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1,2,4-BENZOTHIADIAZINE 1,1-DIOXIDE. V: [1] SYNTHESIS OF BUILT-IN HYDROXYGUANIDINE TRICYCLES AS POTENTIAL ANTICANCER AGENTS

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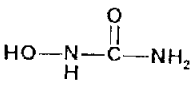
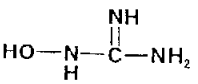
Summary: Two representative built-in hydroxyguanidine tricycles, 10-*N*-hydroxy-2,3-dihydroimidazo[1,2-b][1,2,4]benzothiadiazine 5,5-dioxide (1a) and 11-*N*-hydroxy-2,3-dihydro-4*H*-pyrimido-[1,2-c][1,2,4]benzothiadiazine 6,6-dioxide (1b), were obtained in 78% and 30% yields, respectively by a treatment of 1-(2-nitrobenzenesulfonyl)-2-benzylthio-2-imidazolidine and -4,5-dihydro-6*H*-pyrimidine with zinc in acetic acid under ice-cooling for 30 min.

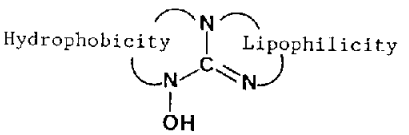
Ribonucleotide reductase is an essential enzyme involved in the DNA synthesis and cell replication[2] and is considered as an important target for the development of anticancer agent *via* an inhibition of DNA synthesis.[3] Initially, it was reported that hydroxyurea and guanidine derivatives possessed antiviral as well as antitumor activities by acting on the site of this enzyme.[4] Later on, hydroxyguanidine derivatives with the combined functional groups of the anticancer agent hydroxyurea and the antiviral agent guanidine, have been reported to have anticancer



Hydroxyurea



Hydroxyguanidine



Built-in hydroxyguanidine tricycles

activity and antiviral activity as well.[5] However, the disadvantage of these compounds, such as a short half-life, rapid metabolic transformation to inactive forms, and myelosuppression, is due to the hydrophilicity and low molecular weight of this type of compounds. Hydrophobicity is known to play an important role in binding a substrate or inhibitor to the active site of enzyme and such hydrophobic region adjacent to the active site of enzyme has been observed on dihydrofolic reductase[6], guanase[7], thymidine phosphorylase[8], and purine nucleoside phosphorylase[9]. Therefore, tricycles with built-in hydroxyguanidine such as 10-*N*-hydroxy-2,3-dihydroimidazo[1,2-b][1,2,4]benzothiadiazine 5,5-dioxide (1a) and 11-*N*-hydroxy-2,3-dihydro-4*H*-pyrimido[1,2-c][1,2,4]benzothiadiazine 6,6-dioxide (1b) can be expected to be more stable and hydrophobic while possessing a rigid structural feature essential to elicit the biological activities of both hydroxyurea and guanidine. To our best knowledge, this type of

built-in hydroxyguanidine has not been synthesized and reported to have anticancer and antiviral activity.

