PREPARATION OF 2-PYRIMIDINONE AND DERIVATIVES*

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4-Thiouracil and its 1-methyl, 1,5-dimethyl, and 5-fluoro derivatives (*Ia–d*) were converted by methylation in alkaline medium to the corresponding 4-methylthio-2-pyrimidinones *II* which afforded the 4-hydrazino-2-pyrimidinones *III* by reaction with hydrazine. Reaction of compounds *III* with silver oxide in water yielded 2-pyrimidinone (*IVa*), 1-methyl-2-pyrimidinone (*IVb*), 1,5-dimethyl-2-pyrimidinone (*IVc*), and 5-fluoro-2-pyrimidinone (*IVd*).

1-(β-D-Ribofuranosyl)-2-pyrimidinone, the 4-deoxyanalogue of uridine, is known as a strong inhibitor of bacterial growth[1,2]. Its mechanism of action *in vivo* consists in selective inhibition of the DNA synthesis *de novo* while neither the over-all proteosynthesis nor the synthesis of RNA *de novo* are affected[2]. On the other hand, the level of some *de novo* synthesised proteins undergoes qualitative changes by the action of the substance mentioned above[3]. It has been shown that the actual active substance is not the ribonucleoside said but the corresponding 2'-deoxyribonucleoside or its 5'-phosphate which are formed from the starting compound by transdeoxyribosylation[4]. The ribonucleoside mediates penetration of the 2-pyrimidinone fragment into the bacterial cell. (Neither 2-pyrimidinone alone nor the corresponding 2'-deoxyribonucleoside penetrate the cell membrane[4].) The *in vivo* synthesized 2'-deoxyribonucleoside is highly effective as the reversible inhibitor of thymidylate synthetase, an enzyme which is the sole catalyst of the synthesis of 2'-deoxythymidine *de novo*. This mechanism was confirmed both *in vivo*[4] and also *in vitro* by means of the purified enzyme[4,5].

The ribonucleosides derived from 2-pyrimidinone and related compounds may be prepared by a direct ribosylation of the corresponding heterocyclic compounds[6]. 2-Pyrimidinone and its derivatives *IV* are accessible by numerous purely synthetic methods such as condensation of malonic dialdehyde derivatives with urea or transformation of other pyrimidine compounds, *e.g.*, reduction of 2-hydroxy-4-chloropyrimidine or hydrolysis of 2-amino-, 2-alkylthio-, 2-alkoxy-, and 2-methylsulfonylpyrimidine[7]. The direct deoxyribosylation of 2-pyrimidinone and derivatives fails as exemplified by the attempted preparation of the corresponding 2'-deoxyribonucleoside; the failure is mainly due to the high sensitivity of products. Consequently, other routes were examined that would start from ready nucleosides of uracil and its

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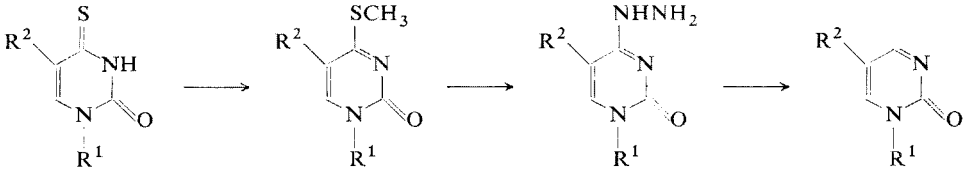
derivatives. One of these routes which was also developed from the preparative standpoint, consists in desulfurisation of the 4-thiouracil nucleosides and affords under suitable conditions the derivatives of 2-pyrimidinone[8]. However, even this route strongly depends on reaction conditions as well as on the quality of the desulfurisation agent (Raney nickel).

A route of choice might consist in the oxidative removal of the hydrazino group by the action of some metallic salts. In the pyrimidine chemistry, this process has been used in the preparation of some alkylpyrimidines[9,10] but not in the preparation of 2-pyrimidinone alone. In the present paper, we wish to report the preparation of 2-pyrimidinone and some its derivatives by this route.

In the present synthesis, the 4-thiouracils *I* were used as the starting material. Compounds *I* are readily accessible from corresponding uracils by reaction with phosphorus pentasulfide. On treatment with methyl iodide in the presence of methanolic sodium methoxide, compounds *I* were converted to the 4-methylthio-2-pyrimidinones *II* which yielded the 4-hydrazino-2-pyrimidinones *III* by the action of hydrazine. Various metallic compounds are used for an analogous replacement of the hydrazine group by the hydrogen atom[11]; in the present case, silver oxide[12] proved as the reagent of choice. Thus, by reaction with an equimolar amount of silver oxide in water at room temperature there were obtained fair yields of 2-pyrimidinone (*IVa*), 1-methyl-2-pyrimidinone (*IVb*), and 1,5-dimethyl-2-pyrimidinone (*IVc*).



