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Synthesis of Uracil Derivatives and Some of Their Reactions

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An efficient one-pot synthesis of 1-phenylcarbamide-3-hydroxy-4,6-pyrimidine-[2,3-a]-5'-hydroxytetrahydro-1,3-thiazine is described. The synthesis is based on the reaction of ethyl cyanoacetate and thiocarbamide in the presence of sodium acetate. The cyclized compounds react with 1,2-epoxychloropropane then treated in medium of ethyl alcohol in peresence of KOH, which recyclized product 1-amino-3-hydroxy-4,6-pyrimidine-[2,3-a]-5'-hydroxy-tetrahydro-1,3-thiazine produced. In the final reaction, this product with phenylisocyanate give a side chain reaction of the obtained 1-phenylcarbamide-3-hydroxy-4,6-pyrimidine-[2,3-a] -5'-hydroxytetrahydro-1,3-thiazine.

Key Words: Ethyl cyanoacetate, Thiocarbamide, 1-Phenyl carbamide-3-hydroxy-4,6-pyrimidine-[2, 3-a]-5'-hydroxy-tetrahydro-1,3-thiazine.

INTRODUCTION

Uracil, thymine and cytosine bases of pyrimidine have most important role in nucleic acid structure of human bodies activity[1-6]. There is so interest in this line of research for example 5-bromouracil that has important mutagenic chemical properties in mutation points inside nucleic acids. Change of this and other nitrogenic bases some inheritance features can produced and 5-bromouracil itself can act as an anticancer.

Uracil is one of the pyrimidine derivatives used in treatment of grand disorder in body tumour. For example, 5-florouracil has a role in treatment of body's tumours[7,8]. Combination of 2,6-dihydroxypyrimidine-4-carboxylic acid has important role in nucleic acid synthesis[9]. Other uracil derivatives such as 5-oxymethyl-4 methyluracil (pentoxil) and 4-methyluracil (metacil) are that used for treatment of catchcold and also have important roles in synthesis of nucleic acid and production of internal protein portion of blood which prevents from anemia.

In respect of all of above mentioned points, the synthesis of uracil derivatives and their properties are are reported in this paper.

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EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were obtained using a Bruker ABM-300 spectrometer. Chemical shifts (δ) are given in ppm using TMS as internal reference. IR spectra were recorded on Spekord 75-IR.

Thin layer chromatography (TLC) was performed on silica gel, plates Silufol UV- 254 nm in chloroform:methanol (20:1 v/v) and chloroform: methanol (9:1 v/v) as solvent systems, plates were visualized with iodine vapour on UV light.

6-Amino-4-hydroxy-2-mercaptopyrimidine (I): In a three headed round bottom flask with thermometer, dropper funnel and 40 mol of pure alcohol stirred with 2.3 g (0.1 mol) of crashed sodium particles and added 5.8 g (0.05 mol) ethyl cyanoacetate, enhance the tempertaure to 50 °C, then added 3.8 g (0/05 mol) thiocarbamide on it. Mixture of reaction carried out for 6 h at 70 °C. End of reaction by thin layer chromatography performed and in order to purify using 100 mL distilled water and acidified reaction medium with acetic acid (pH = 7).

White crystalline precipitate, washed thoroughly with water, 2 g yield of 30 %, 6-amino-4-hydroxy-2-mercaptopyrimidine (**I**) m.p. 220 °C was obtained. Anal. calcd. (%) for $C_4H_5N_3OS$: C, 33.74; H, 3.37; N, 29.17; S, 22.63; Found: C, 33.59; H, 3.52; N, 29.35; S, 22.40.