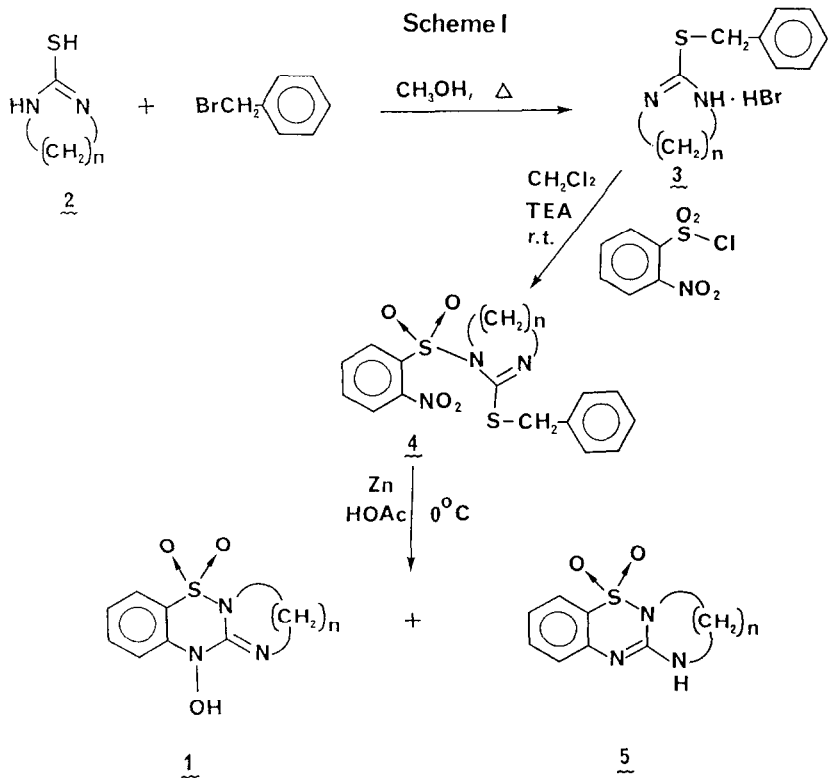
At the outset, we reasoned that compound 4 could be a key intermediate toward the synthesis of 1 *via* appropriate conditions under which the reduction of nitro group on benzene ring with zinc could be stopped at the hydroxyamine stage instead of amine. Subsequently, the nitrogen atom of hydroxylamine would undergo a nucleophilic displacement with the alkylthio group to afford compound 1. Although it has been reported[10] that a treatment of 4-[(4,5-dihydro-2-methylthio)-1-imidazolyl]-1-methyl-5-nitropyrazole with zinc in the presence of acetic acid under ice-cooling led to the formation of the tricycle 1,6,7,8-tetrahydro-1-methyl-4*H*-imidazo[1,2-a]pyrazolo[3,4-d]pyrimidin-4-one instead of the built-in hydroxyguanidine tricycle, we wish to report herein an analogous reaction which leads to the synthesis of tricyclic built-in hydroxyguanidine under similar conditions.

Synthesis of these compounds is illustrated in Scheme I. 2-Benzylthio-2-imidazolidine hydrobromide (3a), obtained from a reaction of 2-imidazolidinthione (2a) with benzyl bromide was reacted with 2-nitrobenzenesulfonyl chloride to give 1-(2-nitrobenzenesulfonyl)-2-benzylthio-2-imidazolidine (4a), which was then treated with zinc in acetic acid under ice-cooling for 30 min. The mixture was then allowed to stir at room temperature for a further 60 min. and filtered. The filtrate was concentrated in vacuo to oily residue. To the residue was added ethanol (30 ml) to get a solid, which was found to be complexed with one equivalent of zinc. Thus, the crude product was dissolved in ethanol and then treated with 0.1 M EDTA to furnish needle crystals of compound 1a [11] in 78% yield, and 2,3-dihydro-1*H*-imidazo[1,2-b][1,2,4]benzothiadiazine 5,5-dioxide (5a) [12] was isolated in 14% yield from the filtrate. However, elongation of the reaction time to 2 days in this reaction resulted in exclusive formation of 5a in 83% yield. The structural assignment of 5a is mainly based on ^{1}H- and ^{13}C-NMR and mass spectral data and elemental analysis. The ^{13}C-NMR spectrum obtained for 5a showed the chemical shift for the C-9a at 146.4 ppm which is in agreement with the values reported[13] by Jackobsen and Treppendahl who studied the structure of benzothiadiazine 1,1-dioxide and is indicative of a double bond existing between N-10 and C-10a. Meanwhile, the ^{13}C-NMR spectrum of 1a demonstrated that the C-9a chemical shift at 138.4 ppm illustrates a hydroxy group at N-10 position with a double bond located between N-10 and C-10a and is in agreement with previous data[1]. The mass spectra of 1a exhibited a molecular ion peak at 239 (M^+) together with a peak at 223 (M^+-16), whereas compound 5a showed the molecular ion peak at 223 (M^+) indicating a loss of oxygen and hence the presence of a hydroxy group in 1a. Although arylhydroxylamines are traditionally made by careful reduction of nitroarenes,[14] the synthesis of 1a is probably due to the inductive and resonance effects of the sulfonyl group which stabilize the hydroxylamine group.

