James A. Bristol

Department of Chemical Research-Medicinals, Schering-Plough Corporation,
Research Division, Bloomfield, NJ 07003

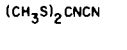
Received May 26, 1978

The sodium hydroxide catalyzed synthesis of several cyclic *N*-cyanoguanidines (**8**,**10**) from dimethyl cyanoimidodithiocarbonate (**2**) and the appropriate aniline derivative (**4**,**5**) is described. Base-induced di-*N*-alkylation to afford **9** and **11** occurs readily.

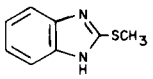
J. Heterocyclic Chem., 15, 1409 (1978)

While the chemistry of acyclic *N*-cyanoguanidines has been explored rather thoroughly, cyclic *N*-cyanoguanidines, in which the terminal amino groups are joined to form a ring, have been studied little. Baltzer and McCarty (1) reported the preparation of **1** by the reaction of dimethyl cyanoimidodithiocarbonate (**2**) with alkyl diamines. Reaction of **2** with 2-aminoaniline gave only the benzimidazole **3**, and not the expected cyanoguanidine.

1: R = H, CH_3; n = 2, 3



2



3

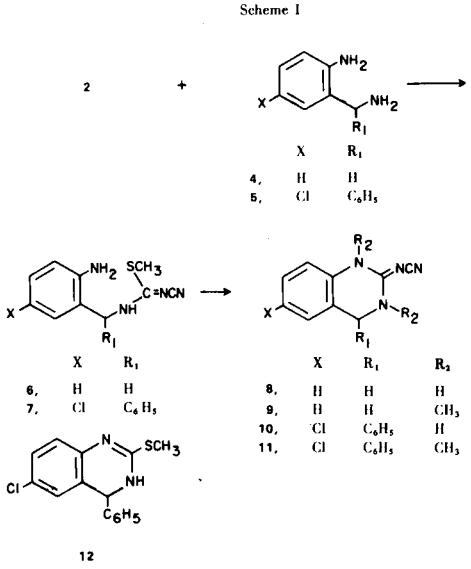
The synthesis and characterization of several 1,2,3,4-tetrahydro-2-quinazolinylidene cyanamides, a novel series of cyclic *N*-cyanoguanidines in which an anilino nitrogen is one of the terminal amino groups of the cyanoguanidine, is reported here; thus, reaction of **2** with 2-aminobenzylamine in ethanol gave **6** in 84% yield, characterized by pmr, ir, and ms. Heating **6** under reflux in xylene for 18 hours gave only recovered starting material; however, **6** was cleanly converted to 1,2,3,4-tetrahydro-2-quinazolinylidene cyanamide (**8**) (95%) by heating under reflux in dioxane containing a catalytic amount of sodium hydroxide. Alkylation of **8** (sodium hydride and excess methyl iodide in 1,2-dimethoxyethane) gave 1,3-dimethyl-1,2,3,4-tetrahydro-2-quinazolinylidene cyanamide (**9**) (54%).

The synthesis of the 4-phenyl congeners took a somewhat different course. Reaction of α-phenyl-2-amino-5-chlorobenzylamine (**5**) with **2** in ethanol gave directly 4-phenyl-1,2,3,4-tetrahydro-2-quinazolinylidene cyanamide (**10**) (11%) without isolation of the presumed intermediate, **7**. Further treatment of the residue from the mother liquor of **10** in boiling dioxane with a catalytic amount of sodium hydroxide provided an additional 43% of **10** by fractional crystallization. Chromatography of the mother liquor gave 5% of 6-chloro-2-methylthio-4-phenyl-3,4-dihydroquinazoline (**12**), which probably is formed either by reaction of the liberated methanethiol with **10**, or by ring closure followed by loss of cyanamide from **7**. Subsequent alkylation of **10** (sodium hydride, methyl iodide) gave 1,3-dimethyl-6-chloro-4-phenyl-1,2,3,4-tetrahydro-2-quinazolinylidene cyanamide (**11**) (43%).

