Notes

Antihypertensive (2-Aminoethyl)thiourea Derivatives. 2

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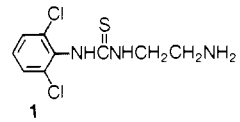
Starting with 2,6-dichlorophenyl isothiocyanate, 1-(2-aminoethyl)-2-cyano-3-(2,6-dichlorophenyl)guanidine (**2**) was prepared in three steps. In contrast to the corresponding thiourea **1**, this compound was essentially inactive as an antihypertensive agent.

The chemistry and pharmacology of the antihypertensive (aminoethyl)thiourea **1** and its congeners are described



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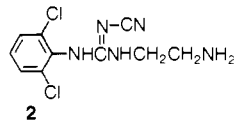

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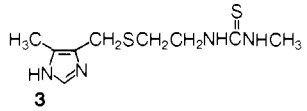

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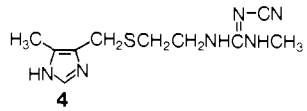

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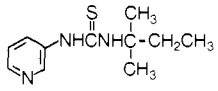

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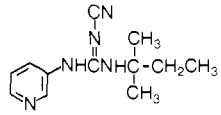
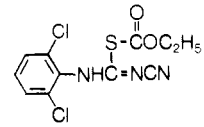


6

in the first paper of this series.[2] The thiourea and cyanoguanidine moieties have been shown to be true bioisosteres in the series of histamine H_2-receptor blocking agents characterized by metiamide (**3**) and cimetidine (**4**).[3] Recently, it was found that substitution of the thiourea sulfur atom of 1-*tert*-pentyl-3-(3-pyridyl)thiourea (**5**) with a cyanoimino group to give **6** resulted in a 250-fold enhancement of antihypertensive potency.[4] These results prompted us to prepare and evaluate the cyanoguanidine **2** in comparison with the thiourea **1** in order to test the relevance of the above findings to the present case.

The isothiocyanate **7**[5] was treated with sodium cyanamide in ethanol to give a solution of **8** which was allowed to react directly with iodomethane, affording the pseudothiourea **9** (Scheme I).[6] In contrast to our expectations,[6,7] reaction of **9** with *N*-acetylethylenediamine (**10**)[8] led to a mixture consisting predominantly of the guanidine **11** (42%), resulting from attack of the nucleophile on the nitrile carbon.

Our previous experience with related systems led us to postulate that attachment of electronegative groups to the pseudothiourea sulfur atom would promote attack at the sulfur-bearing carbon atom. Accordingly, the crude **8** was treated with ethyl chloroformate to give the thiocarbonate **12**. Neither this compound nor the adduct formed in situ



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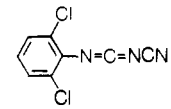

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by reaction of **8** with 2-chloro-1-methylpyridinium iodide[9] gave more than traces of the desired cyanoguanidine **13** when allowed to react with **10**. However, when a THF solution of the sodium salt **8** was treated with mercuric chloride in the presence of excess *N*-acetylethylenediamine (**10**), a 55% yield of **13** was obtained. This transformation presumably proceeds through the intermediacy of the carbodiimide **14**.[10]

Model studies have revealed that attempted acid-catalyzed deacetylation of compounds such as **13** results in preferential hydrolysis of the nitrile moiety. On the other hand, aqueous sodium hydroxide promotes the desired cleavage. Apparently, removal of an acidic cyanoguanidine proton protects this functional group from both inter- and intramolecular attack. Thus, treatment of **13** with sodium hydroxide solution at 50 °C afforded a 77% yield of **2**, isolated as its maleate salt. In model studies, use of higher temperatures, as well as milder bases, caused extensive side reactions.

The cyanoguanidine **2** was evaluated for antihypertensive activity in three of the animal models in which the thiourea **1** was highly active. It was given to spontaneously hypertensive rats (10, 30, and 100 mg/kg, po), producing a slight, but statistically significant ($p < 0.05$, paired t test), reduction in blood pressure (BP) (12.7%) and in heart rate (HR) (12.7%) 3–6 h after the highest dose.[11] In DOCA/salt hypertensive rats, an oral dose of 10 mg/kg evoked a fall in BP (12–20%) of short duration (1–3 h) with no efect on HR. In four renal hypertensive dogs, the drug (1–30 mg/kg, po) was well tolerated. The 10 mg/kg dose produced a small reduction in arterial BP (7%, $p < 0.05$, paried t test) 6 h after dosing; no other statistically