Similarly, treatment of 3,4,5,6-tetrahydro-2-pyrimidinethiol (2b) with benzyl bromide gave 2-benzylthio-1,4,5,6-tetrahydropyrimidine hydrobromide (3b) which was then reacted with 2-nitrobenzenesulfonyl chloride to furnish 1-(2-nitrobenzenesulfonyl)-2-benzylthio-4,5-dihydro-6*H*-pyrimidine (4b). Repeating the above reactions using 4b in place of 4a afforded 11-*N*-hydroxy-2,3-dihydro-4*H*-pyrimido[1,2-c][1,2,4]benzothiadiazine 6,6-dioxide (1b)[15] in 30% yield and 1,2,3,4-tetrahydropyrimido[1,2-c][1,2,4]benzothiadiazine 6,6-dioxide (5b)[16] in 10%

yield. However, it afforded exclusively 5b in 62% yield when the reaction was run for 2 days. The ^{13}C-NMR spectrum obtained for 1b and 5b showed the chemical shift for the C-10a at 138.50 and 145.02 ppm, respectively, which are in agreement with the structures of 1a and 5a.

Scheme I



a, n=2 ; b, n=3

In conclusion, a novel and efficient route to the synthesis of built-in hydroxyguanidine tricycles was developed and these hydroxyguanidine analogs showed very strong activity against several cancer cell lines (KB, Colo 205, Hela and Hep-2, with ED_{50} up to 1.1 μg/ml) and very high stability. The detailed biological results will be published elsewhere.

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11. Compound 1a: mp 195° C. ms: *m/z* 239 (M^+), 223(M^+-16); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.85 (p, 2H, CH_2), 3.97 (p, 2H, CH_2), 7.25 (t, 1H, J=7.7 Hz, Ar-H), 7.47 (d, 1H, J=8.6 Hz, Ar-H), 7.75 (p, 1H, Ar-H), 7.83 (d, 1H, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 44.01, 51.11, 113.41, 120.70, 122.28, 122.72, 135.16, 138.53, 149.59. Anal. Calcd. for $C_9H_9N_3O_3S$ (239.25); C, 45.18; H, 3.79; N, 17.56. Found: 45.18; H, 3.81; N, 17.48.
12. Compound 5a: mp 267° C. ms: *m/z* 223 (M^+), 166, 158; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.57 (t, 2H, J=7.9 Hz, CH_2), 4.03 (t, 2H, J=7.9 Hz, CH_2), 7.17 (t, 2H, J=8.2 Hz, Ar-H), 7.57 (t, 1H, J=7.8 Hz, Ar-H), 7.78 (d, 1H, J=7.8 Hz, Ar-H), 8.23 (s, 1H, NH). ^{13}C-NMR (25 MHz, DMSO-d_6): δ 39.55, 41.78, 122.46, 122.87, 123.34, 125.51, 134.94, 146.37, 155.10. Anal. Calcd for $C_9H_9N_3O_2S$ (223.24): C, 48.42; H, 4.06; N, 18.82. Found: C, 48.78; H, 4.03; N, 18.95.
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15. Compound 1b: mp 180-182° C; ms: *m/z* 253 (M^+), 237 (M^+ -16), 172; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.83-1.97 (m, 2H, CH_2), 3.43 (t, 2H, J=5.6 Hz, CH_2), 3.79 (t, 2H, J=5.6 Hz, CH_2), 7.22 (t, 1H, J=7.5 Hz, Ar-H), 7.56 (d, 1H, J=8.4 Hz, Ar-H), 7.67-7.85 (m, 2H, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 21.36, 39.88, 41.84, 114.40, 121.85, 122.32, 131.07, 138.50, 141.46. Anal. Calcd. for $C_{10}H_{11}N_3O_3S$ (253.28): C, 47.42; H, 4.38; N, 16.59. Found: C, 47.50; H, 4.24; N, 16.54.
16. Compound 5b: mp 245-248° C, ms: *m/z* 237 (M^+), 209, 172, 155; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.95 (m, 2H, CH_2), 3.28 (t, 2H, J=5.8 Hz, CH_2), 3.80 (t, 2H, J=5.5 Hz, CH_2), 7.07 (t, 2H, J=7.9 Hz, Ar-H), 7.52 (t, 1H, J=7.7 Hz, Ar-H), 7.64 (d, 1H, J=8.2 Hz, Ar-H), 8.05 (br s, 1H, NH, D_2O exchangeable); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 21.64, 38.95, 41.95, 120.78, 120.97, 122.86, 124.11, 133.79, 145.02, 148.83. Anal. Calcd for $C_{10}H_{11}N_3O_2S$ (237.28): C, 50.62; H, 4.67; N, 17.71. Found: C, 50.41; H, 4.36; N, 17.53.

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