH_3C_6H_3$	0.15	pyrrolidine	0.17	0.16	18	HI	62	165–168 (MeOH/Et_2O)	$C_{12}H_{16}ClN_3$ · HI (237.7/365.6)
63	3-Cl-4-$CH_3C_6H_3$	0.15	morpholine	0.17	0.16	18	HI	64	190.5–194 (MeOH/Et_2O)	$C_{12}H_{16}ClN_3O$ · HI (253.7/381.6)
64	4-Cl-2-$CH_3C_6H_3$	0.22	pyrrolidine	0.26	0.24	17	HI	71	162–163.5 (EtOH/Et_2O)	$C_{12}H_{16}ClN_3$ · HI (237.7/365.6)
65	4-Cl-2-$CH_3C_6H_3$	0.44	morpholine	0.48	0.45	18	HI	77	223 225 (EtOH)	$C_{12}H_{16}ClN_3O$ · HI (253.7/381.6)
66	5-Cl-2-$CH_3C_6H_3$	0.12	pyrrolidine	0.25	–	18	HI	97	271–273 (MeOH/Et_2O)	$C_{12}H_{16}ClN_3$ · HI (237.7/365.6)
67	5-Cl-2-$CH_3C_6H_3$	0.06	morpholine	0.10	0.07	72	HI	75	250–252 (*i*-PrOH/Et_2O)	$C_{12}H_{16}ClN_3O$ · HI (253.7/381.6)
68	2,3-$(CH_3)_2C_6H_3$	0.25	morpholine	0.28	0.28	18	HI	62	(135) 149–150 (*i*-PrOH)	$C_{13}H_{19}N_3O$ · HI (233.3/361.2)
69	2,4-$(CH_3)_2C_6H_3$	0.15	pyrrolidine	0.16	0.16	18	HI	77	175–178 (EtOH/Et_2O)	$C_{13}H_{19}N_3$ · HI (217.3/345.2)
70	2,4-$(CH_3)_2C_6H_3$	0.15	morpholine	0.16	0.16	18	HI	87	167–177 (EtOH/Et_2O)	$C_{13}H_{19}N_3O$ · HI (233.3/361.2)
71	2,5-$(CH_3)_2C_6H_3$	0.29	pyrrolidine	0.34	0.30	18	HI	90	220–222 (EtOH/Et_2O)	$C_{13}H_{19}N_3$ · HI (217.3/345.2)
72	2,5-$(CH_3)_2C_6H_3$	0.29	morpholine	0.32	0.30	18	HI	86	184–186 (EtOH/Et_2O)	$C_{13}H_{19}N_3O$ · HI (233.3/361.2)
73	2,6-$(CH_3)_2C_6H_3$	0.045	pyrrolidine	0.09	–	96	HI	77	168–170 (polymorph), 191–192 (acetone/Et_2O)	$C_{13}H_{19}N_3$ · HI (217.3/345.2)
74	3,4-$(CH_3)_2C_6H_3$	0.25	morpholine	0.28	0.28	5	HI	79	181–182 (*t*-BuOH/Et_2O)	$C_{13}H_{19}N_3O$ · HI (233.3/361.2)
75	3,5-$(CH_3)_2C_6H_3$	0.08	morpholine	0.09	0.09	18	HI	68	125–128 (*t*-BuOH/Et_2O)	$C_{13}H_{19}N_3O$ · HI (233.3/361.2)
76	3,4-$(CH_2)_3C_6H_3$	0.6	morpholine	0.63	0.6	18	–	82	123–125 (Et_2O)	$C_{14}H_{19}N_3O$ (245.3)