(1) Corresponding address: Chemical Research Department, Hoffmann-La Roche Inc., Nutley, N.J. 07110.
(2) J. W. Tilley, R. W. Kierstead, and M. Cohen, *J. Med. Chem.*, under articles in this issue.
(3) G. J. Durant, J. C. Emmett, C. R. Ganellin, P. D. Miles, M. E. Parsons, H. D. Prain, and G. R. White, *J. Med. Chem.*, **20**, 901 (1977).
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(5) British Patent 1 131 780: *Chem. Abstr.*, **70**, 77561*m* (1969).
(6) H. L. Wheeler and G. S. Jamieson, *J. Am. Chem. Soc.*, **25**, 719 (1903).
(7) F. H. S. Curd, J. A. Hendry, T. S. Kenny, A. G. Murray, and F. L. Rose, *J. Chem. Soc.*, 1630 (1948).
(8) A. J. Hill and S. R. Aspinall, *J. Am. Chem. Soc.*, **61**, 822 (1939).
(9) T. Shibanuma, M. Shiono, and T. Mukaiyama, *Chem. Lett.* 575 (1977).
(10) C. G. McCarty, J. E. Parkinson, and D. M. Wieland, *J. Org. Chem.*, **35**, 2067 (1970).
(11) Compounds **1** and **2** were also compared in SH rats by Dr. M. Cohen using the methodology described in the previous paper.[2] Oral doses of 10, 100, and 300 mg/kg of **2** produced only a slight fall in BP (11%) and HR (17%) at the intermediate dose level, whereas **1** significantly lowered BP (19%) and nonsignificantly lowered HR (10%) after 1 mg/kg.
(12) M. Gerold and H. Tschirky, *Arzneim.-Forsch.* **18**, 1285 (1968).

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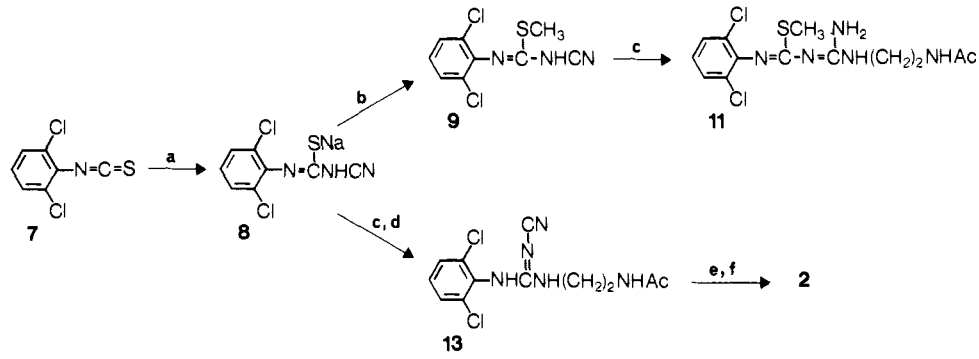
Scheme I[a]



[a] a = sodium cyanamide; b = iodomethane; c = *N*-acetylethylenediamine (**10**); d = mercuric chloride/THF; e = aqueous NaOH; f = acetic acid.

significant BP or HR effects were observed. Although there was a trend toward increased heart rate 3–6 h after the higher doses, the effect did not reach the level of statistical significance at any point.

These results are in marked contrast to those obtained with the thiourea **1**, which in all three models caused a pronounced fall in BP at the lower range of doses employed in the testing of **2**.[2] Thus, in the case of the (aminoethyl)thioureas, replacement of the thiourea moiety with a cyanoguanidine functionality does not lead to enhancement or even retention of the antihypertensive activity of the parent compound.

Experimental Section

Melting points were determined on a Büchi Model 510 capillary apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR 9. NMR spectra were determined on a Varian A-60 or A-100 instrument and mass spectra were recorded on a AEI MS 9 spectrometer. For TLC, precoated silica gel plates (F 254, Merck Darmstadt) were used. Concentration refers to evaporation of the solvent under aspirator vacuum on a rotary evaporator. Spectral data (IR, NMR, MS) were consistent with the assigned structures in all cases.

1-Cyano-3-(2,6-dichlorophenyl)-2-(methylthio)pseudourea (9). To the solution formed from 6.0 g (0.261 mol) of sodium in 400 mL of ethanol was added 11.0 g (0.261 mol) of cyanamide. Finally, 55.0 g (0.270 mol) of 2,6-dichlorophenyl isothiocyanate[5] was added. After 2 h, 50 mL (0.80 mol) of iodomethane was added to the almost clear yellow solution and the reaction was allowed to stir overnight. The mixture was cooled in an ice bath and the product collected: yield 50.95 g (84%); mp 195–198 °C. Recrystallization from ethanol–DMF gave mp 205–209 °C. Anal. ($C_9H_7Cl_2N_3S$) C, H, N, Cl, S.

