Commun. Fac. Sci. Univ. Ank. Series B
V. 38, pp. 1–7 (1991)

SYNTHESIS OF DIFFERENT 5 - METHYL AMINO AND 5 - IMINO DERIVATIVES OF 6 - METHYL - 2 - THIOURACIL

A.A. HAIKAL and A.F. SAYED AHMED

Department of Chemistry, Faculty of Science, Zagazig University, Zagazig / EGYPT.

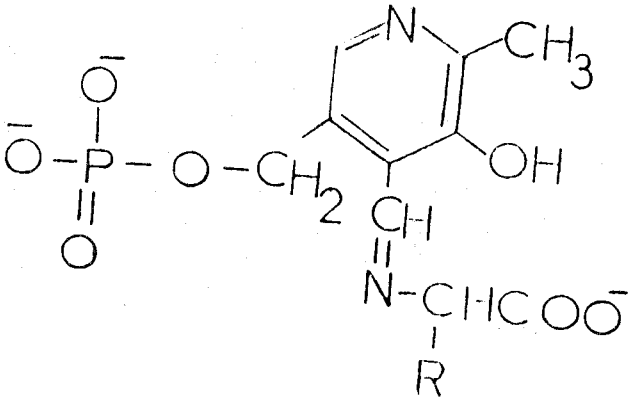
(Received Oct. 15, 1991; Accepted Sept. 11, 1992)

ABSTRACT

Condensations of 5–chloromethyl–6–methyl–2–thiouracil III and the corresponding 5–formyl analogue IV with different amines were completely studied.

INTRODUCTION

It is documented, that the enzymatic decarboxylation of amino acids (with exception of histidine) requires pyridoxal phosphate as coenzyme[1]. The reaction mechanism involves schiff base formation between pyridoxal and usually α–amine group of the amino acid as shown below



In this context, and according to the above fact, it was suggested, that 5–formyl–6–methyl–2–thiouracil IV[2,3] could be considered as a potential substrate in the synthesis of some 5–imino derivatives of 6–methyl–2–thiouracil. On the other hand, 5–chloromethyl–6–methyl

uracil III can be also employed in a cycle of condensation reactions with other amino compounds. 5–Hydroxymethyl–6–methyl–2–thio uracil[5] can be easily transformed into either 5–chloro methyl–6–methyl–2–thio uracil III or 5–formyl analogue IV. It is noteworthy, that the reactions of both chloride III and 5–formyl derivative IV with different amino compounds could offer a pilot way for the synthesis of the required 5–substituted derivatives of the heterobase. It is important to mention, that such 5–substituted derivatives could be easily utilized in the nucleoside scale, especially 2–thio uracil derivatives for the synthesis of the corresponding modified 2–thio uridine derivautilized in the nucleoside scale, especially 2–thio uracil derivatives which are expected to have biological and medicinal activity.

DISCUSSION

The synthesis of 5–hydroxymethyl–6–methyl–2–thio uracil II can be easily performed according to a reported method[5]. Consequently, it was oxidised with manganese dioxide[6] to give the formyl derivative IV. On the other hand, compound II can be reacted with thionyl chloride to afford the chloride III in good yield (80 %).

Further, chloride III was introduced in a cycle of condensation reactions with different amines, in DMF under reflux for 3 hrs to give the corresponding products of di or monosubstituted derivatives, It is noteworthy, that a disubstituted product V was yielded from the reaction of compound III with methyl amine[7] in 60 % yield. It was crystallized from methanol and the structre was confirmed by spectral data, m.s. 339 (M^+) 3.5 %, 324 (M^+–15) 3 %, n.m.r. in deuterated acetone δppm; 3.74 (s. 3H, N–CH_3), 3.65 (s. 2H, –CH_2N–), 3.40 (s. 2H, –NCH_2), 3.25 (s. 6H, 2–CH_2). Therefore, reaction of the chloride III with equimolar amount of ethyl glycinate[1,8] afford a disubstituted derivative VI. Mass spectra of this compound showed 411 (M^+) and fragments of M^+–OC_2H_5 as well as M^+–$COOC_2H_5$, n.m.r. in deuterated acetone showed δppm; 3.65 (s. 2H, –CH_2N–) 3.40 (s. 2H, –N–CH_2–), 3.25 (s. 6H, 2–CH_3).