6-Amino-2-(1'-chloro-2'-hydroxypropylthio)-4-hydroxypyrimidine (II): In a three headed round bottom flask with thermometer, dropper funnel and 50 mol ethanol solution and 14.3 (0.1 mol) compound (**I**) mixed completely by 3 drops of triethyl amine, then slowly 9.3 g (0.1 mol) of 1,2-epoxy-3-chloropropane added dropwise and mixed for 5 h at room temperature. Extract the residue of 1,3-epoxy-3-chloropropane and solution in the reaction with water pump. Yield (**II**) 17.70 g (70 %) and m.p. 120 °C. Anal. calcd. (%) for $C_7H_{10}N_3O_2SCl$: C, 35.82; H, 4.42; N, 13.59; S, 13.78. Found: C, 35.67; H, 4.28; N, 17.83; S, 13.60.

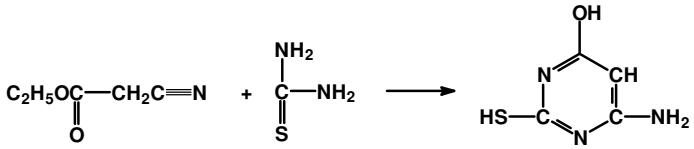
1-Amino-3-hydroxy-4,6-pyrimidine-[2,3-a]-5'-hydroxy-tetrahydro-1,3-thiazine (III): In a three headed round bottom flask with thermometer, dropper funnel and 50 mol of ethanol with 11.8 g (0.05 mol) 6-amino-2-(1'-chloro-2'-hydroxypropylthio)-4-hydroxypyrimidine (**II**) in reaction with 5.6 g (0.1 mol) potasium hydroxide for 5 h at 20 °C were mixed. Excess of KCl was extracted, filtered and solvent was discarded by water pump. The final product was extracted with acetone as a result amount of 5.5 g 1-amino-3-hydroxy-4, 6-pyrimidine-[2, 3-a]-5'-hydroxy-tetrahydro-1,3-thiazine (**III**) with yield 55 % and m.p. 180 °C. Anal. calcd. (%) for $C_7H_{10}N_3O_2S$: C, 41.67; H, 4,71; N, 20.86; S, 16.34. Found: C, 41.98; H, 5.03; N, 20.98; S, 16.01.

1-Phenylcarbamide-3-hydroxy-4,6-pyrimidine-[2,3-a]-5'-hydroxy-tetrahydro-1,3-thiazine (IV): In a three headed round bottom flask, with

thermometer, dropper funnel and 50 mol dried benzene added 10 g (0.05 mol) of compound (**III**) and 3 drops of triethylamine, stirred reaction with dropwise added 5.5 g (0.05 mol) of methylisocianate for 5 h at 60 °C and then cooled. The synthesized pure material was obtained by crystallization from ethanol with yield 92 % and m.p. 180 °C. Anal. calcd. (%) for $C_{14}H_{15}N_4O_3S$: C, 52.86; H, 4.46; N, 17.28; S, 10.36. Found: C, 52.65; H, 4.73; N, 17.54; S, 10.04.

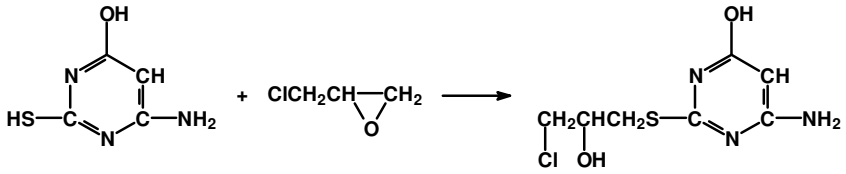
RESULTS AND DISCUSSION

Product of 6-amino-4-hydroxy-2-mercaptopyrimidine is produced by cyclization with reactants of ethyl cyanoacetate and thiocarbamide in presence of sodium acetate.



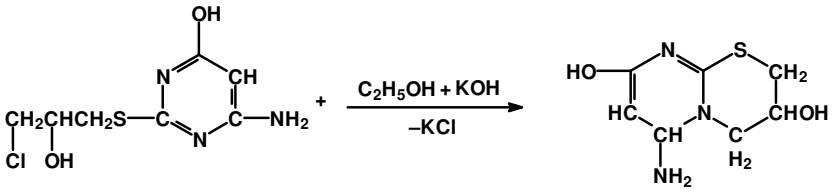
(I)

6-amino-4-hydroxy-2-mercaptopyrimidine (**I**) with 1,2-epoxychloropropane in the reaction with triethyleamine and in ethanolic medium of can produce 6-amino-2-(1'-chloro-2'-hydroxypropylthio)-4-hydroxy-pyrimidine (**II**).



