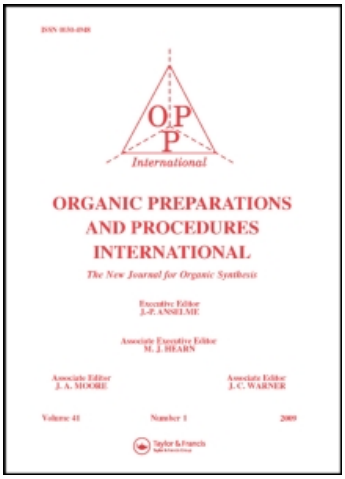

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THE SYNTHESIS AND REACTIONS OF N-CYANO-O-METHYLPSEUDOUREAS

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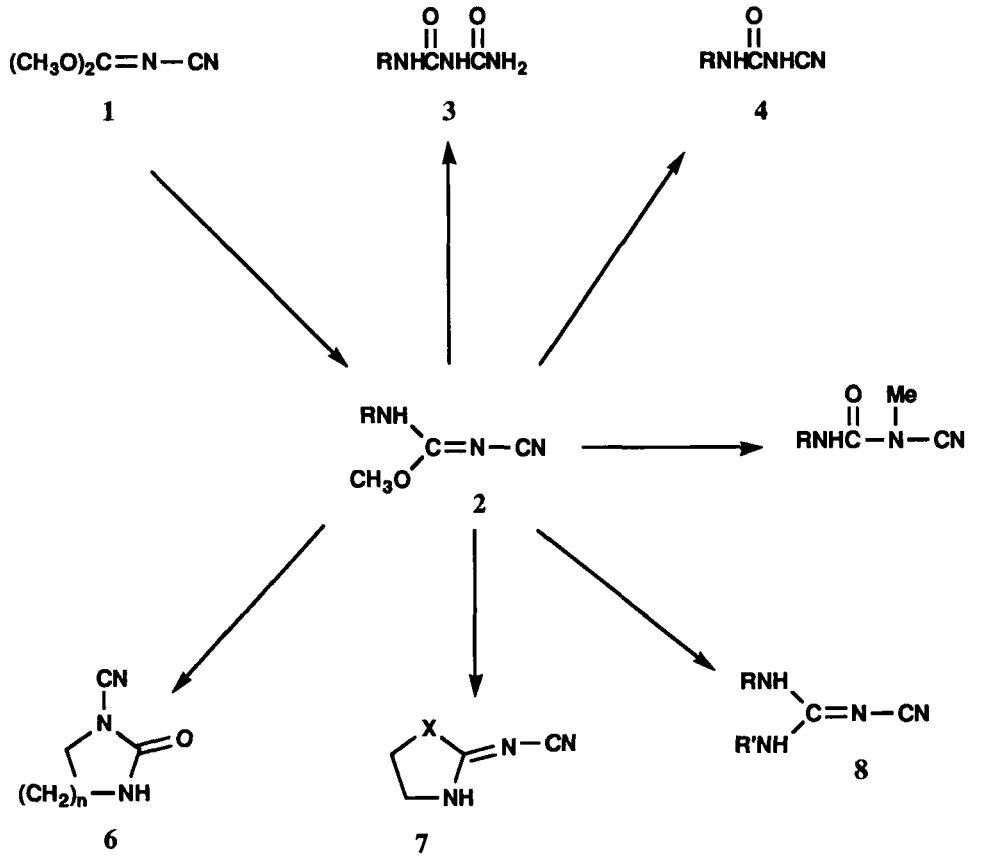
N-Cyanopseudothioureas[1,2] are widely used for the synthesis of compounds such as N-cyanoguanidines,[2-5] 1,2,4-oxadiazoles[6] and 1,2,4-triazoles.[7,8] In contrast, only few N-cyanopseudoureas[9-11] have been reported and their further conversions are seldom studied,[10,12-14] most probably because the lack of convenient methods for their preparation. Our previous work[15] disclosed a convenient synthesis of dimethyl N-cyanoimidocarbonate (**1**), which was converted into N-cyanoguanidines *via* the N-cyano-O-methylpseudoureas.[15] Since the use of the N-cyanopseudoureas has some advantages in comparison to their thio analogues, elimination of methanol instead of methylthiol being the most important for practical reason, we studied the preparation of N-cyano-O-methylpseudoureas (**2**) in more detail and found that a wide variety of pseudoureas can be obtained from **1** by reaction with the corresponding amines.