On the other hand, condensation of compound III with 2–amino pyridine produced a disubstituted product VII in 40 % yield. Mass spectra shows 402 (M^+), n.m.r.$_{(CD_3COCD_3)}$ δppm; 7.36 m. 3H, aromatic), 3.65 (s. 2H, –CH_2N–), 3.40 (s. 2H, –NCH_2), 3.25 (s. 6H, 2–CH_3).

In contrast, a monosubstituted product VIII was given from the reaction of the substrate III with glucose amine in 60 % yield Molecular weight of the resulting product as shown by mass spectra is 333, n.m.r.$_{(CD_3COCD_3)}$ δppm: 5.95 (d,J = 2Hz, 1H, H1'), 3.63 (s. 2H, $-CH_2NH-$), 3.48 (s. 1H, –NH CH–), 3.25 (s. 3H, $-CH_3$).

It was found that the reactions of the substrate III with both of morphaline and diphenyl amine afford compounds IX and X in 75 %, 72 % yield, respectively. Compound V have a molecular weight of 241 as shown by mass spectra and its n.m.r. spectra in deuterated methanol showed δppm: 4.50 (s. 211, $-CH_2N-$), 3.7 (s. 2H, $-N-CH_3$), 3.25 (s. 3H, $-CH_3$). But compound X n.m.r. spectra showed δppm: 8.37 (m, 10H, aromatic), 4.50 (s. 2H, $-CH_2$ N–), 3.71 (s. 3H, CH_3).

From the synthetic point of view, it would be advantageous to condense aldehyde with different amino compounds at pH Ca 4.5–5[9]. 5–Hydroxy methyl–6–methyl–2–thio uracil was oxidised with active manganese dioxide[6] in methylene chloride–acetone solution (1:1 V/V). It was documented, that aromatic thiols can be oxidised with active manganese dioxide to the respective disulphide derivative[10]. However, oxidation of 5–hydroxy methyl–6–methyl–2–thio uridine at the same reported conditions did not lead to either oxidation at 2–position of the heterobase or a disulphide derivative formation.

To perform such type of condensation reactions, equimolar amounts of compound IV and both of hydrazine hydrate and phenyl hydrazine were reacted in methanol. The solution of each reaction was acidified to pH Ca. 5 with formic acid and allowed to react at 50°C for 4 hrs. The reactions gave good yields of the required products XI and XII (64, 67 %) respectively. By means of spectral data, the structures of the product XI and XII were confirmed. Mass spectra showed M^+ 184 for XI and 260 for XII n.m.r.$_{(CD_3COCD_3)}$ for compound XI showed δppm: 3.60 (s. 1H, –CH = N–), 3.25 (s. .3H, $-CH_3$), bur for compound XII showed 7.86 (m. 5H, aromatic), 3.60 (s, 1H, –CH = N–), 3.25 (s. 3H, $-CH_3$).

EXPERIMENTAL

5–hydroxy methyl–6–methyl–2–thio uracil II:

6–methyl–2–thio uracil (14.2 g., 0.1 mol) and paraformaldehyde (4 g., 0.13 mol) were added to an aqueous 0.42N solution of KOH (170

