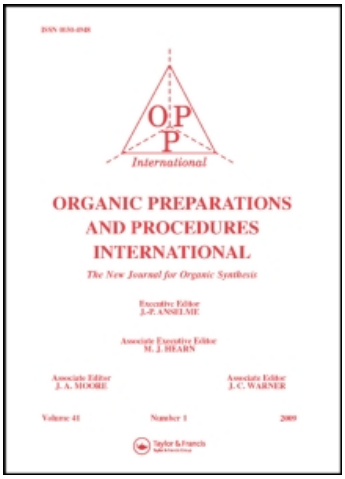


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

THE SYNTHESIS OF SOME GUANIDINE DERIVATIVES

J. Zmitek[a]; B. Jenko[a]; A. Kosak[a]; D. Milivojevic[a]
[a] LEK, Pharmaceutical and Chemical Works, Kolodvorska, YUGOSLAVIA

To cite this Article Zmitek, J. , Jenko, B. , Kosak, A. and Milivojevic, D.(1985) 'THE SYNTHESIS OF SOME GUANIDINE DERIVATIVES', Organic Preparations and Procedures International, 17: 4, 256 — 261
To link to this Article: DOI: 10.1080/00304948509355516
URL: http://dx.doi.org/10.1080/00304948509355516

solvent removed under reduced pressure to yield 0.22 g (79%) of N-hydroxylphenylethylamine. The product exhibited physical properties and spectral characteristics[1] in accord with an authentic sample.

Acknowledgement.- This study was supported by the Department of Energy.

REFERENCES

1. M. Mourad, R. S. Varma and G. W. Kabalka, J. Org. Chem., 50, 133 (1985).

2. M. Mourad, R. S. Varma and G. W. Kabalka, Synth. Commun., 14, 1099 (1984).

3. C. B. Gairaud and G. R. Lappin, J. Org. Chem., 18, 1 (1953).

THE SYNTHESIS OF SOME GUANIDINE DERIVATIVES

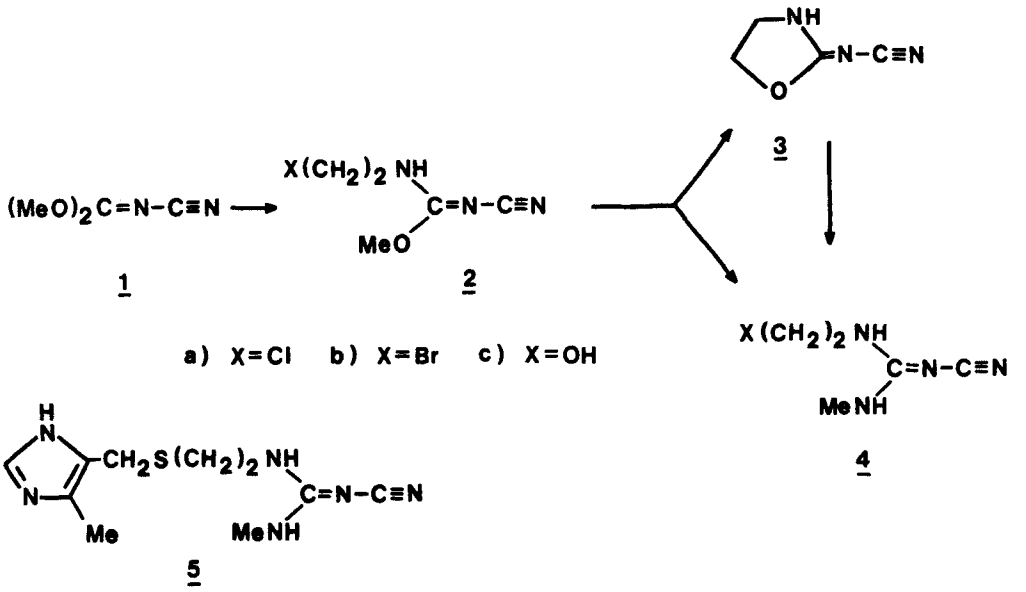
Submitted by J. Zmitek*, B. Jenko, A. Kosak and D. Milivojevic
(12/19/84)

LEK, Pharmaceutical and Chemical Works
61234 Menges, Kolodvorska 27
YUGOSLAVIA

The disclosure of biological activity of cimetidine (5)[1] has prompted renewed activity in guanidine chemistry. Several authors attempted to discover new, potentially active guanidine derivatives derived mainly from dimethyl N-cyanoimidodithiocarbonate (1);[2-4] thus N-cyano-N'-(2-haloethyl)-S-methyl isothioureas were prepared. The goal of our work was to find a convenient way to obtain N-cyano-N'-(2-chloroethyl)-N"-methyl guanidine (4a), which is the key intermediate in the synthesis of cimetidine.[5]