The reactions were carried out in water or alcohols, usually at room temperature. The products in most cases precipitated in high yield and in pure form after relatively short reaction times. Only in the case of reactions with 2-mercaptoethyleneamines, were alkaline conditions required and the hydrolysis of **1** into corresponding salt of N-cyano-N-methylcarbamate was observed as side-reaction. In the cases when the amine contained terminal nucleophilic group such as NHR', SH, or OH, cyclization of pseudoureas **2** into **7** was observed after prolonged reaction time, at higher temperatures or in alkaline media. In the case of α,ω-diamines, pseudoureas could not be isolated in pure form even at room temperature, because of the formation of the corresponding imidazolidines **7b-d**. ^{1}H NMR spectroscopy allowed us to detect the slow O to N rearrangement of the methyl group in pseudoureas **2** at elevated temperatures to yield N-cyano-N-methylureas **5**; the rearrangement was much slower than in case of **1**. In the presence of compounds such as imidazole, slow O-demethylation of **2** occurs by formation of N-methylimidazole and N-cyanoureas (**4**). When heated in conc. hydrochloric acid, pseudoureas **2** were readily hydrolyzed into 1-substituted biurets (**3**) in high yields. The melt cyclization of pseudoureas **2** with halogen atoms on side-chain was also of interest. At the conditions chosen by differential scanning calorimetric analysis, the appropriate pseudoureas **2** were converted into N-cyanoimidazoline-2-one (**6a**) or N-cyanohexahydropyrimidine-

2-one (**6b**), respectively in nearly quantitative yield. With amines, pseudoureas **2** and also thiazolidine **7a** were converted into N-cyanoguanidines **8**. Furthermore, N-cyano-O-methylpseudoureas can be used also for the synthesis of 1,2,4-oxadiazoles and 1,2,4-triazoles in a fashion similar to their thio or phenyl analogues.[16]



2 **a)** R = H **b)** R = Me **c)** R = Et **d)** R = t-Bu **e)** R = $MeCH_2(Me)_2C$ **f)** R = $Me(CH_2)_5$ **g)** R = $Me(CH_2)_{15}$ **h)** R = $MeO(CH_2)_2$ **i)** R = $Me_2N(CH_2)_2$ **j)** R = $Cl(CH_2)_3$ **k)** R = $HS(CH_2)_2$ **l)** R = $PhCH_2$ **m)** furfuryl **n)** R = $(CH_2)_4$ **o)** R = 2-morpholinoethyl **p)** R = $Ph(CH_2)_2MeCH$ **q)** R = 2-[(4-methyl-1H-imidazolyl-5)methyl)thio]ethyl **r)** 2-{[2-(N-cyano-O-methylisoureido) ethyl]dithio}ethyl

3 **a)** R = $Cl(CH_2)_2$ **b)** R = $Br(CH_2)_2$ **c)** R = $HO(CH_2)_2$ **d)** R = $PhCH_2$

6 **a)** n = 1 **b)** n = 2

7 **a)** X = S **b)** X = NH **c)** X = NMe **d)** X = NEt

8 **a)** R = Me, R' = $HS(CH_2)_2$ **b)** R = Me, R' = 2-{[2-(N-cyano-N'-methylguanidino]ethyl}dithio)ethyl **c)** R = Et, R' = $Cl(CH_2)_2$ **d)** R = Me, R' = furfuryl **e)** R = Me, R' = Me **f)** R = H, R' = Me

EXPERIMENTAL SECTION

Melting points were taken on a Kofler micro hotstage. ^{1}H NMR, IR and mass spectra were obtained

on a Varian EM-360 NMR spectrometer, Bio Rad FTS-60 Fourier-Transform instrument and Finnigan 3300 F or CEC 21-110B spectrometer, respectively. TG and DSC analyses were performed on a Mettler TA 2000C thermoanalyser. Elemental analyses for C, H and N were obtained on a Perkin-Elmer CHN Analyser 240 (Table 3).[20]

General Procedures for the Synthesis of N-Cyano-O-methylpseudoureas (2) (Table 1)

Procedure A.- Compound **1** (11.4 g, 0.1 mol) was dissolved in 10-13 ml of conc. aqueous ammonia, methylamine or ethylamine, respectively, and the reaction mixture was stirred at 0-25°. The precipitate was collected, washed with water and dried in vacuum.

