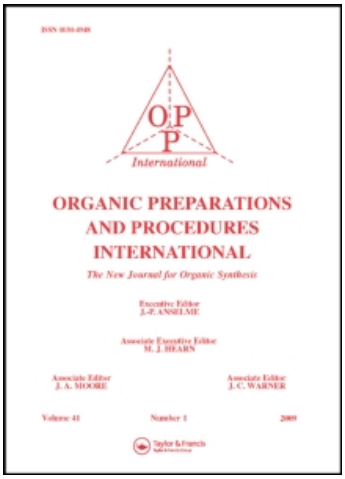

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THE CYANAMIDO MOIETY AS A NOVEL LEAVING GROUP

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THE CYANAMIDO MOIETY AS A NOVEL LEAVING GROUP†

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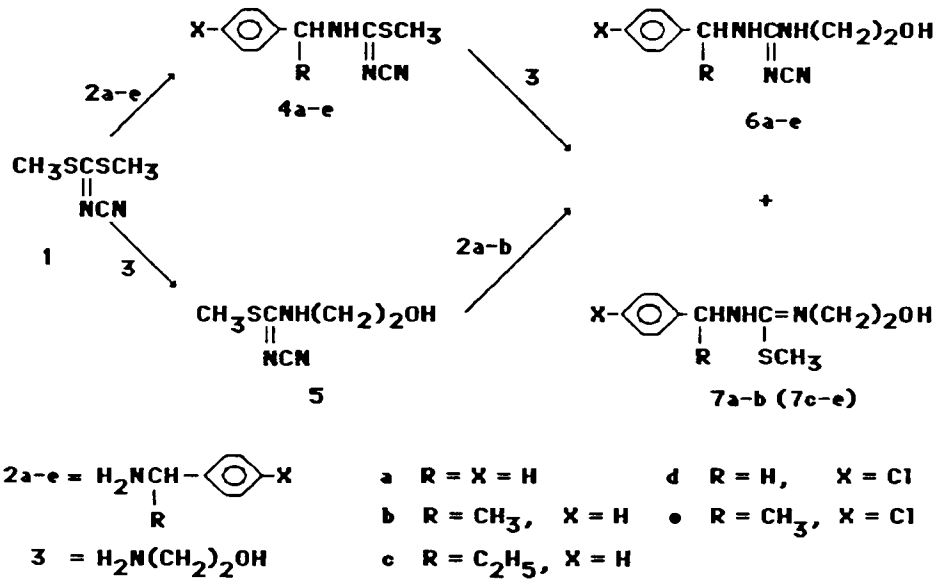
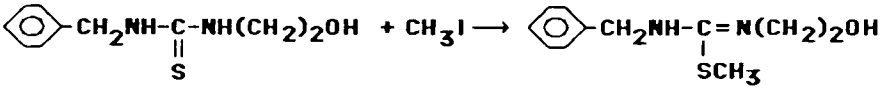
N-Benzyl-N'-ω-hydroxyalkylthioureas posessed diuretic and saluretic activity.[1] In hope of lowering their long term toxicity, it was decided to synthesize the *N*-cyanoguanidine analogues (**6**) by converting dimethyl *N*-cyanocarbonimidodithioate (**1**) either with a benzylamine (**2**, R = H, CH_3, C_2H_5, X = H, Cl) or 2-ethanolamine (**3**) to the corresponding derivatives of **4** (R = H, CH_3, C_2H_5, X = H, Cl) and (**5**), respectively (Scheme 1). Derivatives **4** (R = H, CH_3, C_2H_5, X = H, Cl) and **5** were then reacted with 2-ethanolamine (**3**) or the appropriate benzylamine (**2**, R = H, CH_3, C_2H_5, X = H, Cl) to give the corresponding 1-substituted benzyl-3-cyano-2-(2-hydroxyethyl)guanidine derivatives (**6**, R = H, CH_3, C_2H_5, X = H, Cl).

Scheme 1

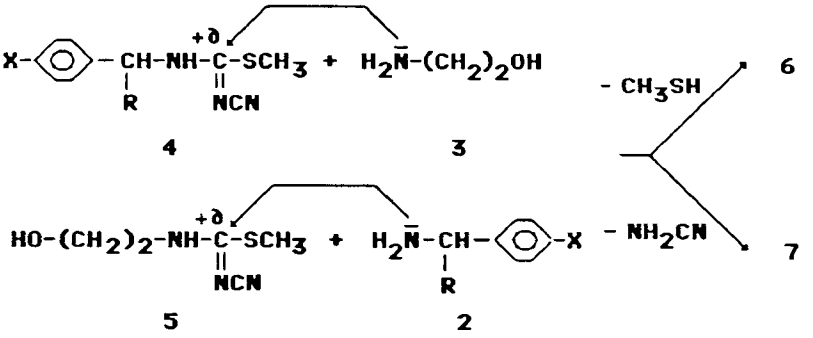


The reaction of **4a** (R = H, X = H) with **3** or the reaction of **5** with **2a** (R = X = H) in boiling 2-propanol gives isothiourea derivative **7a** (R = X = H) besides the main product **6a** (R = X = H). The structure of **7a** (R = X = H) was in accordance with its spectral data. Thus, the CN band was absent in the IR spectra, and in the ^{1}H-NMR spectra the NH group was coupled with the benzylic CH_2, and the $=NCH_2$ and OCH_2 groups appeared as a triplet and a quartet respectively. The isothiourea carbon atom of **7a** appeared at 159.1 ppm in the ^{13}C-NMR . The structure of **7a** was corroborated by the synthesis of an authentic sample, by the methylation of the known 1-benzyl-3-(2-hydroxyethyl)thiourea (**8**)[1] with methyl iodide; similar products were obtained with other benzylamines.