0022-152X/78/081400-02$02.25

In the pmr spectra (DMSO-d_6), the N-*H* protons of **8** and **10** are nonequivalent and are separated by approximately 2 ppm. The methine proton of **10** is a broad singlet which sharpens upon deuterium oxide exchange, indicating coupling with the N_3-*H*, which is the high field N-*H* proton. Consistent with the reported low barrier for syn/anti isomerism of acyclic *N*-cyanoguanidines (2) ($\Delta G < 10$ kcal.), the N-CH_3 compounds, **9** and **11**, each show only two non-equivalent methyl groups. As expected, *N*-methylation does not materially change the uv spectra of **9** and **11** from that of **8** and **10**, respectively.

Scheme I



EXPERIMENTAL

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Pmr spectra were recorded on a Varian A-60-A spectrometer and are reported in ppm from TMS. Ir spectra were recroded on a Perkin Elmer 221 Spectrometer and mass spectra were determined with a Varian MAT CH5 Spectrophotometer. Uv spectra were recorded on a Cary 118 Spectrophotometer.

1,2,3,4-Tetrahydro-2-quinazolinylidene Cyanamide (**8**).

To a stirred solution of 5.5 g. (0.045 mole) of **4** (3) in 100 ml. of ethanol, 6.58 g. (0.055 mole) of **2** (4) was added in one portion. The reagents dissolved and within 1 minute a heavy precipitate separated. After stirring for 3 hours, the product was collected to give 8.36 g. (84%) of **6**, m.p. 157-158°; pmr (DMSO-d_6): 2.59 ppm (s, 3H, S-CH_3), 4.32 (s, 2H, CH_2), 5.01 (broad s, 2H, ArNH_2),

6.40-7.05 (m, 4H, Ar*H*), 8.50 (broad s, 1H, N*H*); ir (Nujol): 3420, 3340, 2175 cm^{-1}; ms: m/e 220 (0.90%), 173 (100%). A solution of **6** (8.15 g., 0.037 mole) in 80 ml. of dioxane was heated under reflux for 48 hours in the presence of 1 pellet of sodium hydroxide. Upon cooling, a solid product was collected to give 6.04 g. (95%) of **8** before recrystallization. A 2.69 g. sample was recrystallized from ethanol to give 1.44 g. (50%) of pure **8**, m.p. 259-261°; pmr (DMSO-d_6): 4.37 ppm (s, 2H, CH_2), 6.79-7.27 (m, 4H, Ar*H*), 8.10 (s, 1H, N*H*), 10.1 (s, 1H, N*H*); ir (Nujol): 2170, 1655 cm^{-1}; uv (methanol): 234 nm (log ϵ = 4.21), 261 (log ϵ = 4.26); ms: m/e 172 (73%), 171 (100%).

Anal. Calcd. for $C_9H_8N_4$: C, 62.78; H, 4.68; N, 32.54. Found: C, 63.12; H, 4.57; N, 32.46.

1,3-Dimethyl-1,2,3,4-tetrahydro-2-quinazolinylidene Cyanamide (**9**).

To a magnetically stirred slurry of 2.67 g. (0.056 mole) of 50% sodium hydride (petroleum ether-washed) in 75 ml. of 1,2-dimethoxyethane under nitrogen, was added 4.0 g. (0.023 mole) of **8**. After stirring for 2.25 hours, methyl iodide (5 ml.) was added to the mixture and stirring was continued for 1.5 hours. The mixture was concentrated and 2-propanol (*ca.* 5 ml.) was added to the residue followed by ice water. Extraction with chloroform followed by washing (brine), drying (potassium carbonate) and concentration of the chloroform gave 3.21 g. of a tan solid after trituration with petroleum ether. This was recrystallized from 20 ml. of ethanol to give 2.5 g. (54%) of **9**, m.p. 130-133°; pmr (DMSO-d_6): 3.24 ppm (s, 3H, CH_3), 3.44 (s, 3H, CH_3), 4.42 (s, 2H, CH_2), 7.01-7.51 (m, 4H, Ar*H*); ir (Nujol): 2160 cm^{-1}; uv (methanol): 240 nm (log ϵ = 4.22), 260 (log ϵ = 4.13); ms: m/e 200 (83.7%), 118 (100%).

Anal. Calcd. for $C_{11}H_{12}N_4$: C, 66.06; H, 6.05; N, 28.01. Found: C, 66.10; H, 6.15; N, 27.83.

6-Chloro-4-phenyl-1,2,3,4-tetrahydro-2-quinazolinylidene Cyanamide (**10**).