Procedure B.- Compound **1** (11.4 g, 0.1 mol) was dissolved in a solvent (Table 1) and an equimolar amount of the appropriate amine was added. The reaction mixture was stirred at room temperature

TABLE 1. Synthesis of N-Cyano-O-methylpseudoureas (**2**)

Cmpd	Proc.	Solvent	Time	Yield (%)	mp. (°C, solvent)
2a	A		20 hrs	92	114-115 (EtOH[a])
2b	A		2 hrs	81	134-135 (EtOH)
2c	A		2 hrs	83	55-57 (cyclohexane)
2d	B	H_2O (50 ml)	24 hrs	26	76-78 (pet ether)
2e	B	MeOH (60 ml)	6 hrs	47	70-73 (water)
2f	B	MeOH (30 ml)	10 hrs	79	32-34 (pet ether)
2g	B	MeOH (30 ml)	5 min.	84	78-80 (pet ether)
2h	B	H_2O (100 ml)	2 hrs	84	94-95 ($CHCl_3$)
2i	B	H_2O (100 ml)	3 hrs	88	77-79 (EtOH) 46-48 (n-hexane)
2j	B	H_2O (80 ml)	15 min	72	76-77 (water)
2k	C	H_2O	2 hrs	61	96-98 (EtOH)
2l	B	H_2O (50 ml)	0.5 h	75	116-117 (EtOH)
2m	B	H_2O (100 ml	2 hrs	93	92-94 (EtOH)
2n	B	MeOH (70 ml)	5 min	62	65-66 (2-propanol)
2o	B	MeOH (80 ml)	1 h	66	77-79 (2-propanol)
2p	B	EtOH (150 ml)	10 min	68	83-85 (2-propanol)
2q	C	H_2O	6 hrs	88	136-138 (EtOH)
2r	C	H_2O	20 hrs	31	147-150 (EtOH)

[a]lit.[11] mp. 127-128° (benzene).

(reflux for **2e**, 0-5° for **2j**) and the precipitate was collected, washed with water and dried. In some cases the reaction mixture was evaporated to dryness and the residue was suspended in ethanol (**2d**,

TABLE 2. ^{1}H NMR Spectra of N-Cyano-O-methylpseudoureas (**2**)

Cmpd	Solvent	Chemical shifts
2a	DMSO-d_6	δ 3.66 (s, 3H), 7.7 (broad, 2H).
2b	$CDCl_3$	δ 2.85 (d, 3H, J = 4 Hz), 3.85 (s, 3H), 7.0-7.75 (broad, 1H).
2c	DMSO-d_6	δ 1.1 (t, 3H, J = 7 Hz), 3.22 (broad q, 2H, J = 7 Hz), 3.86 (s, 3H).
2d	$CDCl_3$	δ 1.35 (s, 9H), 3.87 (s, 3H), 5.3-5.8 (broad, 1H).
2e	$CDCl_3$	δ 0.86 (t, 3H, J = 7Hz), 1.3 (s, 6H), 1.65 (q, 2H, J = 7Hz), 3.86 (s, 3H), 5.1-5.7 (broad, 1H).
2f	$CDCl_3$	δ 0.88 (broad t, 3H, J = 5.5 Hz), 1.07-1.7 (m, 8H), 3.2 (dt, 2H, J = 5.5 Hz), 6.7-7.1 (broad, 1H).
2g	$CDCl_3$	δ 1.28 (s, 33 H), 3.86 (s, 3 H).
2h	DMSO-d_6	δ 3.3 (s, 3 H), 3.32-3.47 (m, 4H), 3.83 (s, 3 H), 8.0-8.6 (broad, 1 H).
2i	$CDCl_3$	δ 1.03 (t, 6H, J = 7 Hz), 2.33-2.8 (m, 6H), 3.03 (t, 2H, J = 6 Hz), 3.87 (s, 3H), 5.9-6.8 (broad, 1H).
2j	DMSO-d_6	δ 1.97 (p, 2 H, J = 7Hz), 3.33 (t, 2 H, J = 7 Hz), 3.67 (t, 2 H, J=7Hz), 3.86 (s, 3 H), 8.33 (broad, 1H).
2k	$CDCl_3$	δ 1.37-1.9 (broad, 1H), 2.67 (t, 2H, CH_2, J = 7 Hz), 3.4 (broad t), 7.3-7.8 (broad, 1H).
2l	$CDCl_3$	δ 3.86 (s, 3H), 4.3 (d, 2H, J = 6Hz), 7.28 (s, 5H), 7.5-7.9 (broad s, 1H).
2m	$CDCl_3$	δ 3.9 (s, 3H), 4.43 (d, 2H, J = 6 Hz), 6.35 (m, 2H), 7.41 (m, 1H), 7.2-755 (broad s, 1H).
2n	DMSO-d_6	δ 1.8-2.1 (m, 4H), 3.2-3.9 (broad, 4H), 3.7 (s, 3H).
2o	$CDCl_3$	δ 2.37-2.7 (m, 6H), 3.2-3.57 (broad m, 2H), 3.67-3.9 (m, 4H), 3.9 (s, 3H).
2p	$CDCl_3$	δ 1.2 (d, 3H, J = 6 Hz), 1.6-2.03 (m, 2H), 2.5-2.83 (m, 2H), 3.5-4.0 (m, 1H), 3.77 (s, 3H), 6.4-6.8 (broad d, 1H, J = 8 Hz), 7.1-7.4 (m, 5H).
2q	DMSO-d_6	δ 2.1 (s, 3H), 2.6 (t, 2H, J = 7 Hz), 3.3 (broad t, 2H, J = 7 Hz), 3.6 (s, 2H), 3.77 (s, 3H), 7.4 (s, 1H), 8.2-8.8 (broad, 1H).
2r	DMSO-d_6	δ 2.95 (broad t, 4H, J = 7 Hz), 3.53 (broad t, 4H, J = 7 Hz), 3.9 (s, 6H), 8.0-9.0 (broad, 1H).