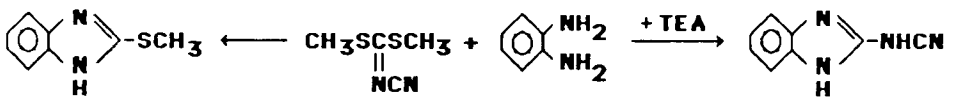
8 **7a (R = X = H)**

The formation of derivatives **7** can be explained by assuming a nucleophilic attack of the nitrogen atom of **3** or **2**, respectively, at the central (and probably the most electrophilic) carbon atom of **4** or **5**, respectively, followed by the elimination of the cyanamido group (NHCN) instead of methylthio (CH_3S) moiety.



The literature provides only one example where the $[NHCN]^-$moiety apparently behaves as a leaving group, namely the reaction of **1** with *o*-phenylenediamine (**9**) which leads to 2-methylthio-benzimidazole (**11**)[3,4] in boiling 95 % ethanol for 48 hrs in the absence of triethylamine (Scheme 2); in this particular experiment, however, the formation of the benzimidazole is probably the driving force of the latter reaction.

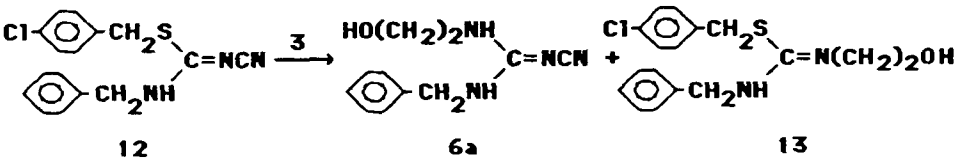
Scheme 2



11 **1** **9** **10**

Once it was established that a **new type of reaction** involving a **new leaving group** was observed, we sought to determine its scope and limitations. The S-methyl group was changed to S-(4-chlorobenzyl) group to give again derivatives type **6a** and **7** (**13**) (Scheme 3).

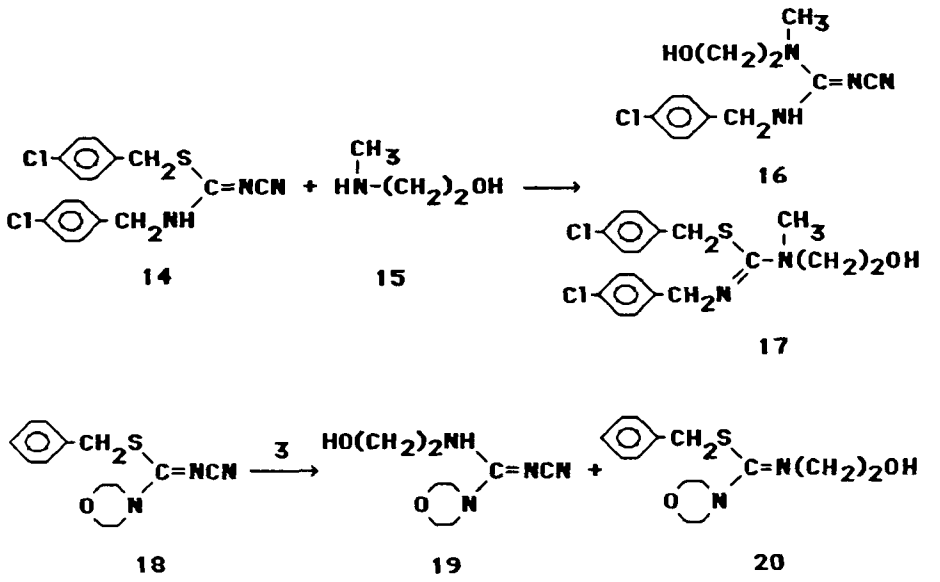
Scheme 3



12 **6a** **13**

Other examples illustrating to the rather **general validity** of the above process are shown in Scheme 4.

Scheme 4



14 **15** **16** **17**

18 **19** **20**

In order to study the reaction conditions leading to the "normal" products of type **6** and those leading to the "abnormal" derivatives of type **7**, the reaction of 1-benzyl-3-cyano-2-methylisothiourea (**4**, R = X = H) with **3** was repeated at different temperatures in different solvents, such as acetonitrile, dimethylformamide, ethanol, 2-propanol and ethyleneglycol (Table 1). Non-protic solvents and low temperature favors the formation of the cyanoimino-guanidine derivatives of type **6** (i.e. the elimination of the alkylthio moiety), whereas **protic solvents** and **higher temperature promotes the formation** of products of type **7** (i. e. the elimination of the cyanoimino moiety).

