paper had recorded the melting point as 106 °C; see D. Vorlander and K. Hobohm, *Ber.*, **29**, 1352 (1896). Our sample melted at 111–112 °C.
(2) C. A. R. Baxter and D. A. Whiting, *J. Chem. Soc. C*, 1174 (1968).
(3) E. L. Eliel and M. H. Gianni, *Tetrahedron Lett.*, 97 (1962); S. Sternhell, *Q. Rev., Chem. Soc.*, **23**, 236 (1969).
(4) For a general review of the significance of $W_{1/2}$ in assigning proton signals from an axial or equatorial C–H bond, see L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed., Pergamon Press, Oxford, 1969, Chapter 4-2.
(5) J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. Reich, *J. Am. Chem. Soc.*, **92**, 1338 (1970).
(6) M. Balasubramanian and N. Padma, *Tetrahedron*, **19**, 2135 (1963).
(7) K. Ramalingam, K. D. Berlin, N. Satyamurthy, and R. Sivakumar, *J. Org. Chem.*, **44**, 471 (1979).

Cyanoimine Chemistry: New Routes to Pyrimidinones and (Carbonylamino)-iminopropanamides

John M. McCall,* David Kloosterman, and Bharat V. Kamdar

Cardiovascular Diseases Research, The Upjohn Company, Kalamazoo, Michigan 49001

Received October 17, 1978

We have investigated the chemistry of 2,4-diamino-6-piperidinopyrimidine 3-oxide, a hypotensive compound.[1] We now report the synthesis of related *N*-alkylpyrimidinones and the preparation of substituted ureas. Pyrimidinones in which particular nitrogens are alkylated are often prepared with difficulty. The direct alkylation of 2-amino-4-hydroxypyrimidines is ambiguous because of multiple sites of possible alkylation.[2] Similarly, condensation route to *N*-alkyl-2-amino-4-hydroxypyrimidines which employ substituted guanidines can in principle give either of two possible products.[3] 3-(Cyanimino)propionic systems are useful precursors of various pyrimidines.[4] We now report their intermediacy in the preparation of *N*-alkylpyrimidinones and complex ureas of clearly defined structure.

N-Alkyl-3-imino-3-ethoxypropanamide hydrochlorides (**2**) are readily prepared from the corresponding *N*-alkyl-2-cyanoacetamides, ethanol, and hydrogen chloride (step 1, Scheme I). Amides of structure **2** react with cyanamide in toluene or methylene chloride (step 2) to yield *N*-alkyl-3-(cyanimino)-3-ethoxypropanamides (**3**). Secondary amines readily displace ethanol from compound **3** to produce *N*-alkyl-3-(cyanimino)-3-(alkylamino)propanamides of structure **4** (step 3).

Amides of structure **4** are versatile intermediates. These 3-(cyanimino)propanamides, when reacted with 2 or more equivalents of potassium *tert*-butoxide, yield 2-amino-3-alkyl-6-(alkylamino)-4-pyrimidinones of structure **5** (step 4). Similarly, *N*-*n*-butyl-3-(cyanimino)-3-ethoxypropanamide, when treated with 2 equiv of base, yields 2-amino-3-*n*-butyl-6-ethoxy-4-pyrimidinone (**6**) (step 5).

Base-mediated intramolecular cyclizations of amides on nitriles are reported in the art.[5] For example, *N*-phenyl-*N'*-(*o*-cyanophenyl)urea, when treated with sodium methoxide, affords 3-phenyl-4-(3*H*)-imino-2(1*H*)-quinazolone.[6]

N-Alkyl-3-[(aminocarbonyl)imino]-3-(alkylamino)propanamides of structure **7** can be prepared by hydrolysis of 3-(cyanimino)propanamide **4** with concentrated hydrochloric acid in acetic acid (Scheme I, step 6).