2i, 2p), water (**2e, 2f**) or 2-propanol (**2n, 2o**), respectively, collected and dried.

Procedure C.- The appropriate amine (0.1 mol) was dissolved in water (40 ml). The pH of the solution was adjusted to 10-11 with 40% aqueous NaOH with cooling to room temperature.

Compound **1** (11.4 g, 0.1 mol; 22.8 g, 0.2 mol for **2r**) was then added and the reaction mixture was stirred at room temperature. The precipitated solid was collected, washed with water and dried in vacuum.

TABLE 3. Elemental Analyses for New Compounds

Cmpd	Formula	Calcd			Found		
		C	H	N	C	H	N
2b	$C_4H_7N_3O$	42.47	6.24	37.15	42.21	6.26	37.29
2c	$C_5H_9N_3O$	47.23	7.14	33.05	47.06	7.45	32.95
2d	$C_7H_{13}N_3O$	54.17	8.44	27.07	53.89	8.17	27.01
2e	$C_8H_{15}N_3 \cdot 0.25\ H_2O$	55.31	8.99	24.19	55.48	8.94	24.44
2f	$C_9H_{17}N_3O$	58.98	9.35	22.93	58.60	9.58	22.79
2g	$C_{19}H_{37}N_3O$	70.53	11.52	12.98	70.40	11.83	13.01
2h	$C_6H_{11}N_3O_2$	45.85	7.05	26.74	45.76	7.37	26.46
2i	$C_9H_{18}N_4O$	54.52	9.15	28.26	54.61	9.07	28.18
2j	$C_6H_{10}ClN_3O \cdot 0.5\ H_2O$	40.01	5.88	23.33	39.72	5.83	23.15
2k	$C_5H_9N_3OS$	37.72	5.70	26.39	37.80	5.96	26.58
2l	$C_{10}H_{11}N_3O$	63.48	5.86	22.21	63.79	6.05	22.11
2m	$C_8H_9N_3O_2$	53.62	5.06	23.45	53.38	5.07	23.14
2n	$C_7H_{11}N_3O$	54.83	7.23	27.43	54.79	7.39	27.27
2o	$C_9H_{16}N_4O_2$	50.92	7.59	26.39	50.81	7.77	26.17
2p	$C_{13}H_{12}N_3O$	67.51	7.41	18.16	67.44	7.55	18.21
2q	$C_{10}H_{15}N_5OS$[a]	47.41	5.97	27.65	46.92	6.27	27.22
2r	$C_{10}H_{16}N_6O_2S_2 \cdot H_2O$[a]	35.92	5.43	25.13	35.92	5.11	24.68
3b	$C_4H_8BrN_3O_2$[a]	22.87	3.84	20.00	23.55	4.06	19.82
3c	$C_4H_9N_3O_3 \cdot H_2O$[a]	29.09	6.71	25.44	29.13	6.29	25.34
6a	$C_4H_5N_3O$	43.24	4.54	37.82	43.07	4.52	38.02
6b	$C_5H_7N_3O$	47.99	5.64	33.58	47.92	5.74	33.5
8c	$C_6H_{11}ClN_4 \cdot 0.25\ H_2O$	40.23	6.47	31.28	40.34	6.28	31.51
8d	$C_8H_{10}N_4O$[a]	53.92	5.66	31.44	53.34	5.72	31.16

a) Some of these compounds appear to retain some water and this may explain why the results of the combustion analyses are outside the generally accepted value of ± 0.30.