TABLE 1. Ratio of **6** to **7** (R = X = H) under Various Reaction Conditions

Solvent	Reaction temperature (°C)	Reaction time (hr)	Products formed **6** (R=H) (%)	**7** (%)	Product ratio 7/6
Acetonitrile	80	18	100	0	0
DMF	90	18	100	0	0
	120	3	100	traces	0
	150	1	>99	<1	~ 0.01
Ethanol	80	18	68	32	0.47
2-Propanol	80	18	73	27	0.37
Ethylene glycol	120	3	18	82	4.55
	150	2	15	85	5.65
	170*	1	10	79	7.9

*At this temperature and above, large amounts of decomposition products were observed

EXPERIMENTAL SECTION

Mps were determined on a Koffler-Boëtius micro apparatus and are uncorrected. The infrared spectra were obtained using potassium bromide pellets on a Perkin-Elmer 577 spectrophotometer. The ^{1}H-nmr and the ^{13}C-nmr measurements were performed using Varian XL-100, Brucker WM-250 and Brucker WP-80 SY instruments. The hplc determinations were performed using a Varian 8500 pump, a Variscan spectrophotometer, a Varian Stop-Flow sampler and a Varian A-25 recorder. All TLC determinations were carried out on DC-Alufolien Kieselgel 60 F_{154} (Merck) plates using a 3:1 (v/v) mixture of benzene and ethanol as eluent. The spots were detected by UV.

3-Cyano-1-(1-phenylethyl)-2-methylisothiourea (**4b**, R = CH_3, X = H).- To a solution of 4.39 g (0.03 mole) of dimethyl N-cyanocarbonimidodithioate (**1**)[5] in 10 ml of 2-propanol was added with stirring a solution of 3.64 g (0.03 mole) of 1-phenethylamine (**2b**, R = CH_3, X = H)[6] in 5 ml of 2-propanol at room temperature; during the reaction, methyl mercaptan was liberated. The crystallized product was collected and washed with 2-propanol to yield 4.9 g (75 %) of the title *product*, mp. 98-99°C. The mother liquor was concentrated to about 5 ml to give a second crop of crystals (1.3 g, 20 %), mp. 97-99°C increasing the total yield to 95 %. IR: 2175 cm^{-1}(CN). ^{1}H-NMR ($CDCl_3$): δ 1.58 (d, 3H, CH_3), 2.50 (s, 3H, SCH_3), 5.10 (dq, 1H, CH), 7.23 (s, 5H, ArH).

Anal. Calcd. for $C_{11}H_{13}N_3S$: C, 60.24; H, 5.98; N, 19.16; S, 14.62
Found: C, 60.36; H, 6.11; N, 19.03; S, 14.49

3-Cyano-1-(1-phenylpropyl)-2-methyl-isothiourea (**4c**, R = C_2H_5, X = H).- The same procedure was used as in the preparation of **4b** starting from 4.06 g (0.03 mole) of 1-phenylpropylamine (**2c**, R = C_2H_5, X = H);[7] yield 5.9 g (84 %), mp. 117-118°C; second crop 0.8 g (11 %), mp. 115-116°C; total yield 95 %. IR: 2170 cm^{-1}(CN). ^{1}H-NMR ($CDCl_3$): δ 0.88 (t, 3H, CH_3), 1.89 (dq, 2H, CH_2), 2.50 (s, 3H, SCH_3), 4.90 (q, 1H, CH), 7.30 (s, 5H, ArH).

Anal. Calcd. for $C_{12}H_{15}N_3S$: C, 61.77; H, 6.48; N, 18.01; S, 13.74
Found: C, 61.81; H, 6.66; N, 17.89; S, 13.60

1-(4-Chlorobenzyl)-3-cyano-2-methylisothiourea (**4d**, R = H, X = Cl).- The same procedure was used as in the preparation of **4b** starting from 4.25 g (0.03 mole) of 4-chlorobenzylamine (**2d**, R = H, X = Cl);[8] yield 6.45 g (90 %), mp. 189-191°C. IR: 2170 cm^{-1}(CN). ^{1}H-NMR (DMSO-d_6): δ 2.62 (s, 3H, SCH_3), 4.47 (t, 2H, NCH_2), 7.32 and 7.40 (dd, 4H, ArH), 8.9 (t, 1H, NH).

Anal. Cacd. for $C_{10}H_{10}ClN_3S$: C, 50.10, H, 4.20, Cl, 14.79, N, 17.53, S, 13.38
Found: C, 50.23, H, 4.33, Cl, 14.85, N, 17.44, S, 13.31

1-[1-(4-Chlorophenyl)ethyl]-3-cyano-2-methylisothiourea (**4e**, R = CH_3, X = Cl).- The same procedure was used as in the preparation of **4b** starting from 4.67 g (0.03 mole) of 1-(4-chlorophenyl)ethylamine (**2e**, R = CH_3, X = Cl);[9] yield 6.87 g (90 %), mp. 146-147°C (ethanol); IR: 2170 cm^{-1}(CN). ^{1}H-NMR (DMSO-d_6): δ 1.54 (d, 3H, CCH_3), 2.70 (s, 3H, SCH_3), 5.20 (dq, 1H, CH), 7.43 (s, 5H, ArH), 8.7 (d, 1H, NH).

