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[A0042]

# SYNTHESIS OF NOVEL HYDROXYLAMINO CARBONIC ACID STRUCTURES SYNTHESIS OF NOVEL HYDROXYLAMINO CARBONIC ACID STRUCTURES

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**Abstract: Synthetic routes to various types of novel O-(-aminoalkyl) substituted hydroxylamino carbonic acid derivatives have been elaborated. Some of the new compounds exhibited significant cardiovascular or CNS activity, and induced the cellular heat shock protein synthesis** *in vitro* **and** *in vivo***.**

## INTRODUCTION

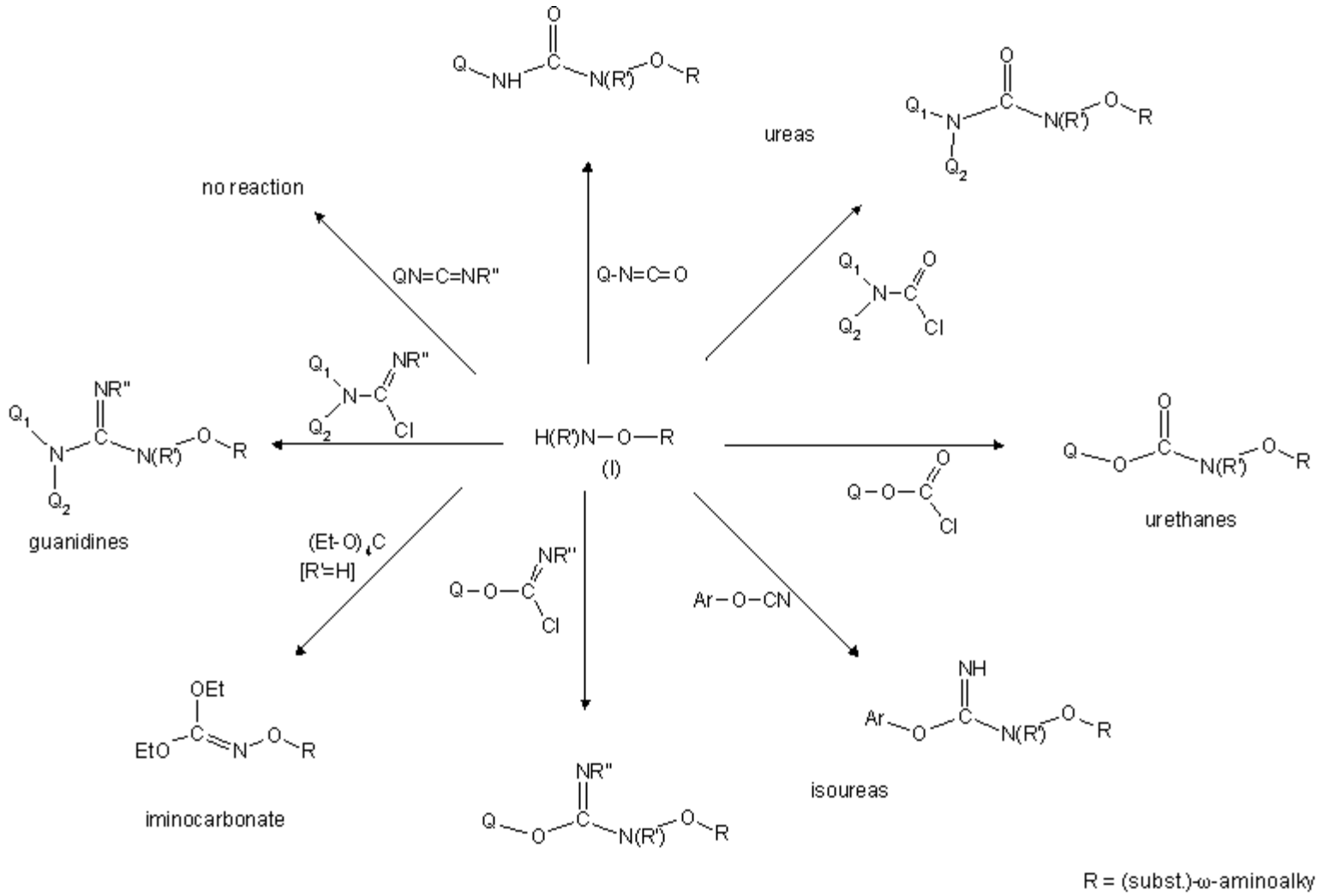
**As a part of our research program directed towards synthesis and biological investigations of novel hydroxamic acid derivatives1, and in view of the pronounced pharmaceutical activity exhibited by such compounds, we wanted to extend our research to analogous hydroxylamino carbonic acid structures.**

**Hydroxylamino carbonic acid derivatives are relatively rare in the literature; those with functionalised (N)-O-substituents are almost unprecedented. Introduction of pharmacophoric aminoalkyl substituents into this position led to entirely novel types of such compounds: N-(-aminoalkoxy) substituted ureas, isoureas, iminocarbonates, urethanes and guanidines. We now report on the first synthesis of these novel, potentially biologically active compounds.**

**1 L. Ürögdi et al.: XIIIth International Symposium on Medicinal Chemistry (Paris, France, Sept.19 - 23,1994)**

**E. Márványos et al.: IXth European Symposium on Organic Chemistry (Warszawa, Poland, June 18 - 23, 1995)**

## SYNTHESIS




**Compounds were synthesized by acylation of the appropriate O-substituted hydroxylamine derivatives (I).**

**N-unsubstituted compounds of (I) are well known from the literature (Ger. Offen. 2651083 & Jpn. Kokai Tokkyo Koho JP 01,246,256).**