N-(2-Chloroethyl)biuret (3a).- N-Cyano-N'-(2-chloroethyl)-O-methylpseudourea[15] (10 g) was suspended in conc. HCl (10 ml) and heated to obtain boiling solution. Then the reaction mixture was cooled and the precipitate was collected to yield 3 g (29%) of the product, mp. 136-138° (methanol), lit.[17] mp. 138-140°. ^{1}H NMR (DMSO-d_6): δ 3.3-3.8 (m, 4H), 6.0-7.3 (broad s,2H), 7.98 (broad t, 1H, J = 6 Hz), 8.82 (broad s, 1H). MS (m/e): 165 (M^+).

N-(2-Bromoethyl)biuret (3b).- The product was obtained by the same procedure as **3a** using N-cyano-N'-(2-bromoethyl)-O-methylpseudourea[15] (3 g) and conc. HCl (3 ml). The precipitate was collected, washed with water and dried to yield 2.2 g (71%) of the product, mp. 150-152° (methanol). ^{1}H NMR (DMSO-d_6): δ 3.3-3.8 (m, 4H), 6.0-7.3 (broad, 2H), 7.83 (broad t, 1H), 8.82 (broad s, 1H). MS-FAB (m/e): 210 ((M^+1)$^+$).

N-(2-Hydroxyethyl)biuret (3c).- The title compound was obtained by the same procedure described for **3a** using N-Cyano-N'-(2-hydroxyethyl)-O-methylpseudourea[15] (1 g) and conc. HCl (1 ml). The precipitate was collected, washed with water and ethanol, and dried to yield 0.3 g (29%) of the product, mp. 120-123° (methanol). ^{1}H NMR (DMSO-d_6): δ 3.26-3.8 (m, 4H), 6.63 (broad s,2H), 7.9-7.6 (broad t, 1H), 8.6 (broad s, 1H). MS (m/e): 147 (M^+).

N-Benzylbiuret (3d).- The compound was obtained by the same procedure described for **3a** using pseudourea **2l** (2 g). The precipitate was collected, washed with ethanol and dried to yield 1.2 g (60%) of the product, mp. 164-166° (ethanol), lit.[18] mp. 174.5-175°.

1-Cyano-imidazolidin-2-one (6a).- This compound was obtained by heating 5 mmol of N-cyano-N'-(2-bromoethyl)-O-methylpseudourea[15] at 130-140° or N-cyano-N'-(2-chloroethyl)-O-methylpseudourea[15] at 180-190° until bubbles were emitted from the melt (ca. 5 minutes). The melt was then cooled to yield 0.55 g (99%) of the pure product, mp. 110-113°. ^{1}H NMR (DMSO-d_6): δ 3.2-3.6 and 3.7-4.1 (two m, 4H), 7.8 (broad s, 1H). MS (m/e): 111 (M^+).

1-Cyanohexahydropyrimidin-2-one (6b).- This product was obtained at 170-180° essentially as described for compound **6a** from pseudourea **2j** (0.5 g); yield 0.35 g (98%) of the pure product, mp. 147° (ethanol). ^{1}H NMR ($CDCl_3$): δ 2.03 (p, 2H, J_1 = 5.6 Hz), 3.38 (dt, 2H, J_1 = 5.6Hz, J_2 = 2 Hz), 3.78 (t, 2H, J_1 = 5.6 Hz), 6.8-7.1 (broad, 1H). MS (m/e): 125 (M^+).

2-(N-Cyanoimino)thiazolidine (7a).- A reaction mixture, prepared as described for the synthesis of compound **2k** (procedure C) and was stirred at room temperature overnight. The precipitate was collected, washed with water and dried to yield 21 g (48%) of the product, mp. 168-170°, lit.[2] mp. 156°.

2-(N-Cyanoimino)imidazolidine (7b).- A mixture of compound **1** (2 g) and 1,2-diaminoethane (1.7 ml) was stirred in methanol (8 ml) at room temperature for 2 hrs. The reaction mixture was cooled to 0° and the precipitate was collected, washed with ethanol and dried to yield 1.2 g (62%) of the product, mp. 203-205° (ethanol), lit.[2] mp. 210°.