An attempt to obtain 4a from the relatively slow reaction of methylamine with N-cyano-N'-(2-chloroethyl)-S-methyl isothiourea afforded a

large number of degradation products of 4a. We thus synthesized dimethyl N-cyanoimidocarbonate (1). The first step involves the preparation of



dimethyl imidocarbonate by chlorination of sodium cyanide in a mixture of sodium hydroxide and methanol in water in contrast to the previous procedures[6] which used cyanogen chloride or bromide. Simultaneous addition of conc. hydrochloric acid and cyanamide to the iminocarbonate afforded compound 1 which was then transformed into the isoureas 2. Compound 2a was converted completely into guanidine 4a with aqueous methylamine in 0.5 hr , while more than a day was required for the same reaction in ethanol at room temperature. As compound 4a is relatively unstable, higher temperatures and long reaction times should be avoided; a pure product was obtained in high yield in water at room temperature. The analogous reaction between isourea 2b and methylamine afforded compound 4b which is even less stable than 4a; the appearance of 4b in the reaction mixture could only be detected by mass spectrometry and its isolation was not possible. Compound 4c can be prepared either from isourea 2c or from

oxazolidine 3, which is much more conveniently formed from 1 with 2-aminoethanol after prolonged heating than from N-cyano-N'-(2-hydroxyethyl)-S-methyl isothiourea.[3]

EXPERIMENTAL SECTION

Melting points were taken on a Kofler micro hot stage. ^{1}H NMR, IR and mass spectra were obained on a Varian EM-360 NMR spectrometer, Perkin-Elmer instrument 727B and Finnigan 3300 F mass spectrometer respectively.

Dimethyl N-cyanoimidocarbonate[7] (1).- Sodium cyanide (10 g) and sodium hydroxide (16.3 g) were dissolved in water (89 ml). After addition of methanol (24.4 ml), the mixture was cooled to about 0° and chlorine (14.4 g) was introduced at such a rate that the temperature did not exceed 5°. The pH of the reaction mixture was then adjusted with conc. hydrochloric acid to 8.5 and a further amount of hydrochloric acid (10.6 ml) and cyanamide (50% aqueous solution, 12.9 ml) were added simultaneously at 0-5°. The final pH was 6.5. The reaction mixture was stirred for an additional hour at 0° and the precipitate was collected to yield 8.9 g (38%) of colorless crystals, mp. 53-55° (petroleum ether).

^{1}H NMR ($CDCl_3$): τ 5.98 (s); MS (m/s): 114 (M^+).

Anal. Calcd. for $C_4H_6N_2O_2$: C, 47.11; H, 5.30; N, 24.55

Found: C, 41.54; H, 5.21; N, 24.35

N-Cyano-N'-(2-chloroethyl)-O-methylisourea (2a).- To a solution of 2-chloroethylamine hydrochloride (3.48 g) in water (12 ml) was added at 10-15° a solution of sodium hydroxide (1.2 g) in 3 ml of water. The solution was stirred for 5 minutes and then compound 1 (3.42 g) was added. After 70 minutes of additional stirring at 15°, the crystalline product was collected, washed with water and dried in vacuum at 40° to yield 4.5 g (93%) of the title product, mp. 111-112° (ethanol).

^{1}H NMR ($CDCl_3$): τ 6.40-6.56 (4H, m), 6.2 (3H, s), 2.3-2.7 (1H, broad); MS (m/s): 161 (M^+).

Anal. Calcd. for $C_5H_8ClN_3O$: C, 37.16; H, 4.99; N, 26.00

Found: C, 37.02; H, 5.05; N, 26.00

N-Cyano-N'-(2-bromoethyl)-O-methylisourea (2b).- To a solution of 2-bromoethylamine hydrobromide (3.6 g) dissolved in water (10 ml) was added at 10-15° a solution of sodium hydroxide (0.7 g) in 1.8 ml of water. The solution was stirred for 5 minutes and then compound 1 (2 g) was added. After 60 minutes of additional stirring below 15°, the crystalline product was collected, washed with water and dried in vacuum at 40° to yield 3.02 g (84%), mp. 129-132° (methanol).

^1H NMR (DMSO-d_6): τ 6.42-6.65 (2H, m), 6.25 (3H, s), 1.55-1.90 (1H, broad); Ms (m/s): 205 (M^+).

Anal. Calcd. for $C_5H_8BrN_3O$: C, 29.15; H, 3.91; N, 20.39

Found: C, 29.16; H, 3.91; N, 20.23

N-Cyano-N'-(2-hydroxyethyl)-O-methylisourea (2c).- Dimethyl N-cyanoimino carbonate (1) (1 g) and 2-aminoethanol (0.53 ml) were heated in ethanol (2 ml) under reflux for 15 minutes. After cooling in ice, the precipitate was collected and washed with ethanol to yield 0.85 g (68%) of white crystals, mp. 70-74° (ethanol). ^1H NMR ($CDCl_3$): τ 6.8-6.05 (4H, m), 6.2 (3H, s), 3.1-2.7 (1H, broad). MS (m/s: 13 (M^+).