I *II* *III* *IV*

In formulae *I*–*IV* *a*: $R^1 = R^2 = H$; *b*: $R^1 = CH_3$, $R^2 = H$; *c*: $R^1 = R^2 = CH_3$; *d*: $R^1 = H$, $R^2 = F$.

The above mentioned route has also been used in the preparation of 5-fluoro-2-pyrimidinone (*IVd*). This compound which has recently become attractive because of its biological activity as the metaphase arresting agent of liver cells[13], has been hitherto accessible with considerable difficulty only. Its preparation by desulfurisation of he thio derivative *Id* with Raney nickel[14] strongly depends on reaction conditions and the quality of the catalyst, being susceptible to the formation of higher-hydrogenated by-products[8]. Another procedure[15] consists in a multistep total synthesis of the heterocyclic system. The present process starts from the readily accessible

5-fluorouracil[16] which is converted to 5-fluoro-4-thiouracil (*Id*) by reaction with phosphorus pentasulfide in dioxane. This modification[8,17] is more advantageous than the earlier procedure[18]. The preparation of the methylthio derivative *IId*, the hydrazino derivative *IIId*, and 5-fluoro-2-pyrimidinone (*IVd*) was performed analogously to the above procedures. The yield of the last step, *i.e.*, of the reaction of compound *IIId* with silver oxide is somewhat lower than in preparations of compounds *IVa–c*. The losses are due to the formation of the insoluble silver salt of compound *IVd* and this formation might be ascribed to the special character of compound *IVd*. The silver salt cannot be decomposed by usual agents such as hydrogen sulfide because of the susceptibility of the C–F bond to fission. Notwithstanding, despite the lower yield of the last step, the present method of preparing 5-fluoro-2-pyrimidinone (*IVd*) is more advantageous than the earlier procedures because of the readily accessibility of the starting material and high yields of the preceding steps.

TABLE I

Hydrazino Derivatives *III* and 2-Pyrimidinones *IV*

Compound (yield, %)	Formula (m. wt.)	Calculated/Found			M. p., °C (solvent)
		% C	% H	% N	
IIIa	$C_4H_6N_4O$	38·09	4·80	44·42	does not melt up to 350[a]
(74)	(126·1)	37·92	4·81	44·47	(water)
IIIb	$C_5H_8N_4O$	42·85	5·75	39·98	177–179
(87)	(140·1)	42·92	5·86	39·81	(dioxane)
IIIc	$C_6H_{10}N_4O$	46·74	6·54	36·34	169–172
(93)	(154·2)	46·71	6·51	36·61	(dioxane)
IIId	$C_4H_5FN_4O$[b]	33·33	3·50	38·89	does not melt up to 250
(67)	(144·1)	33·26	3·46	39·19	(water)
IVa	$C_4H_4N_2O$	50·00	4·20	29·15	178–180[c]
(79)	(96·1)	49·59	4·12	29·05	(ethanol–ether)
IVb	$C_5H_6N_2O$	54·54	5·49	25·44	125–127[d]
(65)	(110·1)	54·59	5·46	25·54	(benzene)
IVc	$C_6H_8N_2O$	58·05	6·50	22·57	132–134[e]
(70)	(124·1)	58·42	6·48	22·85	(toluene)
IVd	$C_4H_3FN_2O$[f]	42·10	2·64	24·56	171–172[g]
(34)	(114·1)	42·24	2·85	24·83	(sublimation)

[a] Reported[20], m. p. 305–310°C; [b] calculated: 13·18% F; found: 12·88% F; [c] reported[21], m. p. 179–181°C; [d] reported[22], m. p. 125–126°C; [e] reported[23], m. p. 132°C; [f] calculated: 16·65% F; found: 16·32% F; [g] reported [14], m. p. 170–171°C.

The above results demonstrate the route how to convert the uracil derivatives (including those substituted on the N^1 nitrogen atom) into the corresponding compounds of the 2-pyrimidinone series. Owing to the mild reaction conditions in all steps of the sequence, the present route could be most probably used also in the series of uracil nucleosides.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). Analytical samples were dried at 0·1 Torr and room temperature for 8 h. Solutions were taken down on a rotatory evaporator at 35—40°C/15 Torr. The UV spectra were recorded on a Zeiss Specord apparatus in aqueous solutions. Thin-layer chromatography was performed on ready-for-use Silufol UV_{235} (Kavalier Glassworks, Votice, Czechoslovakia) silica gel foils containing fluorescent indicator, in the solvent systems S_1, chloroform–ethanol (85 : 15), and S_2, chloroform–ethanol (95 : 5).