3-[(2-Acetamidoethyl)amidino]-1-(2,6-dichlorophenyl)-2-(methylthio)pseudourea (11). A solution of 2.00 g (7.68 mmol) of **9** and 2.00 g (19.6 mmol) of *N*-acetylethylenediamine[6] in 5 mL of ethanol was refluxed for 18 h. The reaction mixture was diluted with water and extracted with (3 × 25 mL) methylene chloride. The combined organic layers were dried (Na_2SO_4) and evaporated to a foam, which was chromatographed on 200 g of silica gel. Elution with 1:9 methanol–chloroform gave 1.02 g (42%) of **11**, mp 147–150 °C. Recrystallization from ethyl acetate–hexane gave mp 152–153 °C. Anal. ($C_{13}H_{17}Cl_2N_5OS$) C, H, N, Cl, S. Hydrochloride mp 188–190 °C. Anal. ($C_{13}H_{17}Cl_2N_5OS$·HCl) C, H, N, Cl, S.

1-Cyano-3-(2,6-dichlorophenyl)-2-thiourea Sodium Salt (8). To the solution formed from 15.0 g (0.65 mol) of sodium in 1 L of ethanol was added a solution of 28.3 g (0.67 mol) of cyanamide dissolved in 200 mL of ethanol, followed by 137.3 g (0.67 mol) of 2,6-dichlorophenyl isothiocyante.[5] The resulting clear yellow solution was stirred for 1 h, concentrated, and diluted with ether to give 157.6 g (88%) of crude **8**, mp >340 °C, which was used as is in the next steps.

***S*-[Cyanoimino[(2,6-dichlorophenyl)amino]methyl]-carbonothioic Acid *O*-Ethyl Ester (12).** In a 50-mL round-bottom flask was placed 1.00 g (3.73 mmol) of **8** in 10 mL of anhydrous THF to give a cloudy solution. The mixture was cooled to 5–10 °C as 0.40 mL (4.1 mmol) of ethyl chloroformate was added dropwise. An exothermic reaction ensued, and the mixture was allowed to stir at room temperature overnight. The reaction mixture was filtered and the residue on evaporation was recrystallized from methylene chloride to give 0.40 g (42%) of **12**, mp 115–116 °C. Anal. ($C_{11}H_9Cl_2N_3O_2S$) C, H, N, Cl, S.

1-(2-Acetamidoethyl)-2-cyano-3-(2,6-dichlorophenyl)-guanidine (13). A solution of 60 g (0.22 mol) of **8** and 60.0 g (0.48 mol) of *N*-acetylethylenediamine[8] in 1 L of THF was cooled to 0 °C and treated with 55 g (0.20 mol) of mercuric chloride. The reaction mixture was stirred at 0 °C for 3 h and allowed to warm to room temperature overnight. Dilution with 50 mL of water and filtration gave a nearly clear solution, which was extracted with methylene chloride. Washing, drying (K_2CO_3), and evaporation gave 38.5 g (55%) of **13**, mp 178–181 °C. Recrystallization from ethanol gave 31.5 g, mp 183–185 °C. Anal. ($C_{12}H_{13}Cl_2N_5O$) C, H, N, Cl.

1-(2-Aminoethyl)-2-cyano-3-(2,6-dichlorophenyl)guanidine Maleate (2). A solution of 20.0 g (0.063 mol) of **13** in 220 mL of 28% sodium hydroxide solution and 200 mL of water was heated to a bath temperature of 50 °C for 8 h. The reaction mixture was filtered to remove a flocculant impurity, and the filtrate was cooled in an ice bath as the pH was adjusted to 8.5 (pH meter) by the dropwise addition of acetic acid. The rate of addition was controlled so that the internal temperature did not rise above 30 °C. The resulting white precipitate was collected, suspended in water, and treated with 8.6 g (1.0 equiv) of maleic acid. The resulting solution was evaporated to dryness and the residue was crystallized from ethanol–water to give 19.0 g (77%) of **2**, mp 159–161 °C. Two further recrystallizations gave mp 166–168 °C. Anal. ($C_{10}H_{11}Cl_2N_5 \cdot C_4H_4O_4$) C, H, N, Cl.

Blood-Pressure Testing. Blood-pressure (BP) and heart-rate (HR) effects were evaluated in groups of five conscious male spontaneously hypertensive (SHR) or DOCA–Na hypertensive rats using the tail-cuff method.[12] After two control measurements, the test compounds were administered orally via a stomach tube and BP and HR were measured 1, 3, 6, and 16 h after dosing. SHR weighed about 300 g and had a mean basal systolic BP of 190–205 mmHg and a HR of 380–400 beats/min. Hypertension was induced in 250-g male Fullinsdorfer albino rats by unilateral nephrectomy and subcutaneous implantation of a 25-mg 11-deoxycorticosterone acetate pellet. The animals were maintained on 1% sodium chloride drinking water, and 5 weeks were allowed for hypertension to develop (BP 170–220 mmHg).

In female renal hypertensive dogs, BP was measured oscillometrically and HR by palpation using a modification of the Van Leersum carotid artery loop technique. The test compounds were given by stomach tube to fasted animals, and BP and HR were measured 0.5, 1, 1.5, 3, 6, and 22 h after each dose.

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