**The appropriate N-substituted derivatives of (I) were prepared from the N-substituted hydroxylamines by N-protection, followed by treatment of these with -amino-alkylating agents and finally N-deprotections of the latter compounds were carried out.**

**Halo-carbonic acid derivatives or their cumulated analogs were used as acylating agents.**

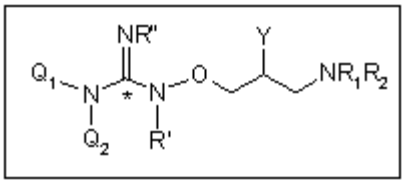
**The reactivity of the amino-oxy groups are weaker than that of amines; no reactions take place with weak electrofiles such as carbodiimides or isothiocyanates.**

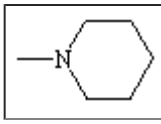
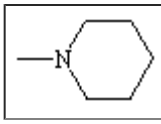
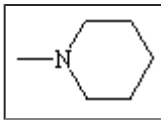
**Despite of this, we performed acylations even in presence of sterically hindered amino- or hydroxyl functions.**

**Yields usually were satisfactory or good; products generally were isolated in their salt forms.**

**TYPICAL REPRESENTATIVES OF THE SYNTHESIZED COMPOUNDS**

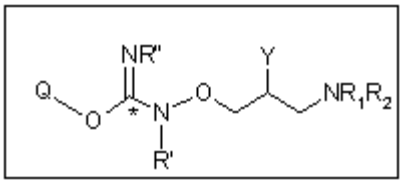
*GUANIDINES*

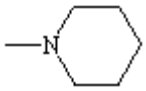
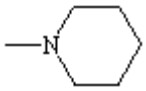
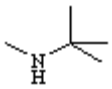


| Q1Q2N | R' | R'' | Y | NR1R2 | Yield (%) | IR (,cm-1) | 13C NMR(*) |
|---|---|---|---|---|---|---|---|
| Me2N | H | Ph | OH |  | 35 | 1610 | 153.9 ppm |
| Me2N | Me | Ph | H |  | 30 | 1605 | 156.6 ppm |
| PhNH | H | Benzyl | H |  | 40 | 1620 | 151.9 ppm |

*Preparation of chloroformamidines* **[Houben-Weyl: Methoden der organischen Chemie E/IV]**

*ISOUREAS*

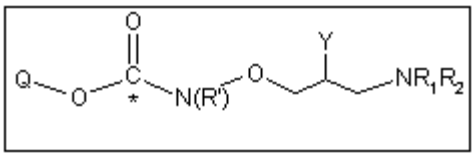


| Q | NR'' | R' | Y | NR1R2 | Yield (%) | IR (,cm-1) | 13C NMR(*) |
|---|---|---|---|---|---|---|---|
| Ph | NH | H | H |  | 46.9 | 1662 | 152.4 ppm |
| *p*-Cl-Ph | NH | H | H |  | 20 | 1670 | 157.8 ppm |
| CH3CH2 | NPh | H | OH |  | 35 | 1650 | 155.7 ppm |

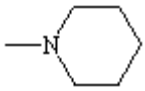
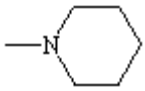
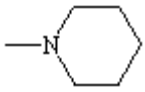
*Preparation of aryl cyanates* **[R.A.Moss et al.: J.Org Chem., Vol. 47, No.22, p.4177]**

*Preparation of chloroformimidate* **[Houben-Weyl: Methoden der organischen Chemie E/IV]**

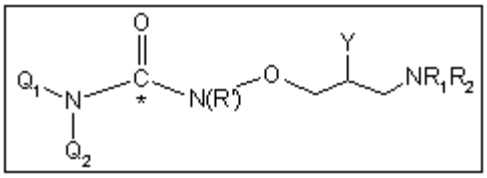
*URETHANES*

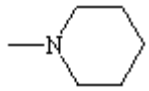
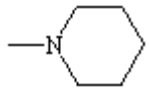
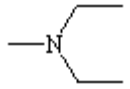


| Q | R' | Y | NR1R2 | Yield (%) | IR (,cm-1) | 13C NMR(*) |
|---|---|---|---|---|---|---|
| | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| ethyl | H | OH |  | 30.5 | 1739 | 158.2 ppm |
| ethyl | CH3 | H |  | 70.4 | 1710 | 157.5 ppm |
| benzyl | benzyl | OH |  | 50.1 | 1726 | 157.4 ppm |

*UREAS*



| Q1Q2N | R' | Y | NR1R2 | Yield (%) | IR (,cm-1) | 13C NMR(*) |
|---|---|---|---|---|---|---|
| n-hexyl-NH | H | OH |  | 27.2 | 1666 | 159.8 ppm |
| N,N-diphenyl- | H | OH |  | 61.5 | 1645 | 157.5 ppm |
| m-Cl-C6H4NH | benzyl | H |  | 62.5 | 1671 | 157.1 ppm |


**Summary**

**Synthetic routes to various types of novel O-(-aminoalkyl) substituted hydroxylamino carbonic acid derivatives have been elaborated. Some of the new compounds exhibited significant cardiovascular or CNS activity, and induced the cellular heat shock protein synthesis** *in vitro* **and** *in vivo***.**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**Comments**

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