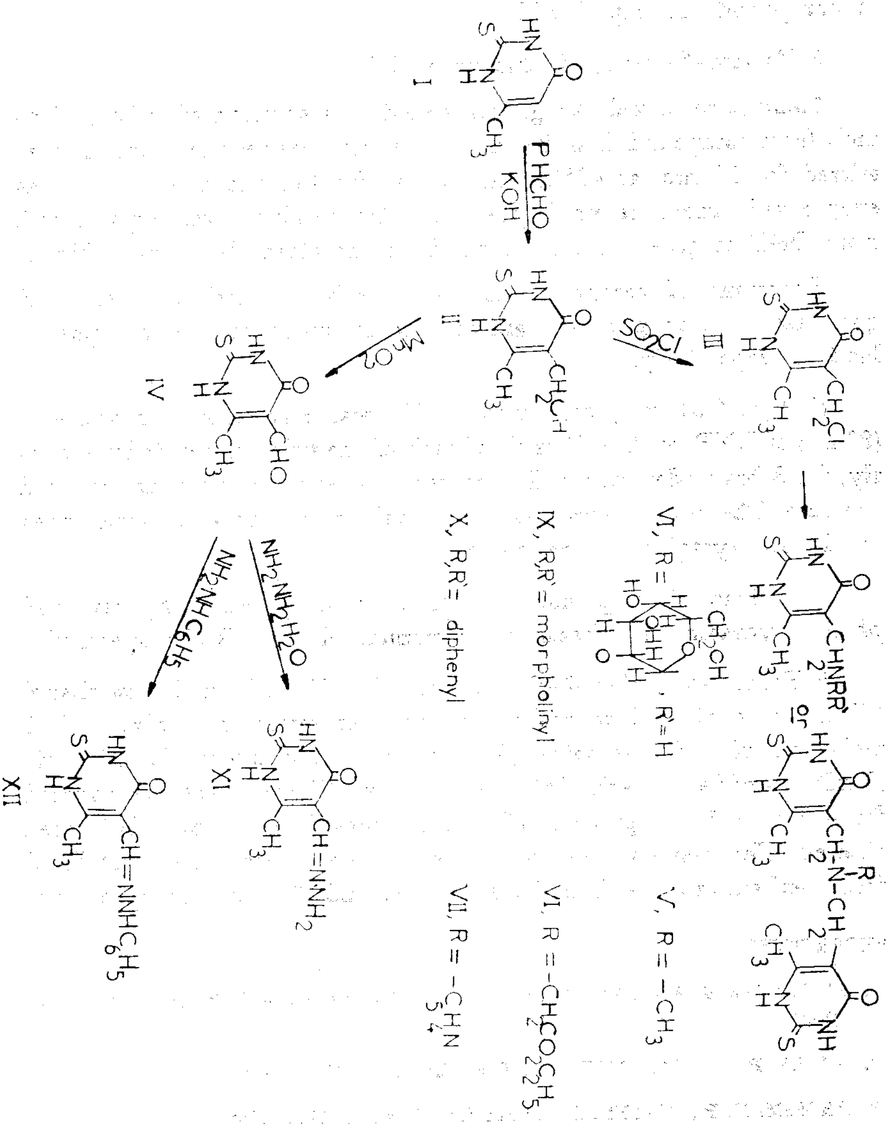
ml). The mixture was allowed to stand for 72 h. at 50°C, then it was monitored by TLC, diluted with distilled water (450 ml). The mixture was stirred with 40 g. of freshly washed Dowex 50 / H^+ form, and then filtered. The slightly acidic filtrate was concentrated under reduced pressure to 30 ml, and refrigerated. The product was cyrstallized from water, yield 13.76 g. (80 %), m.p. 282°C.

Table 1.

Compound	Mol. Formula (Mol. Wt.)		Analysis %	
			Calc.	Found
III	$C_6H_7N_2SOCl$ (190.5)	C	37.79	37.5
		H	3.67	3.5
		N	14.69	14.3
		S	16.79	16.6
		Cl	18.63	18.5
IV	$C_6H_6N_2SO$ (154)	C	46.75	46.5
		H	3.89	3.6
		N	18.18	18.2
		S	20.77	20.5
V	$C_{13}H_{17}N_3S_2O_2$ (339)	C	46.01	46.1
		H	5.01	4.9
		N	20.64	20.4
VI	$C_{16}H_{21}N_3S_2O_4$ (411)	C	46.71	46.4
		H	5.10	4.9
		N	17.03	16.8
VII	$C_{17}H_{18}N_6S_2O_2$ (414)	C	49.27	48.9
		H	4.34	4.2
		N	20.28	20.1
VIII	$C_{12}H_{19}N_3SO_6$ (333)	C	43.24	42.9
		H	5.70	5.2
		N	12.61	12.4
IX	$C_{10}H_{16}N_2SO_2$ (242)	C	49.58	49.2
		N	6.61	6.5
		N	17.35	17.1
X	$C_{18}H_{18}N_4SO$ (324)	C	66.66	66.3
		H	5.55	5.4
		N	12.96	12.8
XI	$C_6H_8N_8SO$ (184)	C	39.13	38.9
		H	4.34	4.3
		N	30.43	30.1
XII	$C_{12}H_{12}N_4SO$ (260)	C	55.38	55.2
		H	4.61	4.5
		N	21.53	21.3