Anal. Calcd. for $C_{11}H_{12}ClN_3S$: C, 52.07, H, 4.77, Cl, 13.97, N, 16.56, S, 12.64
Found: C, 51.89, H, 4.92, Cl, 13.88, N, 16.46, S, 12.55

3-Cyano-1-(2-hydroxyethyl)-2-methylisothiourea (**5**).- The same procedure was used as in the preparation of **4b** starting from 1.95 g (0.03 mole) of 2-aminoethanol (**3**); yield 3.4 g (71 %), of the title *product*, mp. 135-137°C. IR: 2160 cm^{-1}(CN). ^{1}H-NMR (DMSO-d_6): δ 2.60 (s, 3H, SCH_3), 3.39 bs, 4H, CH_2CH_2), 4.7 (t, 1H, $N\underline{H}CH_2$), 8.0 (b, 1H, OH).

Anal. Cald. for $C_5H_9N_3OS$: C, 37.72, H, 5.70, N, 26.39, S, 20.14
Found: C, 37.76, H, 6.33, N, 26.16, S, 19.99

1-Benzyl-3-cyano-2-(2-hydroxyethyl)guanidine (**6a**, R = X = H) and *1-Benzyl-3-(2-hydroxyethyl)-2-methylisothiourea* (**7a**, R = X = H) obtained by the reaction of **4a** with **3**.- A mixture of 2.05 g (0.01 mole) of 1-benzyl-3-cyano-2-methylisothiourea (**4a**, R = X = H)[10], 0.74 g (0.012 mole) of 2-aminoethanol (3) and 15 ml of 2-propanol was boiled under reflux for 16 hrs. TLC of the reaction mixture showed spots of both derivatives, **6a** (R = X = H) (R_f = 0.18) and **7a** (R = X = H) (R_f = 0.62). After cooling, the solution was evaporated to dryness and the residue was chromatographed on a silica gel column [eluent 1: 2 (v/v) mixture of benzene and ethyl acetate] to yield 0.81 g (37 %) of 1-benzyl-3-cyano-2-(2-hydroxyethyl)guanidine (**6a**, R = X = H), mp. 74-75°C (ethyl acetate). IR: 2160 cm^{-1}(CN). ^{1}H-NMR ($CDCl_3$): δ 3.27 (q, 2H, $NHC\underline{H}_2CH_2$), 3.63 (q, 2H, OCH_2), 4.36 (d, 2H, $NHCH_2$), 6.15 (t, 1H, OH), 6.6 (t, 1H, NH), 7.30 (s, 5H, ArH).

Anal. Calcd. for $C_{11}H_{14}N_4O$: C, 60.53, H, 6.47, N, 25.67
Found: C, 60.80, H, 6.72, N, 25.75

Further elution with a 1: 2 (v/v) mixture of benzene and ethyl acetate gave 0.22 g (10 %) of 1-benzyl-3-(2-hydroxyethyl)-2-methylisothiourea (**7a**, R = X = H) mp. 88-89°C (2-propanol). IR: 1620 and 1570 cm^{-1} (CN), 3320 cm^{-1}(OH). ^{1}H-NMR (DMSO-d_6): δ 2.10 (s, 3H, SCH_3), 2.55 (t, 2H, $NC\underline{H}_2CH_2$), 3.25 [q (+D_2O t), 2H, OCH_2],

4.25 [d (+D_2O s), 2H, $NHCH_2$), 5.80 (t, 1H, OH), 6.55 (t, 1H, NH), 7.3 (s, 5H, ArH). ^{13}C-NMR ($CDCl_3$): δ 15.2 (SCH_3), 34.7 (NCH_2), 39.1 ($NHCH_2$), 44.1 (OCH_2), 127.0, 127.1 and 128.5 (Ar), 159.1 (N=C-S).

Anal. Calcd. for $C_{11}H_{16}N_2OS$: C, 58.90, H, 7.19, N, 12.49, S, 14.29

Found: C, 58.84, H, 7.07, N, 12.34, S, 14.42

1-Benzyl-3-cyano-2-(2-hydroxyethyl)guanidine (**6a**, R = X = H) and *1-Benzyl-3-(2-hydroxyethyl)-2-methylisothiourea* (**7a**, R = X = H). From **2a** (R = X = H) and **5**.- A mixture of 1.59 g (0.01 mole) of 3-cyano-1-(2-hydroxyethyl)-2-methylisothiourea (**5**), 1.07 g (0.01 mole) of benzylamine (**2a**, R = X = H) and 15 ml of 2-propanol was boiled under reflux for 10 hrs. TLC of the reaction mixture showed spots for both derivatives, **6a** (R = X = H) (R_f = 0.18) and **7a** (R = X = H) (R_f= 0.62). After cooling, the solution was evaporated to dryness and the residue chromatographed on a silica gel column [eluent 1: 2 (v/v) mixture of benzene and ethyl acetate] to yield 0.44 g (20 %) of 1-benzyl-3-cyano-2-(2-hydroxyethyl)guanidine (**6a**, R = X = H), mp. 73-75°C (ethyl acetate). The product is identical (mixed mp., IR) with that of **6a** obtained above; and 0.36 g (16 %) of 1-benzyl-3-(2-hydroxyethyl)-2-methylisothiourea (**7a**, R = X = H), mp. 88- 89°C (2-propanol). The product is identical (mixed mp., IR) with **7a** obtained above.