77	5-Cl-2-$CH_3OC_6H_3$	0.1	pyrrolidine	0.21	–	18	HI	82	185–186.5 (t-BuOH/Et_2O)	$C_{12}H_{16}ClN_3O \cdot HI$ (253.7/381.6)
78	2-Cl-4-($C_6H_5CH_2O$)C_6H_3	0.006 (base)	pyrrolidine	0.011[r]	–	18	HI	55	166–168 (t-BuOH/Et_2O)	$C_{18}H_{20}ClN_3O \cdot HI$ (329.8/457.7)
79	3,4-(OCH_2O)C_6H_3	0.15	pyrrolidine	0.18	0.23	18	HI	94	257–259 (MeOH/EtOH)	$C_{12}H_{15}N_3O_2 \cdot HI$ (233.3/361.2)
80	3,4-(OCH_2O)C_6H_3	0.15	morpholine	0.17	0.23	18	HI	89	252–254 (dec) (MeOH/EtOH)	$C_{12}H_{15}N_3O_3 \cdot HI$ (249.3/377.2)
81	3,4-(OCH_2O)C_6H_3	0.12	tetrahydro-1,4-thiazine	0.14	0.21	18	HCl	92	181–183 (EtOH/Et_2O)	$C_{12}H_{15}N_3O_2S \cdot HCl$ (265.3/301.8)
82	3,4-(OCH_2O)C_6H_3	0.06	piperidine	0.12	–	18	HI	78	171–172.5 (t-BuOH/Et_2O)	$C_{13}H_{17}N_3O_2 \cdot HI$ (247.3/375.2)
83	3,4-(OCH_2O)C_6H_3	0.05	HN(CH_3) c-C_6H_{11}	0.1	–	18	–	51	122.5–124 (t-BuOH)	$C_{15}H_{21}N_3O_2$ (275.4)
84	3,4-(CH_3O)$_2C_6H_3$	0.02	pyrrolidine	0.04	–	18	HI	90	221–222 (MeOH/i-PrOH)	$C_{13}H_{19}N_3O_2 \cdot HI$ (249.3/377.2)
85	2,4,5-(CH_3)$_3C_6H_2$	0.25	morpholine	0.28	0.28	9	HI	73	195–196 (t-BuOH/Et_2O)	$C_{14}H_{21}N_3O \cdot HI$ (247.3/375.3)
86	2,5-(CH_3)$_2$-4-$CH_3OC_6H_2$	0.06	pyrrolidine	0.12	–	18	HI	98	166 (polymorph), 236.5–239 (MeOH/t-BuOH)	$C_{14}H_{21}N_3O \cdot HI$ (247.3/375.3)
87	2,5-(CH_3)$_2$-4-$CH_3OC_6H_2$	0.04	piperidine	0.08	–	18	HI	98	177–179.5 (t-BuOH/Et_2O)	$C_{15}H_{23}N_3O \cdot HI$ (261.4/389.3)
88	2-pyrimidinyl	0.11	piperidine	0.2	–	18	–	60	206–208 (MeOH)	$C_{10}H_{15}N_5$ (205.3)
89	2-pyridinyl	0.05	pyrrolidine	0.1	–	18	HI	79	218–220 (MeOH/i-PrOH)	$C_{10}H_{14}N_4 \cdot HI$ (190.3/318.2)
90	3-pyridinyl	0.3	morpholine	0.6	–	20	–	86	188–190 (i-PrOH)	$C_{10}H_{14}N_4O$ (206.2)
91	exo-bicyclo[2.2.1]-heptan-2-yl	0.08	pyrrolidine	0.16	–	18	HI	77	160–163 (acetone)	$C_{12}H_{21}N_3 \cdot HI$ (207.3/335.2)
92	exo-bicyclo[2.2.1]-heptan-2-yl	0.08	morpholine	0.16	–	18	HI	61	198–199.5 (acetone)	$C_{12}H_{21}N_3O \cdot HI$ (223.3/351.2)
93	1-naphthalenyl	0.05	pyrrolidine	0.1	–	24	HI	64	209–211 (i-PrOH)	$C_{15}H_{17}N_3 \cdot HI$ (239.3/362.2)
94	1-naphthalenyl	0.2	HN(C_2H_5)$_2$	0.8	–	48	fumaric acid	56	208–210 (dec) (MeOH/Et_2O)	$C_{15}H_{19}N_3 \cdot C_4H_4O_4$ (241.3/357.4)
95	1-naphthalenyl	0.07	HN(CH_3) (c-C_6H_{11})	0.14	–	6	–	74	132–133 (acetone/Et_2O)	$C_{18}H_{23}N_3$ (281.4)
96	2-naphthalenyl	0.01	pyrrolidine	0.015	–	18	HI	30	237–239 (i-PrOH)	$C_{15}H_{17}N_3 \cdot HI$[s] (239.3/367.2)
97	9H-fluoren-9-yl	0.01	pyrrolidine	0.02	–	2	HI	87	247–248 (dec)(t-BuOH)	$C_{18}H_{19}N_3 \cdot HI$ (277.4/405.3)
98	$-CH(C_6H_5)_2$	0.2	pyrrolidine	0.4	–	4	HI	73	205–206 (CH_2Cl_2/EtOAc)	$C_{18}H_{21}N_3 \cdot HI$ (279.4/407.3)
99	$-CH(C_6H_5)_2$	0.05	morpholine	0.1	–	18	–	53	122–124(acetone/Et_2O)	$C_{18}H_{21}N_3O$ (295.4)

[h] Footnotes a–g are located under Table 1.

[i] Satisfactory microanalyses obtained except where indicated: C ±0.38, H ±0.41, N ±0.24.

