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SYNTHESIS OF SOME PYRIMIDINE DERIVATIVES VIA THE REDUCTION OF SCHIFF BASE TYPE INTERMEDIATES

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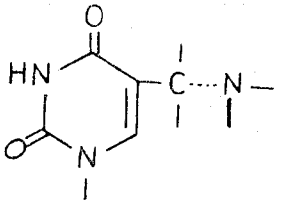
ABSTRACT

Reactions of 5–formyl derivatives of uracil, 4–thiouracil and 2′, 3′,–O-isopropylideneuridine with glucosamine via schiff base intermediate have been described. The antimicrobial activity of the prepared compounds has been also studied.

5–Substituted derivatives[1'2] of both 4–thiouracil[3] and uridine could be utilized to make juncture between C_5 atom of the hetero base and glucosamine.



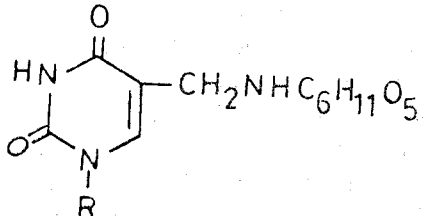
5–Hydroxymethyl derivatives of uracil, thiouracil and uridine have been reported[4'5] to be the suitable substrate for such transformation because they can be easily converted into the 5–formyl derivatives[6]. It should be also noticed that, condensation of 5–formyl derivatives of pyrimidine base with glucosamine could be transfered into the nucloside level by employing a potential substrate such as 5–formyl derivative of 2′,3′, O– isopropylideneuridine, in fact the latter compound is soluble in methanol and gives a reasonable yield of the final product.

The study described in this manuscript shows that, when equimolar quantitites of 5–formyluracil and glucosamine in methanol were allowed to react then, sodium cyanoborohydride was added and

the pH of the reaction mixture was adjusted at a value ca, 5 compound 3 was obtained in 58 % yield. As a point of interest in this area, it has been documented that, synthesis of Schiff base type intermediate requires an acid catalysis[7,8]. The optimum pH falls in the region, where not all of the amine is converted into RNH_3^+ form and there is sufficient concentration of the conjugate acid of the carbonyl function. $NaBH_3CN$ was used as the suitable reducing agent "in situ" because it is stable at pH up to 3 and reduces the aldehyde function much slower than the imine function at the same pH value[9–11]. Mass–spectrum of compound 3 showed a molecular ion peak at m/e = 303 and its ^{1}H–NMR–spectrum displayed signals at 8.36–8.28 (ds, 1H; H_6), 7.06–6.95 d(d, J = 2Hz, 1H, H_1 glucose), and 3.65 (s, 2H;–CH_2N–).

On the other hand, condensation of 5–formyl–2′,3′–O–isopropylideneuridine and glucosamine at room temperature in the presence of $NaBH_3CN$ gave 2′, 3′–O–isopropylidene–5–glucosylaminomethyl uridine 4 in 42 % yield. Mass–spectrum of this compound showed a molecular ion peak at m/e = 475 whereas its ^{1}H–NMR–spectrum revealed signals at 8.42–8.34 (ds, 1H; H_6), 7.26–7.18 (dd, J = 3Hz, 1H; H_1), 7.08–6.98 (dd, J = 1.7 Hz, 1H; H_1 glucose), 3.85 (s, 2H; –CH_2N), and 1.55–1.30 [ds, 6H; $C(CH_3)_2$].

When the isopropylidene derivative 4 was heated with 50 % acetic acid for 45 minutes, deprotection took place and the final nucloside, 5–glucosylaminomethyl uridine 5 was obtained in quantitative yield. Mass–spectrum of 5 exhibited a molecular ion peak at m/e = 435 and its ^{1}H–NMR–spectrum did not show the characteristic signal for the isopropylidene group.

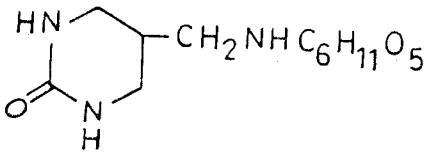


3; R = H (5–glucosylaminomethyl uracil).

4; R = $C_8H_{13}O_4$ (2′, 3′–O–isoprophylidene–5–glucosylaminomethyl uridine).

5; R = $C_5H_9O_4$ (5–glucosylaminomethyl uridine).