Scheme I

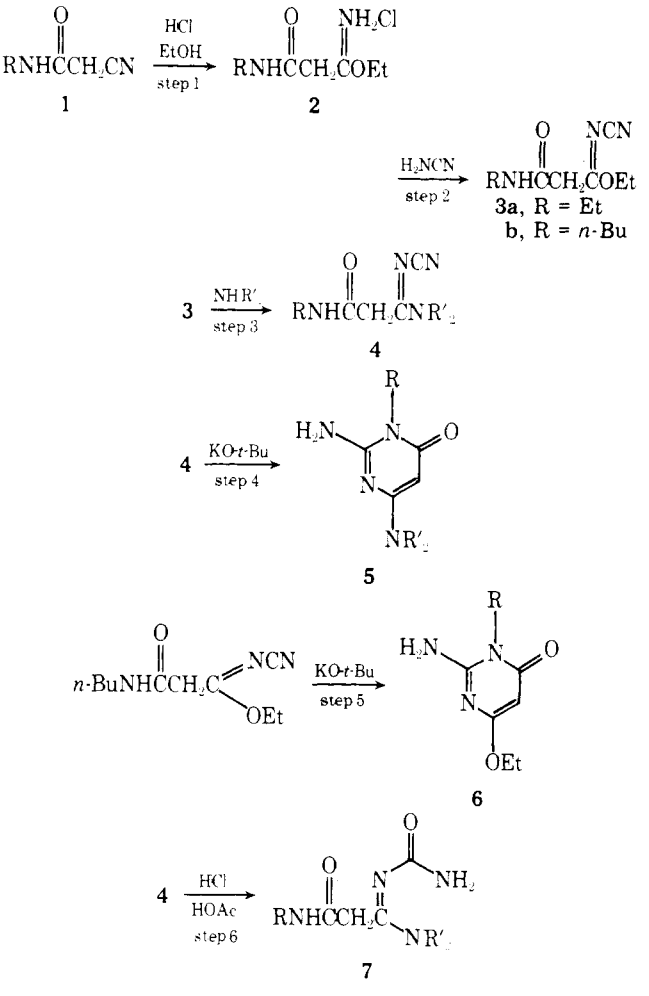

Table I

compd[a]	R	NR^1_2	yield of **4**, %	mp, °C	yield of **5**, %	mp, °C	yield of **7**, %	mp, °C
a	Et		87	117–118.5[d,i]	87	276–277[e]	89	126–127.5[e,j]
b	Et		84	188–189.5[d]	58	240–241[e]	52	115–115.5[f,g]
c	*n*-Bu		88.7	oil[b]	77	197–198[g]	52	133–141[h]
d	*n*-Bu		38	105–110[c,f]	47	195–196.5[g]	77	109–110[g]
e	*n*-Bu	NEt_2	44	oil[b]	77	120–120.5[g]	72	164–165.5[g]

[a] Unless otherwise noted, these compounds gave satisfactory elemental analyses (±0.4% C, N, N). [b] Not analyzed. [c] Sublimation point. [d] Crystallized from toluene. [e] Crystallized from ethyl acetate. [f] Crystallized from methylene chloride/cyclohexane. [g] Crystallized from ethyl acetate/cyclohexane. [h] From ethyl acetate. [i] C analysis is 0.78 off. [j] N analysis is 0.47 off.

0022-3263/79/1944-1562$01.00/0

Experimental Section

Melting points were determined in capillary tubes with Thomas-Hoover apparatus and are uncorrected. Column chromatography was performed on a medium-pressure system which included a Milton Roy D pump and LDC chromatography columns. Columns were packed with Merck 230–400 mesh silica gel 60. Preparations of representative compounds are given below. Reaction data for all products are summarized in Table I and supplementary material.

***N*-Ethyl-3-(cyanimino)-3-ethoxypropanamide (3a).** Dry HCl gas was bubbled into a solution of 17.03 g (0.152 mol) of *N*-ethyl-2-cyanoacetamide and 6.98 g (0.152 mol) of dry ethanol in 300 mL of dry THF at 0 °C for 10 min. After being stirred for 2 h, the mixture was concentrated in vacuo. The residue was crystallized from ethyl acetate to yield 15.52 g (0.0798 mol, 52%) of iminium ester hydrochloride **2**. This material was stirred for 16 h in 600 mL of toluene with 3.35 g (0.0798 mol) of cyanamide which had been purified by ether extraction. The toluene was filtered through cotton. The filtrate was concentrated in vacuo to yield 6.24 g (43%) of crystalline *N*-ethyl-3-(cyanimino)-3-ethoxypropanamide. This was recrystallized from EtOAc/cyclohexane, mp 68.5–70.0 °C, and used without further purification.