5–chloromethyl–6–methyl–2–thio uracil III:

A solution of thionyl chloride (3.3. ml, 0.044 mol) in dry chloroform (19 ml) was added dropwise into a solution of compound II (6.02 g., g., 0.035 ml) in dry chloroform (60 ml) containing 3 ml of dry pyridine.


I
HCHO
KOH
II
SO_2Cl
III
IV
$CHNRR'$
or
V, R = $-CH_3$
VI, R = $-CH_2CO_2C_2H_5$
VII, R = $-C_5H_4N$
VI, R' = H
IX, R,R' = morpholinyl
X, R,R' = diphenyl
$NH_2NH_2 H_2O$
$NH_2NHC_6H_5$
XI
XII
$CH=NNH_2$
$CH=NNHC_6H_5$

The mixture was then allowed to react for 1h. under reflux in anhydrous condition. The product was separated by diethyl ether and the residue was crystallized from a solution of DMF and H_2O to give (6 g., 80 %) of compound III m.p. 335°C.

5–Formyl–6–methyl–2–thio uracil IV:

Manganese dioxide 25 g. was added to a solution of (5.16 g, 0.30 mol) from compound II in 200 ml of acetone. The reaction mixture was stirred for 18 hrs. at 40°C, then it was filtered and the solvent was evaporated under reduced pressure. The product was crystallized. from DMF to give (5 g., 60 % yield) of the aldehyde IV m.p. 318°C.

Reactions of compound III with each of, methylamine, ethyl glycinate, 2–aminopyridine, glucose amine, morphaline and diphenylamine, respectively:

(1.9 g., 0.01 mol) of compound III was reacted in a mixture of (80 ml) of DMF, with (0.05 mol) of each of the title amines, independently, for 3 hrs under reflux. The solvent was evaporated under reduced pressure. The residue was washed several times with cold water, then dried and crystallised from MeOH.

Reactions of compound IV with both of hydrazine hydrate and phenyl hydrazine, synthesis of compounds XI and XII respectively:

5–Formyl–6–methyl–2–thio uracil IV (0.01 mol) in dry methanol (70 ml) was allowed to react with both of hydrazine hydrate (0.01 mol) and phenyl hydrazine (0.01 mmol), respectively. Formic acid (9 ml) was added to each of the two reactions. The reactants were stirred for 4 hrs at 50°C (progress of reaction was followed by TLC), then filtered. The solvent was evaporated. The residues were crystallised from methanol to give XI and XII in 64 % and 67 % yield, respectively.

REFERENCES

1. SAYED Ahmed, A.F., Ph. D. Thesis, Technical University of Lodz (POLAND), Dec. (1987).

2. WILEY R.., . YAMAMOTO, J., Org. Chem., **25**, 1906 (1966).

3. BROSSMAN, R., ZIGLER, D., Tetrahedron Lett., **43**, 5253 (1966).

4. CARBON J. A., J. Org. Chem., **25**, 1731 (1960).

5. CLINE, R.E., FINK, R.M. K, K., J. Am. Chem. Soc., 81, 2521 (1959).

6. ARMSTRONG, V.W., ECKSTEIN, F., Nucleic Acid Res., Spec. Publ., **1**, 97 (1975).

7. CARBON, J., DAVID, H., STUDIER, M.H., Science, **161**, 1146 (1966).

8. BRENNER, M., MULLER H.R., PFISTER, W., Helv. Chim. Acta, **33**, 568 (1950). TUTTMANN, S., BIOSSONNAS, R.W., Helv. Chim. Acta, **41**, 1952 (1958).

9. ROBERTS, J.D., CASERIO, M.C., "Principles of Organic Chemistry", New York–Amsterdam (1964).

10. WALLACE, T.J., J. Org. Chem. **31**, 1217 (1966).