3-Cyano-2-(2-hydroxyethyl)-1-(1-phenylethyl)guanidine (**6b**, R = CH_3, X = H) and *3-(2- Hydroxyethyl)-2-methyl-1-(1-phenylethyl)isothiourea* (**7b**, R = CH_3, X = H). From **4b** (R = CH_3, X = H) and **3**.- A mixture of 2.19 g (0.01 mole) of 3-cyano-2-methyl-1-(1-phenylethyl)isothiourea (**4b**, R = CH_3, X = H), 0.74 g (0.012 mole) of 2-aminoethanol (**3**) and 10 ml of 2-propanol was boiled under reflux for 15 hrs. TLC of the reaction mixture showed the spots of both derivatives, **6b** (R = CH_3, X = H) (R_f = 0.45) and **7b** (R = CH_3, X = H) (R_f = 0.65). After cooling, the solution was evaporated to dryness and the residue chromatographed on a silica gel column [eluent 1: 2 (v/v) mixture of benzene and ethyl acetate] to yield 1.05 g (45 %) of 3-cyano-2-(2-hydroxyethyl)-1-(1-phenylethyl)guanidine (**6b**, R = CH_3, X = H), mp. 97-98°C (ethyl acetate). IR: 2160 cm^{-1}(CN), 1600 and 1570 cm^{-1}(C=N). ^{1}H-NMR ($CDCl_3$): δ 1.47 (d, 3H, CH_3), 3.29 (t, 2H, NCH_2CH_2), 3.62 (q, 2H, OCH_2), 4.77 (dq, 1H, CH), 5.75 (t, 1H, OH), 6.45 (d, 1H, NH), 7.25 (s, 5H, ArH).

Anal. Calcd. for $C_{12}H_{16}N_4O$: C, 62.05, H, 6.94, N, 24.12

Found: C, 62.21, H, 6.84, N, 23.96

Further elution with a 1: 2 (v/v) mixture of benzene and ethyl acetate gave 0.23 g (10 %) of 3-(2-hydroxyethyl)-2-methyl-1-(1-phenylethyl)isothiourea (**7b**, R = CH_3, X = H), mp. 74-76°C (2-propanol). IR: 1625 and 1570 cm^{-1} (C=N). ^{1}H-NMR ($CDCl_3$): δ 1.45 (d, 3H, CH_3), 2.13 (s, 3H, SCH_3), 2.57 (t, 2H, NCH_2), 3.30 [q (+D_2O t), 2H, OCH_2], 4.80 [dq (+D_2O q), 1H, CH], 7.2-7.4 (m, 5H, ArH).

Anal. Calcd. for $C_{12}H_{18}N_2OS$: C, 60.47, H, 7.61, N, 11.75, S, 13.45

Found: C, 60.51, H, 7.80, N, 11.63, S, 13.32

3-Cyano-2-(2-hydroxyethyl)-1-(1-phenylpropyl)guanidine (**6c**, R = C_2H_5, X = H) and *3-(2-Hydroxyethyl)-2-methyl-1-(1-phenylpropyl)isothiourea* (**7c**, R = C_2H_5, X = H). From **4c** (R = C_2H_5, X = H) and **3**.- A mixture of 2.33 g (0.01 mole) of 3-cyano-2-methyl-1-(1-phenylpropyl)isothiourea (**4c**, R = C_2H_5, X = H), 0.74 g (0.012 mole) of 2-aminoethanol (**3**) and 10 ml of 2-propanol was boiled under reflux for 15 hrs. TLC of the reaction mixture showed the spots of both derivatives, **6c** (R = C_2H_5, X = H) (R_f = 0.49) and **7c** (R = C_2H_5, X = H) (R_f = 0.68). After cooling, the solution was evaporated to dryness and the residue chromatographed on a silica gel column [eluent 1: 2 (v/v) mixture of benzene and ethyl acetate] to yield 1.4 g (57 %) of 3-cyano-2-(2-hydroxyethyl)-1-(1-phenylpropyl)guanidine (**6c**, R = C_2H_5, X = H), mp. 98-99°C (ethyl acetate). IR: 2170 cm^{-1}(CN), 1600 and 1565 cm^{-1}(C=N). ^{1}H-NMR ($CDCl_3$): δ 0.93 (t, 3H, CH_3), 1.90 (dq, 2H, CCH_2), 3.45 (q, 2H, NCH_2), 3.69 (q, 2H, OCH_2), 4.70 (q, 1H, CH), 5.9 (t, 1H, OH), 6.65 (d, 1H, NH).