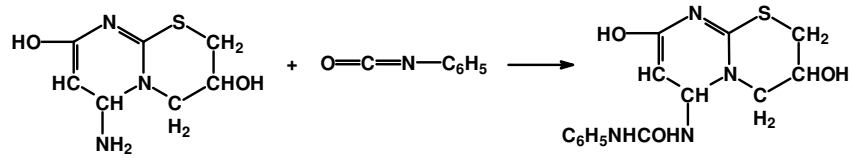
(II)

Combination (**II**) in ethanolic medium and in the presence of potassium hydroxide can produce 1,3-thiazine (**III**).



(III)

In 1,3-thiazine (**III**) by presence of primary amine with reaction by phenylisocyanate convert to 1-phenyl carbamide-3-hydroxy-4,6-pyrimidine [2,3-a]-5'-hydroxy tetrahydro-1,2-thiazine (**IV**).



(IV)

In synthetic molecule **I**, thio group (divalence) absorbs appearance in 1600, 1570 and 1565 cm^{-1} in IR spectrum. In the new product **II**, these areas are not observed. It shows oxirane ring with sulfure of thio group will go ahead through a reaction in order to gain a final product.

In IR spectra, bonds due to properties of $-NH_2$ are appear at 3450-3435 cm^{-1} region. Absorbance in 3610-3570 and 3580-3560 cm^{-1} regions show free group -OH are incorporation of valance vibration of internal hydrogen bonding. While no change is observed for valance vibrations of -OH group in band absorption areas according to spectroscope of above compound in the CCl_4 0.005 M solutions. Besides it shows the presents of the bond between -OH group with chlorine atom that will be appeared as internal hydrogen bonding.

^1H NMR spectra were recorded and proved for structure of these compounds (**I-IV**) in $-CH_2S$ and $-CH_2Cl$ groups, diastereotopical protons on one carbon and methine proton on assymetric carbon show NMR spectra using ABM spectrometer with two triplets spine.

The existing protons in methylene group connecting to sulphur atom appear multiplet in NMR spectra in the field of 3.25-3.38 MHz. Two of four same create from combination of neighbour spin-spin coupling forms J_{AX} = 5.5 Hz and J_{BX} = 2.0 Hz.

The result of unequivalent protons of $-CH_2Cl$ appears in the field of 3.55-3.57 MHz. This fact shows that between hydroxyl group in Gauch conformation with -Cl atom produce internal hydrogen bonding. Vibration of free hydroxyl group for synthesized compound **III** in IR spectra in area of 3605-3585 cm^{-1} completely be proved and below area of absorption bond (3547-3542 cm^{-1}) show internal hydrogen bonding.

So, with the formation of synthesized cyclic structure **III**, the importance of unequivalent protons in $-CH_2S$ and $-CH_2N$ will be increased, for example, resonance protons in $-SCH_2$ group distinguished with two shielded quartet spectra and their parameters are:

σ_A =3.25-3.30; σ_B =3.15-3.19 MHz, $^2J_{AB}$ = 13.0 Hz, $^3J_{BX(cis)}$ = 3.6 Hz

The comparison of components of proton's multiplet in $-CH_2N$ are showed below:

$\sigma_{A'}$ = 4.18-4.35; $\sigma_{B'}$ = 4.27-4.42 MHz. $^3J_{A'X(trans)}$ = 5.8;

$^3J_{B'X(cis)}$ = 2.6; $^2J_{A'B'}$ = 13.0 Hz

In all of synthesized compounds, carbon atom signal in uracil molecule in ^{13}C NMR spectra are:

164 (C^4), 157 (C^2), 153 (C^6), 98-102 MHz (C^5).

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