Anal. Calcd for $C_8H_{13}N_3O_2$: C, 52.44; H, 7.15; N, 22.94. Found: C, 52.46; H, 7.24; N, 22.22.

***N*-*n*-Butyl-3-(cyanimino)-3-ethoxypropanamide (3b).** The basic procedure for the *N*-ethyl compound (vide supra) was followed. Thus, 36 g (0.257 mol) of 2-cyano-*N*-*n*-butylacetamide and 11.82 g (0.257 mol) of ethanol were converted to the iminium ester hydrochloride, which was dissolved in 500 mL of methylene chloride and reacted with 10.8 g (0.26 mol) of cyanamide. After 20 h, the solution was filtered. The filtrate was partitioned with aqueous sodium bicarbonate, dried over sodium sulfate, and concentrated in vacuo to give 38.21 g (70% overall) of a yellow oil which was *N*-*n*-butyl-3-(cyanimino)-3-ethoxypropanamide. This was clean by TLC. Spectral data were consistent with the assigned structure. This material was used without further purification.

***N*-Ethyl-3-morpholino-3-(cyanimino)propanamide (4b).** A 2.60-g (0.0142-mol) sample of *N*-ethyl-3-ethoxy-3-(cyanimino)propanamide was stirred with 2.94 g (0.034 mol) of morpholine in 250 mL of toluene. After 3 h, the resultant white crystalline product was filtered to yield 2.66 g (84%) of pure *N*-ethyl-3-morpholino-3-(cyanimino)propanamide, mp 188–189.5 °C.

Anal. Calcd for $C_{10}H_{16}N_4O_2$: C, 53.55; H, 7.19; N, 24.98. Found: C, 53.54; H, 7.52; N, 25.01.

2-Amino-3-ethyl-6-piperidino-4-pyrimidinone (5a). A solution of 1.21 g (0.00545 mol) of *N*-ethyl-3-(cyanimino)-3-piperidinopropanamide (**4a**) in 40 mL of tetrahydrofuran and 5 mL of dimethylformamide was stirred with 2.42 g (0.022 mol) of potassium *tert*-butoxide for 2 h. The mixture was partitioned between methylene chloride and aqueous sodium bicarbonate. The organic phase was dried over sodium sulfate and concentrated in vacuo. The residue was chromatographed (4% methanol/methylene chloride on silica gel) to yield 1.05 g (87%) of crystalline product. This was recrystallized from ethyl acetate to yield 0.95 g of pyrimidinone **5a**, mp 276–277 °C.

Anal. Calcd for $C_{11}H_{18}N_4O$: C, 59.43; H, 8.16; N, 25.21. Found: C, 59.48; H, 8.26; N, 25.47.

2-Amino-3-*n*-butyl-6-ethoxy-4-pyrimidinone (6). A solution of 7.60 g (0.036 mol) of *N*-*n*-butyl-3-(cyanimino)-3-ethoxypropanamide in 100 mL of tetrahydrofuran was treated with 8.07 g (0.072 mol) of potassium *tert*-butoxide. After 10 h, the mixture was partitioned between aqueous sodium bicarbonate and methylene chloride. The organic phase was dried over sodium sulfate and concentrated in vacuo. The residue was chromatographed (4% ethanol in methylene chloride on silica gel) and crystallized from ethyl acetate and cyclohexane to yield 1.22 g (17%) of white crystalline **6**, mp 109–111 °C.

Anal. Calcd for $C_{10}H_{17}N_3O_2$: C, 56.85; H, 8.11; N, 19.89. Found: C, 56.92; H, 8.69; N, 20.32.

***N*-Ethyl-3-[(aminocarbonyl)imino]-3-morpholinopropanamide (7b).** A solution of 1.00 g (0.00446 mol) of *N*-ethyl-3-(cyanimino)-3-morpholinopropanamide (**4b**) in 10 mL of acetic acid and 1 mL of concentrated hydrochloric acid was stirred for 6.5 h. The mixture was partitioned between sodium carbonate and methylene chloride. The organic phase was dried over sodium sulfate and concentrated in vacuo to give 0.56 g (52%) of crystalline **7b**. This was recrystallized from methylene chloride/cyclohexane to yield 0.54 g of **7b**, mp 115–115.5 °C.