Anal. Calcd. for $C_{13}H_{18}N_4O$: C, 63.39, H, 7.37, N, 22.75
Found: C, 63.28, H, 7.43, N, 22.61

1-(4-Chlorobenzyl)-3-cyano-2-(2-hydroxyethyl)guanidine (**6d**, R = H, X = Cl) and *1-(4-Chlorobenzyl)-3-(2-hydroxyethyl)-2-methylisothiourea* (**7d**, R = H, X = Cl). From **4d** (R = H, X = Cl) and **3**.- A mixture of 2.39 g (0.01 mole) of 1-(4-chlorobenzyl)-3-cyano-2-methylisothiourea (**4d**, R = H, X = Cl), 0.74 g (0.012 mole) of 2-aminoethanol (**3**) and 10 ml of 2-propanol was boiled under reflux for 15 hrs. TLC of the reaction mixture showed the spots of both derivatives, **6d** (R = H, X = Cl) (R_f = 0.42) and **7d** (R = H, X = Cl) (R_f = 0.71). After cooling, the solution was evaporated to dryness and the residue chromatographed on a silica gel column [eluent 1: 2 (v/v) mixture of benzene and ethyl acetate] to yield 1.45 g (57 %) of 1-(4-chlorobenzyl)-3-cyano-2-(2-hydroxyethyl)-guanidine (**6d**, R = H, X = Cl), mp. 119-121°C (2-propanol). IR: 2160 cm^{-1}(CN), 1580 cm^{-1}(C=N). ^{1}H-NMR ($CDCl_3$): δ 3.30 (t, 2H, NCH_2CH_2), 3.68 (t, 2H, OCH_2), 4.31 [d (+ D_2O s), 2H, $NHCH_2$], 4.8 (t, 1H, OH), 6.5 (t, 1H, NH), 7.3 (s, 4H, ArH).

Anal. Calcd. for $C_{11}H_{13}ClN_4O$: C, 52.28, H, 5.18, N, 22.17, Cl, 14.03
Found: C, 52.19, H, 5.03, N, 22.38, Cl, 13.90

1-[1-(4-Chlorophenyl)-ethyl]-3-cyano-2-(2-hydroxyethyl)guanidine (**6e**, R = CH_3, X = Cl) and *1-[1-(4-Chlorophenyl)-ethyl]-3-(2-hydroxyethyl)-2-methylisothiourea* (**7e**, R = CH_3, X = Cl). From **4e** (R = CH_3, X= Cl) and **3**.- A mixture of 2.39 g (0.01 mole) of 1-[1-(4-chlorophenyl)-ethyl]-3-cyano-2-methylisothiourea (**4e**, R = CH_3, X = Cl), 0.74 g (0.012 mole) of 2-aminoethanol (**3**) and 10 ml of 2-propanol was boiled under reflux for15 hrs. TLC of the reaction mixture showed the spots of both derivatives, **6e** (R = CH_3, X = Cl) (R_f = 0.39) and **7e** (R = CH_3, X = Cl) (R_f = 0.67). After cooling, the solution was evaporated to dryness and the residue chromatographed on a silica gel column [eluent 1: 2 (v/v) mixture of benzene and ethyl acetate] to yield 1.42 g (53 %) of 1-[1-(4-chlorophenyl)-ethyl]-3-cyano-2-(2-hydroxyethyl)guanidine (**6e**, R = CH_3, X = Cl), mp. 99- 100°C (ethyl acetate). IR: 2160 cm^{-1}(CN), 1600 and 1570 cm^{-1}(C=N). ^{1}H-NMR ($CDCl_3$): δ 1.25 (d, 3H, CCH_3), 3.10 (q, 2H, NCH_2),

3.40 (q, 2H, OCH_2), 4.60 (dq, 1H, NH), 6.1 (t, 1H, OH), 6.9 (d, 1H, NH), 7.1 (s, 4H, ArH).

Anal. Calcd. for $C_{12}H_{15}ClN_4O$: C, 54.03, H, 5.67, N, 21.01, Cl, 13.29
Found: C, 54.14, H, 5.70, N, 21.08, Cl, 13.12

1-Benzyl-3-(2-hydroxyethyl)-2-methylisothiourea (**7a**, R = X = H) *by Methylation of* **8**.- To the solution of 2.1 g (0.01 mole) of 1-benzyl-3-(2-hydroxyethyl)thiourea (**8**)[1] in 10 ml of methanol 1.0 ml (2.13 g, 0.015 mole) of methyl iodide was added and let to stand at room temperature for 24 hrs. The solution was evaporated *in vacuo* to dryness, the residue was dissolved in 50 ml of water (charcoal), made alkaline with conc. ammonium hydroxide, the solution obtained was extracted with 50 ml of chloroform, the layers were separated, the chloroform layer was washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo* to dryness to yield 1.35 g (60 %) of the title *product*, mp. 88-89°C (2-propanol). The product is identical (mixed mp., IR) with **7a** obtained in the reaction of **4a** and **3**.

1-Benzyl-2-(4-chlorobenzyl)-3-cyanoisothiourea (**12**).- To the solution of 7.34 g (0.02 mole) of di-(4-chlorobenzyl) N-cyanocarbonimidodithioate[11] in 150 ml of acetonitrile 2.2 ml (2.14 g, 0.02 mole) of benzylamine (**2a**, R = X = H) was added and boiled under reflux for 2 hrs. After cooling the solution obtained was evaporated *in vacuo* to dryness and the residue recrystallized from ethyl acetate to yield 5.0 g (79 %) of the title *product*, mp. 154-156°C. IR: 2160 cm^{-1}(CN), 1550 and 1535 cm^{-1}(C=N). ^{1}H-NMR (DMSO-d_6): δ 3.41 (s, 2H, SCH_2), 4.40 (d, 2H, $NHCH_2$), 7.15-7.3 (m, 9H, ArH), 9.3 (bs, 1H, NH).