[j] Reference 25 reported the mp of the free base of this guanidine, which was prepared under Scheme **C** conditions. No analytical data were reported, however.

[k] Not analyzed. This guanidine was converted directly to the corresponding **5** derivative, N'-(2-chlorophenyl)-N-(1-methyl-2-pyrrolidinylidene)-4-morpholinecarboximidamide hydroiodide.

$C_{16}H_{21}ClN_4O \cdot HI$ (448.7)	calc.	C 42.83	H 4.94	N 12.49
	found	43.04	4.54	12.50

[l] H_2O calc. 1.36, found 1.32.

[m] Not analyzed. This guanidine was converted to the corresponding **5** derivative, N,N-diethyl-N''-(4-chlorophenyl)-N'-(1-methyl-2-pyrrolidinylidene)guanidine (E)-2-butenedioate (1 : 1).

$C_{16}H_{23}ClN_4 \cdot C_4H_4O_4$ (422.9)	calc.	C 56.80	H 6.44	N 13.25
	found	56.77	6.48	13.16

[n] C calc. 35.93, found 36.41. The corresponding **5** derivative, N-(1-methyl-2-pyrrolidinylidene-N'-[3-(trifluoromethyl)phenyl]-4-morpholinecarboximidamide (E)-2-butenedioate (1 : 1), gave a correct analysis:

$C_{17}H_{21}F_3N_4O \cdot C_4H_4O_4$ (470.5)	calc.	C 53.61	H 5.36	N 11.91
	found	53.69	5.38	11.89

[o] The yield includes a second crop, obtained as the acetate in 34% yield by treatment of the mother liquors with acetic acid; mp 119–123 °C, from t-BuOH/Et_2O.

[p] Acetonitrile used as solvent for the reaction.

[q] Not analyzed. This guanidine's corresponding **5** derivative, N-cyclohexyl-N''-(4-methoxy phenyl)-N-methyl-N'-(1-methyl-2-pyrrolidinylidene)guanidine (E)-2-butenedioate (1 : 1), gave a correct analysis:

$C_{20}H_{30}N_4O \cdot C_4H_4O_4$ (458.55)	calc.	C 62.86	H 7.47	N 12.22
	found	62.72	7.47	12.36

[r] Methanesulfonic acid (0.006 mol) is added as the proton source.

[s] This compound was isolated as a by-product resulting from the reaction of methyl N-(1-methyl-2-pyrrolidinylidene)-N'-(2-naphthalenyl)carbamimidothioate hydroiodide (1 mol) with pyrrolidine (2 mol) in boiling t-BuOH.

amount of CH_3I at room temperature or under reflux (Table 1). The products are isolated by solvent removal under reduced pressure followed either by recrystallization or by conversion to free base (Table 1, entries 44, 51) or to an alternate salt form (entry 12), and purified. TLC is carried out on silica gel GF 1×3-inch slides with toluene/Et_2O/MeOH/28% NH_4OH (4:3:1:0.1) or toluene/Et_2O/MeOH (12:8:1) as eluting solvents.

Guanidines 4; General Procedure:

A three-necked flask, equipped with an N_2 inlet tube, a stirrer, and a reflux condenser with an N_2 exit fitting and tubing connected successively to an empty backup trap, two traps containing 25% aq. NaOH and, finally, a trap containing 5% aq. NaOCl is charged with an appropriate amount of the methyl carbamimidothioate hydroiodide **2** and a minimal amount of *t*-BuOH. To this mixture is added the amine **3** (~ 1.1–1.2 mol equiv) and, when appropriate, a similar amount of Et_3N. The mixture is heated under reflux, with a slow stream of N_2 passing through the liquid to entrain evolved MeSH, until the reaction is complete. The crude guanidine hyroiodide salts are obtained by dilution with Et_2O, filtration, and recrystallization. For the free bases or other salts of **3**, the mixture is taken to dryness and the residue is converted in CH_2Cl_2 to its respective free base with cold 10% aq. NaOH. The CH_2Cl_2 phase is dried (K_2CO_3) and evaporated and the base is either recrystallized or converted to another salt and purified by recrystallization. The reactions are monitored by TLC on Silica Gel GF (1×3-inch slides) with MeOH/28% NH_4OH (28%) (99:1 or 95:5) and acetone/toluene/acetone/28% NH_4OH (5:4:2:0.75) as eluting solvents.

4-[Amino(4-chlorophenylimino)methyl]tetrahydro-1,4-thiazine Hydrochloride (Table 2, entry 15):

In this instance, methyl *N'*-(4-chlorophenyl)carbamimidothioate hydroiodide is converted to its free base with cold 10% aq. NaOH and extracted into CH_2Cl_2. The organic extract is dried (K_2CO_3), filtered, and the solvent removed. The free base is taken up in *t*-BuOH and treated successively with tetrahydro-1,4-thiazine hydrochloride and Et_3N. The reaction is then conducted as described in Table 2.