Anal. Calcd for $C_{10}H_{18}N_4O_3$: C, 49.57; H, 7.49; N, 23.13. Found: C, 49.59; H, 7.39; N, 22.94.

Registry No.—**1** (R = Et), 15029-36-4; **1** (R = *n*-Bu), 39581-21-0; **2** (R = Et), 69309-04-2; **2** (R = *n*-Bu), 69309-05-3; **3a**, 69309-06-4; **3b**, 69309-07-5; **4a**, 69308-94-7; **4b**, 69308-95-8; **4c**, 69352-31-4; **4d**, 69352-32-5; **4e**, 69331-25-5; **5a**, 69308-96-9; **5b**, 69308-97-0; **5c**, 69308-98-1; **5d**, 69308-99-2; **5e**, 69331-24-4; **6**, 69309-08-6; **7a**, 69331-23-3; **7b**, 69309-00-8; **7c**, 69309-01-9; **7d**, 69309-02-0; **7e**, 69309-03-1; cyanamide, 420-04-2; pyrrolidine, 123-75-1; morpholine, 110-91-8; diethylamine, 109-89-1.

Supplementary Material Available: Full NMR data for the above compounds (1 page). Ordering information is given on any current masthead page.

References and Notes

(1) J. M. McCall, R. E. TenBrink, and J. J. Urpsrung, *J. Org. Chem.*, **40**, 3304 (1975); J. M. McCall and R. E. TenBrink, *Synthesis*, 673 (1978).
(2) D. J. Brown, Ed., "The Chemistry of Heterocyclic Compounds: The Pyrimidines", Vol. 16, Supplement I, Wiley-Interscience, New York, 1970. pp 269–283.
(3) D. J. Brown, Ed., "The Chemistry of Heterocyclic Compounds: The Pyrimidines", Vol. 16, Wiley-Interscience, New York, 1962, p 357.
(4) T. Hirayama, M. Kamada, M. Mimura, and H. Tsurumi, *Heterocycles*, **2**, 461, 457 (1974); references from footnote 1 above.
(5) E. C. Taylor and A. McKillop, "The Chemistry of Cyclic Enaminonitriles and *o*-Aminonitriles", Wiley-Interscience, New York, 1970, pp 229 and 296–299.
(6) E. C. Taylor and R. V. Ravindranathan, *J. Org. Chem.*, **27**, 2622 (1962).

Hydrolysis of Model Compounds for α-Hydroxylation of the Carcinogens *N*-Nitrosopyrrolidine and *N'*-Nitrosonornicotine

Stephen S. Hecht* and Chi-hong B. Chen

Division of Environmental Carcinogenesis, Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, New York 10595

Received November 16, 1978

The environmental carcinogens *N*-nitrosopyrrolidine (**1**) and *N'*-nitrosonornicotine (**2**) are most likely converted to their ultimate carcinogenic forms by metabolic α-hydroxylation.[2-5] Since the resulting α-hydroxynitrosamines (**10**, **12a,b**, Scheme I) are unstable, the chemistry of α-hydroxylation is best studied by the use of model compounds. α-Acetoxynitrosamines have been proven to be useful compounds in studying the chemical and biological properties of α-hydroxynitrosamines.[3,6-12] In order to determine the nature of the products of α-hydroxylation of **1** and **2**, the hydrolyses of 2-acetoxy-*N*-nitrosopyrrolidine (**9b**), 2'-acetoxy-*N'*-nitrosonornicotine (**6**), and 5'-acetoxy-*N'*-nitrosonornicotine (**9a**) were studied. To further clarify the chemistry of these α-oxidized cyclic nitrosamines, the hydrolyses of nitrosourethanes **13** and **16** were also studied.

The syntheses of 2-acetoxy-*N*-nitrosopyrrolidine (**9b**) and 4-(*N*-carbethoxy-*N*-nitrosamino)butanal (**16**) have been described.[3,4] For the preparation of **6** and **9a**, **2** was converted to a mixture of α-carbanions with lithium diisopropylamide. Reaction with dimethyl disulfide[13] gave a mixture of 2'-thiomethyl-*N'*-nitrosonornicotine (**3**) and 5'-thiomethyl-*N'*-nitrosonornicotine (**4**) in which the former predominated. The