Anal. Calcd. for $C_{16}H_{14}ClN_3S$: C, 60.84, H, 4.47, N, 13.30, S, 10.15, Cl, 11.23
Found: C, 61.04, H, 4.62, N, 13.19, S, 10.31, Cl, 11.18

1-Benzyl-3-cyano-2-(2-hydroxyethyl)guanidine (**6a**, R = X = H) and *1-Benzyl-2-(4-chlorobenzyl)-3-(2-hydroxyethyl)isothiourea* (**13**). From **12** and **3**.- The mixture of 3.16 g (0.01 mole) of 1-benzyl-2-(4-chlorobenzyl)-3-cyanoisothiourea (**12**), 0.73 g (0.012 mole) of 2-aminoethanol (**3**), 40 ml of 2-propanol and 40 ml of dimethylformamide was boiled under reflux for 30 hrs. TLC of the reaction mixture showed spots of both derivatives, **6a** (R = X = H) (R_f = 0.18) and **13** (R_f = 0.57). The solution obtained was evaporated *in vacuo* to dryness and the residue chromatographed on a silica gel column [eluent 1: 2 (v/v) mixture of benzene and ethyl acetate] to yield 1.23 g (56 %) of 1-benzyl-3-cyano-2-(2-hydroxyethyl)guanidine (**6a**, R = X = H), mp. 74-75°C (2-propanol). The *product* is identical (mixed mp., IR) with that of **6a** obtained in the reaction of **4a** with **3**; further elution with a 1: 2 (v/v) mixture of benzene and ethyl acetate gave 0.39 g (12 %) of 1-benzyl-2-(4-chlorobenzyl)-3-(2-hydroxyethyl)isothiourea (13), mp. 126-128°C (2-propanol). IR: 1625 and 1570 cm^{-1}(C=N). ^{1}H-NMR ($CDCl_3$): δ 2.51 (s, 2H, SCH_3), 3.39 (t, 2H, $=NCH_2$), 3.62 (q, 2H, OCH_2), 4.38 (d, 2H, $NHCH_2$), 5.6 (b, 1H, OH), 6.7 (t, 1H, NH), 7.1- 7.3 (m, 9H, ArH).

Anal. Calcd. for $C_{17}H_{19}ClN_2OS$: C, 60.97, H, 5.72, N, 8.37, S, 9.58 Cl, 10.59,
Found: C, 61.13, H, 5.98, N, 8.44, S, 9.65 Cl, 10.45,

1-(4-Chlorobenzyl)-2-(4-chlorobenzyl)-3-cyanoisothiourea (**14**).- To the solution of 5.51 g (0.015 mole) of bis-(4-chlorobenzyl) N-cyanocarbonimidodithioate[11] in 40 ml of ethanol 2.1 g (0.015 mole) of 4-chloro-benzylamine (2d, R = H, X = Cl) was added and boiled under reflux for 3 hrs. After cooling the crystals precipitated were filtered off to yield 3.15 g (60 %) of the title *product*, mp. 204-206°C. IR: 2150 cm^{-1} (CN), 1550 and 1535 cm^{-1}(C=N). ^{1}H-NMR (DMSO-d_6): δ 3.42 (s, 2H, SCH_2), 4.54 (d, 2H, $NHCH_2$), 7.15-7.55 (m, 8H, ArH), 9.4 (bs, 1H, NH).

Anal. Calcd. for $C_{16}H_{13}Cl_2N_3S$: C, 54.86, H, 3.74, N, 12.00, S, 9.15, Cl, 20.24
Found: C, 54.91, H, 4.01, N, 11.84, S, 9.35, Cl, 19.98

1-(4-Chlorobenzyl)-3-cyano-2-(2-hydroxyethyl)-2-methylguanidine (**16**) and *1-(4-chlorobenzyl)-2-(4-chlorobenzyl)-3-(2-hydroxyethyl)-3-methylisothiourea* (**17**).- The mixture of 3.5 g (0.01 mole) of 1-(4-chlorobenzyl)-2-(4-chlorobenzyl)-3-cyanoisothiourea (**14**), 0.90 g (0.012 mole) of 2-methylaminoethanol (**15**), 40 ml of 2-propanol and 40 ml of dimethylformamide was boiled under reflux for 10 hrs. TLC of the reaction mixture showed the spots of both derivatives, **16** (R_f = 0.34) and **17** (R_f = 0.73). The solution was evaporated *in vacuo* to dryness and the residue chromatographed on a siliga gel column [eluent 1: 2 (v/v) mixture of benzene and ethyl acetate] to yield 0.23 g (9 %) of 1-(4-chlorobenzyl)-3-cyano-2-(2-hydroxyethyl)-2-methylguanidine (**16**), mp. 136-138°C (2-propanol). IR: 2180 cm^{-1} (CN), 1600 and 1540 cm^{-1}(C=N). ^{1}H-NMR ($CDCl_3$): δ 2.75 (t, 2H, NCH_2), 2.86 (s, 3H, NCH_3), 3.52 (q, 2H, OCH_2), 4.23 (d, 2H, $NHCH_2$), 5.1 (t, 1H, NH), 7.2 (s, 4H, ArH).