Anal. Calcd. for $C_5H_9N_3O$: C, 41.95; H, 6.34; N, 29.36

Found: C, 41.84; H, 6.26; N, 29.29

N-Cyano-N'-methyl-N"-(2-chloroethyl)guanidine (4a).- Compound 2a (5 g) was added to aqueous methylamine (40%, 6 ml) and the reaction mixture was stirred at 20-25° for 30 minutes. The mixture was then extracted with methylene chloride (15 ml); the organic phase was dried over sodium sulfate, filtered and evaporated at 30°. The oily residue crystallized upon addition of water (10 ml) at 0-5°. The precipitate was collected and dried in vacuum at room temperature to yield 3.2 g (65%) of white solid,

mp. 80-84° (methylene chloride-petroleum ether). ^{1}H NMR ($CDCl_3$): τ 7.16 (3H, t, J = 5Hz), 6.35-6.52 (4H, m), 3.8-4.2 (1H, broad), 4.25-4.65 (1H, broad); MS (m/s): 160 (M^+).

Anal. Calcd. for $C_5H_9ClN_4$: C, 37.39; H, 5.65; N, 34.88

Found: C, 37.61; H, 5.64; N, 34.55

N-Cyano-N'-methyl-N"-(2-bromoethyl)guanidine (4b).- Isourea 2b (1 g) was stirred in liquid methylamine (2 ml) at about 0° for 10 minutes. Methylamine was then removed in vacuum at 0° and the title product was detected in the oily residue by mass spectrometry; MS (m/e): 204 (M^+). All attempts to isolate the title product failed.

2-(N-cyanoimino)-1,3-oxazolidine (3).- Isourea 2c (0.5 g) was heated in ethanol (2 ml) for 4 hrs under reflux. The product precipitated after concentration to one half the original volume and cooling on ice to yield 0.35 g (90%) of white solid, mp. 116-118°, lit.[3] mp. 119-120°. ^{1}H NMR (DMSO-d_6): τ 6.32 (2H, t, J = 8Hz), 5.35 (2H, t, J = 8Hz), 0.72 (1H, broad); MS (m/s): 111 (M^+).

Anal. Calcd. for $C_4H_5N_3O$: C, 43.24; H, 4.53; N, 37.82

Found: C, 43.07; H, 4.52; N, 38.02

N-Cyano-N'-methyl-N"-(2-hydroxyethyl)guanidine (4c).- Oxazolidine 3 (0.5 g) was heated under reflux in ethanolic methylamine (33%, 3 ml) for 0.5 hr. The reaction mixture was then evaporated to dryness, dissolved in ethanol (2 ml) and poured onto ice. The precipitate was collected to yield 0.5 g (78%) of white crystals, mp. 104-106°, lit.[2] mp. 110-111°. The same compound was obtained from compound 2c in essentially the same way as from 3. The identity of the product was confirmed by spectral and elemental analyses.

REFERENCES

1. Ger. Offen. 2211454; Chem. Abs., 77, 164704y (1972).

2. Belg. Pat. 876201; Chem. Abs., 92, 93921p (1980).

3. Gen. Offen. 2205745; Chem. Abs., 79, 146548 (1973).

4. Jap. Pat. 8211954; Chem. Abs., 96, 217282 (1982).

5. Brit. U. K. Patt. Appl. 2019842; Chem. Abs., 93, 71768n (1980).

6. Eur. Pat. Appl. 14064; Chem. Abs., 94, 83632x (1981).

7. Ger. Offen. 3225249; Chem. Abs., 99, 157854y (1983).

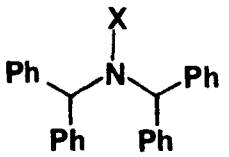
SYNTHESIS OF DIBENZHYDRYLNITROSAMINE

Submitted by Jack E. Baldwin*
(02/25/85)
The Dyson Perrins Laboratory
South Parks Road
Oxford OX1 3QY, ENGLAND

Stephen E. Branz*

Department of Chemistry
San Jose State University
San Jose, CA 95192-0101

It is now well-accepted that the mutagenic and carcinogenic activity of nitrosamines is due to their α-hydroxylated metabolites.[1] Observable α-hydroxynitrosamines were first synthesized by mild reduction of α-peroxynitrosamines.[2] We had unsuccessfully sought to prepare α-hydroxynitrosamines by direct low-temperature oxygenation[3] of N,N-dibenzylnitrosamine and N,N-dibenzhydrylnitrosamine (1b). While the former is well-known, the latter could not be prepared by standard methodology.[4]



a) X = H b) X = NO c) $X = NO_2$