However, it is important to mention that, the reaction of 5–formyl 4–thiouracil 2 with glucosamine in presence of $NaBH_3CN$ yielded–5–glucosylaminomethyl–2–oxo–hexahydroprimidine 6. Elemental and chemical analysis of this compound showed the absence of sulphur. Mass–spectrum of 6 revealed a molecular ion peak at m/e = 291 as well as its ^{1}H–NMR–spectrum displayed signals at 7.04–6.94 (dd, J = 2Hz, 1H; H_1 glucose), and 4.24 (s, 2H; $-CH_2N-$).



The antimicrobial activity of compounds 3,5, and 6 was tested[12] for the bio–assay. Three different gram positive bacteria namely, Bacillus subtilis, B–cereus and B–megatatrum were used for this purpose. On the bases of the results obtained, only compound 6 showed antimicrobial activity against the previously mentioned microorganisms (c.f Table 2).

Experimental Part:

Melting points: uncorrected. ^{1}H–NMR–spectra (CD_3COCD_3): Varian EM–390–90 MHZ instrument, TMS as internal reference (Chemical shift δ in ppm). Antimicrobial activity: Cup–plate technique.

Compounds: 2′, 3′–O–isopropylideneuridine[1], 4–thiouracil[3], 5–hydroxymethyl uracil[4], 5–hydroxymethyl uridine[5], 5–formyl uracil, and 5–formyl uridine[6] were prepared according to the literature methods.

5–Hydroxymethyl–4–thiouracil 1:

A mixture of 4–thiouracil (20 mmol) and paraformaldehyde (1g) in 40 ml 0.5 N aqueous KOH solution was allowed to react at 50°C for 24 h. (progress of the reaction was controlled by TLC). After dilution with water and addition of Dowex–50 (H^+ form), the filtrate was concentrated under reduced pressure and refrigerated. The separated solid was crystallized from the proper solvent (Table 1).

5- Formyl-4-thiouracil 2:

MnO_2 (20 g, 230 mmol) was added to a solution of 5-hydroxymethyl-4-thiouracil 1 (20 mmol) in 90 ml mixture of methylene chloride and acetone (1:1 v/v). The reaction mixture was stirred at 40°C for 18 h. The solid obtained after filteration of the solvent was crystallized from the suitable solvent (Table. 1).

Table 1. Physical Data of Compounds 1-6.

Comp.	mp °C	Solvent Yield %	Mol. Formula (Mol. Wt.)	Analysis calculated / found C	H	N
1	> 300	Et-OH 81	$C_5H_6N_2O_2S$ (158.2)	38.0 38.0	3.82 3.80	17.7 17.5
2	180-181	Et-OH 62	$C_5H_4N_2O_2S$ (156.2)	38.5 38.3	2.58 2.55	17.9 17.7
3	227-228	Me-OH 58	$C_{11}H_{17}N_3O_7$ (303.3)	43.6 43.3	5.65 5.61	13.9 13.6
4	188-190	Me-OH 66	$C_{19}H_{29}N_3O_{11}$ (475.5)	48.0 47.8	6.15 6.12	8.8 8.5
5	212-215	Me-OH 42	$C_{16}H_{25}N_3O_{11}$ (435.4)	44.1 43.8	5.79 5.76	9.7 9.4
6	218-219	Me-OH 36	$C_{11}H_{21}N_3O_6$ (291.3)	45.4 45.3	7.27 7.26	14.4 14.3

Mass spectrum of this compound showed the fragment peak of M^+-CHO and its ^{1}H-NMR-spectrum exhibited the characteristic singlet peak 1H of -CHO at δppm above 9.

Reaction of 5-formyl derivatives of uracil, 2',3'-O-isopropylideneuridine, and 4-thiouracil with glucosamine: Formation of 3-6:

A mixture of the appropriate 5-formyl derivative (10 mmol), glucosamine (10 mmol), and formic acid (9 mmol) in 70 ml dry methanol was stirred at room temperature for 3h. (progress of the reaction was controlled by TLC). After filteration and basification by few drops of trimethylamine, the solvent was evaporated under reduced pressure. The obtained residue was crystallized from proper solvent (Table 1).

Antimicrobial Activity:

The biological activity of the prepared compounds 3, 5, and 6 was tested on Bacillus subtilis, B-cereus and B-megatarum bacreria.

The biological assay was determined according to filter paper disc method. Assay plates were incubated at 30 °C for 24 h. and the diameters of the inhibition zones (in mm) were measured. A summary of the biological results is shown in Table 2.

Table 2. Antimicrobial Activity of the Compounds Considered.

Comp.*	Micro-organism		
	B. Subtilis	B. Cereus	B. Megatarum
3	—	—	—
5	—	—	—
6	5	7	15

*The solvent is dimethyl sulphoxide (DMSO)

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