Anal. Calcd. for $C_{12}H_{15}ClN_4O$: C, 54.03, H, 5.67, N, 21.01, Cl, 13.29
Found: C, 54.11, H, 5.78, N, 20.88, Cl, 13.20

Further elution with a 1: 2 (v/v) mixture of benzene and ethyl acetate gave 0.45 g (12 %) of 1-(4-chlorobenzyl)-2-(4-chlorobenzyl)-3-(2-hydroxyethyl)-3-methylisothiourea (**17**), mp. 74-75°C (2-propanol). IR: 3330 cm^{-1}(OH), 1610 and 1520 cm^{-1}(C=N). ^{1}H-NMR ($CDCl_3$): δ 2.50 (t, 2H, NCH_2), 2.82 (s, 3H, NCH_3), 3.40 (q, 2H, OCH_2), 3.60 (s, 2H, SCH_2), 4.30 (s, 2H, $=NCH_2$), 7.15 (s, 8H, ArH).

Anal. Calcd. for $C_{18}H_{20}Cl_2N_2OS$: C, 56.40, H, 5.26, N, 7.31, S, 8.36, Cl, 18.50
Found: C, 56.52, H, 5.46, N, 7.45, S, 8.28, Cl, 18.37

S-Benzyl-N-cyano-thiocarbamoylmorpholine (**18**).- To the solution of 8.95 g (0.03 mole) of dibenzyl N-cyanocarbonimidodithioate[12] in 100 ml of ethanol 2.79 g (0.032 mole) of morpholine was added and let to stand at room temperature for 24 hrs. The mixture obtained was evaporated *in vacuo* to dryness and the residue recrystallized from 2-propanol to yield 6.2 g (79 %) of the title *product*, mp. 111-112°C. IR: 2180 cm^{-1}(CN), 1115 cm^{-1}(COC), 1550 cm^{-1}(C=N). ^{1}H-NMR ($CDCl_3$): δ 3.37 (t, 4H, NCH_2), 3.69 (t, 4H, OCH_2), 4.45 (s, 2H, SCH_2), 7.28 (s, 5H, ArH).

Anal. Calcd. for $C_{13}H_{15}N_3OS$: C, 59.75, H, 5.79, N, 16.08, S, 12.27
Found: C, 59.78, H, 6.01, N, 16.05, S, 12.46

N-Cyano-N'-(2-hydroxyethyl)-guanylmorpholine (**19**) and *S-benzyl-N-(2-hydroxyethyl)-thiocarbamoyl-morpholine* (**20**). From **18** and **3**.- The mixture of 2.61 g (0.01 mole) of S-benzyl-N-cyano-thiocarbamoyl-morpholine (**18**), 0.74 g (0.012 mole) of 2-aminoethanol (**3**) and 50 ml of 2-propanol was boiled under reflux for 10 hrs. TLC of the reaction mixture showed the spots of both derivatives, **19** (R_f = 0.22) and **20** (R_f = 0.59). The solution was evaporated *in vacuo* to dryness and the residue chromatographed on a siliga gel colunm [eluent 1: 2 (v/v) mixture of benzene and ethyl acetate] to yield 0.8 g (40 %) of N-cyano-N'-(2-hydroxyethyl)-guanyl-morpholine (**19**), mp. 167- 168°C (acetonitrile). IR: 2180 cm^{-1}(CN), 1595 and 1540 cm^{-1}(C=N), 1120 cm^{-1}(C-O). ^{1}H-NMR (DMSO-d_6): δ 3.25- 3.75 (m, 12H, all NCH_2+ OCH_2), 4.65 (t, 1H, OH), 7.05 (t, 1H, NH).

Anal. Calcd. for $C_8H_{14}N_4O_2$: C, 48.47, H, 7.12, N, 28,27

Found: C, 48.63, H, 7.19, N, 28.03

Further elution with a 1: 2 (v/v) mixture of benzene and ethyl acetate gave 0.4 g (14 %) of S-benzyl-N-(2-hydroxy-ethyl)-thiocarbamoylmorpholine (**20**), mp. 67-69°C (from a 1:4 (v/v) mixture of cyclohexane and ethyl acetate). IR: 3335 cm^{-1}(OH), 1625 and 1545 cm^{-1}(C=N), 1117 cm^{-1}(C-O). ^{1}H-NMR (DMSO-d_6): δ 3.19 (t, 2H, $=NCH_2$), 3.23 (t, 4H, NCH_2), 3.35 (s, 2H, SCH_2), 3.53 (t, 4H, OCH_2), 3.74 (q, 2H, $C\underline{H}_2OH$), 7.2-7.4 (m, 5H, ArH). ^{13}C-NMR (DMSO-d_6): δ 159.1 (N=$\underline{C}$-S).

Anal. Calcd. for $C_{14}H_{20}N_2O_2S$: C, 59.97, H, 7.19, N, 9.99, S, 11.44

Found: C, 60.08, H, 7.40, N, 10.12, S, 11.23

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