A solution of **5** (5) (9.8 g., 0.042 mole) in 75 ml. of ethanol was added dropwise to a solution of **2** (6.16 g., 0.042 mole) in 100 ml. of ethanol. After stirring overnight, the solid precipitate was collected to give 1.3 g. of **10**. The filtrate was concentrated and the residue was suspended in 100 ml. of dioxane and heated under reflux for 24 hours in the presence of two pellets of sodium hydroxide. Upon cooling, the solid product was collected and washed with dioxane to give an additional 5.15 g. of **10** (54% before recrystallization). A 3.0 g. sample was recrystallized from 125 ml. of 2-methoxyethanol to give 2.0 g. (36%) of pure **10**, m.p. 316-318° dec.; pmr (DMSO-d_6): 5.65 ppm (broad s, 1H, C*H*), 6.97-7.37 (m, 8H, Ar*H*), 8.77 (broad s, 1H, N*H*), 10.4 (broad s, 1H, N*H*); ir (Nujol): 2150 cm^{-1}; uv (methanol): 220 nm (log ϵ = 4.40), 241 (sh) (log ϵ = 4.16), 268 (log ϵ = 4.35); ms: m/e 282/284 (34%/11.4%), 205/207 (100%/31.4%).

Anal. Calcd. for $C_{15}H_{11}ClN_4$: C, 63.66; H, 3.92; N, 19.80. Found: C, 63.63; H, 3.80; N, 19.86.

6-Chloro-2-methylthio-4-phenyl-3,4-dihydroquinazoline (**12**).

The dioxane filtrate from **10** was concentrated and the residue was chromatographed on silica gel with chloroform-methanol to give 2.0 g. of **12**. Recrystallization from diisopropyl ether gave 0.57 g. (5%) of pure **12**, m.p. 134-137°; pmr (DMSO-d_6): 2.44 ppm (s, 3H, CH_3), 5.63 (s, 1H, C*H*), 6.76-7.52 (m, 8H, Ar*H*), 8.37 (broad s, 1H, N*H*); uv (methanol): 226 nm (log ϵ = 4.30), 295 (log ϵ = 4.07); ms: m/e 288/290 (38.6%/14.5%), 211/213 (100%/39.8%).

Anal. Calcd. for $C_{15}H_{13}ClN_2S$: C, 62.38; H, 4.53; Cl, 12.27; N, 9.69; S, 11.10. Found: C, 62.60; H, 4.59; Cl, 12.12; N, 9.60; S, 11.35.

1,3-Dimethyl-6-chloro-4-phenyl-1,2,3,4-tetrahydro-2-quinazolinylidene Cyanamide (**11**).

A mixture of **10** (3.30 g., 0.0116 mole) and 50% sodium hydride (1.23 g., 0.025 mole) (washed once with petroleum ether) in 75 ml. of 1,2-dimethoxyethane was allowed to stir for 2 hours. Methyl iodide (5.0 ml.) was added in one portion and the reaction mixture was allowed to stir overnight. The mixture was concentrated and the residue was partitioned between chloroform and water. The chloroform was dried (potassium carbonate) and concentrated to give 3.35 g. of crude **11**. Recrystallization from 20 ml. of 2-propanol gave 1.37 g. (43%) of **11**, m.p. 152-154°; pmr (DMSO-d_6): 3.30 ppm (s, 3H, CH_3), 3.45 (s, 3H, CH_3), 5.71 (s, 1H, C*H*), 7.09-7.50 (m, 8H, Ar*H*); ir (Nujol): 2160 cm^{-1}; uv (methanol): 218 nm (log ϵ = 4.36), 245 (log ϵ = 4.19), 269 (log ϵ = 4.21); ms: m/e 310/312 (50%/17.3%), 233/235 (100.0%/32.1%).

Acknowledgement.

I thank the staff of the Department of Physical and Analytical /Research, Schering-Plough Corporation, for providing pmr, ir, uv and mass spectral data.

REFERENCES AND NOTES

(1) C. M. Baltzer and C. G. McCarty, *J. Org. Chem.*, **38**, 155 (1973).

(2) C. G. McCarty and D. M. Wieland, *Tetrahedron Letters*, 1787 (1969).

(3) R. E. Orth and J. W. Jones, *J. Pharm. Sci.*, **50**, 866 (1961).

(4) T. Suyama and K. Odo, *J. Synth. Org. Chem. Japan*, **29**, 65 (1971).

(5) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1691 (1962).