Received: 22 October 1986; revised: 2 December 1987

(1) The present work was originally performed under the sponsorship of McNeil Pharmaceutical, Spring House, PA 19477-0776, USA.
(2) Visiting Scientist from Cilag Chemie, Schaffhausen, Switzerland, 1976.
(3) Rasmussen, C.R., Villani, F.J., Jr., Weaner, L.E., Reynolds, B.E., Hood, A.R., Hecker, L.R., Nortey, S.O., Hanslin, A., Costanzo, M.J., Powell, E.T., Molinari, A.J. *Synthesis* **1988**, 456.
(4) Presented in part at the 174th and the 192nd National Meetings of the American Chemical Society, Chicago, Illinois, 29 August–1 September, 1977, abstract MEDI 18, and Anaheim, California, Sept. 7–12, 1986, abstract MEDI 31, respectively.
(5) Abraham, W., Barnikow, G. *Tetrahedron* **1973**, *29*, 691.
(6) Abraham, W., Barnikow, G. *Tetrahedron* **1973**, *29*, 699.
(7) Kiselev, L.A., Titova, E.B., Ryabova, A.N., Shvetsova-Shilovskaya, K.D., Melnikov, N.N. *Khim. Sredstva Zashch. Rast.* **1972**, *2*, 399; *C.A.* **1975**, *82*, 86179.
(8) Kiselev, L.A., Ryabova, A.N., Shvetsova-Shilovskaya, K.D. *Khim. Sredstva Zashch. Rast.* **1976**, *7*, 51; *C.A.* **1979**, *91*, 175291.
(9) Kiselev, L.A., Ruchkin, V.E., Osipova, N.M., Melnikov, N.N., Shvetsova-Shilovskaya, K.D. *Zh. Org. Khim.* **1966**, *2*, 2186; *J. Org. Chem. USSR* **1966**, *2*, 2144.
(10) Maryanoff, C.A., Stanzione, R.C., Plampin, J.N., Mills, J.E. *J. Org. Chem.* **1986**, *51*, 1882.
(11) Tutwiler, G.F., Tuman, R.W., Joseph, J.M., Mihan, B.B., Fawthrop, H., Brentzel, H.J. *Drug Dev. Res.* **1986**, *9*, 273.
(12) Bartram, A. *Ber. Dtsch. Chem. Ges.* **1982**, *25*, 48.
(13) Gruenfeld, N. *British Patent* 1131191 (1968), J.R. Geigy A.G.; *C.A.* **1969**, *70*, 47457.
(14) Kramer, C.R., Schelenz, T., Barns, E. *Biochem. Physiol. Pflanz.* **1984**, *179*, 419.
(15) Briody, T.A., Hegarty, A.F., Scott, F.L. *Tetrahedron* **1977**, *33*, 1469.
(16) Fasson, A.P.T., Pyman, F.L. *J. Chem. Soc.* **1931**, 2991.
(17) Jaeken, S., van Goethem, H.V. *German Patent* 1161138 (1964), Gevaert Photo-Production N.V.; *C.A.* **1964**, *60*, 10851.
(18) King, H., Tonkin, I.M. *J. Chem. Soc.* **1946**, 1063.
(19) Zeile, K., Hauptmann, K.H., Stähle, H. *US Patent* 3202660 (1965) ≡ *Belg. Patent* 623305 (1963), Boehringer Ingelheim, GmbH; *C.A.* **1966**, *64*, 2096.
(20) Hughes, J.L., Liu, R.C., Enkoji, T., Smith, C.M., Bastian, J.W., Luna, P.D. *J. Med. Chem.* **1975**, *18*, 1077.
(21) Najer, H., Giudicelli, R., Sette, J. *Bull. Soc. Chim. Fr.* **1961**, 2114.
(22) Poyser, R.H., Fake, C.S., Miller, D. *German Offen.* 2040374 (1971), Beecham Group Ltd.; *C.A.* **1971**, *74*, 100048.
(23) Baxter, J.N., Cymerman-Craig, J., Moyle, M., White, R.A. *J. Chem. Soc.* **1956**, 659.
(24) Winthrop, S.O., Sybulski, S., Gavin, G., Grant, G. *J. Am. Chem. Soc.* **1957**, *79*, 3496.
(25) Citerio, L., Rivera, E., Saccarello, M.L., Stradi, R., Gioia, B. *J. Heterocycl. Chem.* **1980**, *17*, 97.