1-Methyl-2-(N-cyanoimino)imidazolidine (7c).- N-Methylethylendiamine (4.4 ml) was added to a solution of **1** (5.7 g) in ethanol (10 ml). The solution was stirred at the room temperature overnight, and the precipitate was collected, washed with ethanol and dried to yield 3.6 g (58%) of the product,

mp. 134-137° (ethanol), lit.[2] mp. 138° (2-propanol). ^{1}H NMR (DMSO-d_6): δ 2.7 (s,3H), 3.4 (m, 4H), 7.1-8.1 (broad, 1H).

1-Ethyl-2-(N-cyanoimino)imidazolidine (7d).- N-Ethylethylenediamine (4.3 ml) was added to a solution of **1** (4.5 g) in ethanol (10 ml). The solution was stirred at room temperature for 2 hrs, and then for additional 2 hrs under reflux. After cooling, the product was collected and dried to yield 2.7 g (50%) of the product, mp. 97-99° (butyl acetate), lit.[2] mp. 108°.

N-Cyano-N'-methyl-N"-(2-thioethyl)guanidine (8a).- Thiazolidine **7a** (2 g) was stirred for 4 hrs in aqueous methylamine (10 ml, 40%) at room temperature. The reaction mixture was evaporated at 40° and ethyl acetate (2 ml) was added to the residue. The precipitate was filter off and the filtrate evaporated to yield 1.6 g (64%) of an oily product identical to the authentic compound.[19] The title compoud can be obtained in the same way also from pseudourea **2k**, yield 53%.

2,2'-Dithiobis(ethyl-(N-cyano-N'-methyl))guanidine (8b).- Pseudourea **2r** (1 g) was stirred for 5 hrs in aqueous methylamine (5 ml, 40%) at room temperature. Water (10 ml) was added and the mixture was cooled. The precipitate was collected, washed with water and dried to yield 0.8 g (80.5%) of the product, mp. 168-170° (ethanol); lit.[19] mp. 158-160°.

N-Cyano-N'-ethyl-N"-(2-chloroethyl)guanidine (8c).- N-Cyano-N'-(2-chloroethyl)-O-methylpseudourea[15] (4.02 g) was stirred overnight in a mixture of water (10 ml) and aqueous ethylamine (5 ml, 70%) at room temperature. The precipitate was collected, washed with water and dried to yield 0.7 g (16%) of the product, mp. 89-92° (water). ^{1}H NMR (DMSO-d_6): δ 1.11 (t, 3H, J = 7 Hz), 3.2 (q, 2H, J = 7 Hz), 3.62 (t, 2H, 8 Hz), 3.83 (t, 2H, J = 8 Hz). MS-FAB (m/e): 175 ($(M+1)^+$).

N-Cyano-N'-methyl-N"-furfurylguanidine (8d).- Pseudourea **2m** (0.3 g) was stirred in ethanolic methylamine (1 ml, 33%) overnight at room temperature. The reaction mixture was then evaporated and the residue was suspended into ethanol (0.5 ml). The precipitate was collected and dried to yield 0.27 g (90%) of the product, mp. 94-95° (ethanol). ^{1}H NMR (DMSO-d_6): δ 2.75 (d, 3H, MeNH, J = 5 Hz), 4.35 (d, 2H, J = 6 Hz), 6.27 (d, 1H, J_1 = 3 Hz), 6.4 (dd, 1H, J_1 = 3 Hz, J_2 = 1.5 Hz), 7.1 (broad q, 1H, J = 5 Hz), 7.43 (broad t, 1H, J = 6 Hz), 7.6 (m, 1H). MS (m/e): 178 (M^+).

N-Cyano-N,N'-dimethylguanidine (8e).- Compound **1** (40 g) was heated in aqueous methylamine (80 ml, 40%) for 3 hrs at reflux. After solvent evaporation, water (20 ml) was added to the residue and the precipitate collected to yield 33 g (84%) of the product, mp. 173-175° (2-propanol), lit.[9] mp. 175° (ethanol).

N-Cyano-N'-methylguanidine (8f).- Pseudourea **9a** (1 g) was stirred in aqueous methylamine (3 ml, 40%) for 3 hrs at room temperature. Water (3 ml) was added and the precipitate was collected, washed with water and dried to yield 0.82 g (83%) of the product, mp. 99-101°, lit.[9] mp. 91°.

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