5-Fluoro-4-thiouracil (*Id*)

A suspension of 5-fluorouracil[16] (5·5 g; 42 mmol) and phosphorus pentasulfide (9 g) in dioxane (120 ml) was refluxed for 3 h, filtered while hot, and the solid washed with dioxane (100 ml). The filtrate and washings were evaporated under diminished pressure, the residue dissolved in hot water (150 ml), the hot solution filtered with active charcoal, and the filtrate evaporated under diminished pressure. Crystallisation of the residue from water yielded 5·3 g (86%) of compound *Id*, m.p. 275°C; reported[18], m.p. 275°C. For $C_4H_3FN_2OS$ (146·1) calculated: 32·88% C, 2·07% H, 13·00% F, 19·18% N, 21·94% S; found: 33·18% C, 1·79% H, 13·45% F, 20·01% N, 22·03% S. R_F values: 0·60 (S_1) and 0·45 (S_2); 5-fluorouracil: 0·34 (S_1).

1,5-Dimethyl-4-methylthio-2-pyrimidinone (*IIc*)

To a solution of compound[8] *Ic* (1·56 g; 10 mmol) in a mixture of 50% aqueous dioxane (50 ml) and 1M methanolic sodium methoxide (10 ml) there was added methyl iodide (0·78 ml; 1·78 g; 12 mmol), and the whole mixture stirred in a closed vessel at room temperature for 1 h. The mixture was then evaporated and the residue purified by thin-layer chromatography on silica gel in chloroform and sublimation to afford 1·57 g (92%) of compound *IIc*, m.p. 104—106°C. For $C_7H_{10}N_2OS$ (170·2) calculated: 49·41% C, 5·92% H, 16·46% N, 18·83% S; found: 49·51% C, 5·92% H, 16·72% N, 18·96% S.

5-Fluoro-4-methylthio-2-pyrimidinone (*IId*)

To a solution of compound *Id* (5·3 g; 36·3 mmol) in a mixture of methanol (60 ml) and 1M methanolic sodium methoxide (37 ml) there was added methyl iodide (2·6 ml; 5·92 g; 39·8 mmol) and the whole mixture stirred in a closed flask at room temperature for 4 h. The mixture was then evaporated under diminished pressure and the residue crystallised from ethanol to afford 5·0 g (79%) of compound *IId*, m.p. 221—223°C; reported[18], m.p. 222—224°C. For $C_5H_5FN_2OS$ (160·2) calculated: 37·48% C, 3·14% H, 11·86% F, 17·49% N, 20·02% S; found: 37·66% C, 3·04% H, 12·03% F, 17·90% N, 20·24% S. R_F values: 0·90 (S_1) and 0·59 (S_2).

4-Hydrazino-2-pyrimidinones *IIIa*—*IIIc*

A solution of the corresponding 4-methylthio-2-pyrimidinone *IIa* (ref.[19]), *IIb* (ref.[19]) or *IIc* (2 mmol each) in water (20 ml) was refluxed with 78% hydrazine hydrate (1 ml) for 3 h. Compound *IIIa* was obtained by cooling down the reaction mixture and concentrating the mother liquors; in the case of compounds *IIIb* and *IIIc*, the reaction mixture was evaporated under diminished pressure and the residue crystallised from dioxane. For yields, melting points, and analyses see Table I.

5-Fluoro-4-hydrazino-2-pyrimidinone (*IIId*)

A suspension of compound *IId* (5·0 g; 28·7 mmol) in a mixture of water (25 ml) and 80% hydrazine hydrate (6·5 ml) was refluxed for 3 h with stirring, cooled down, the product collected with suction, washed with water, ethanol, and ether, and dried under diminished pressure. R_F value: 0·25 (S_1). For the yield, melting point, and analysis see Table I.

2-Pyrimidinones *IVa*—*IVc*

A mixture of the corresponding hydrazino derivative *IIIa*—*IIIc* (2 mmol each), water (25 ml), and silver oxide (2 mmol) was kept at room temperature for 24 h, filtered with suction through a layer of Celite with the addition of active charcoal, the filtrate evaporated, and the residue recrystallised. For solvents, yields, melting points, and analyses see Table I.

5-Fluoro-2-pyrimidinone (*IVd*)

A suspension of compound *IIId* (2·5 g; 17·9 mmol), silver oxide (4·25 g; 18 mmol), and water (100 ml) was stirred at room temperature for 12 h, filtered with suction through a layer of Celite, and washed with hot water (100 ml) and methanol (100 ml). The filtrate and washings were combined and evaporated under diminished pressure. The residue was chromatographed on a loose layer (40 × 16 × 0·4 cm) of the fluorescent indicator containing silicagel (produced by Service Laboratories of this Institute) in the solvent system chloroform–ethanol (8 : 2). The main band (R_F 0·45) was eluted with methanol, the eluate evaporated, and the residue sublimed at 95°C/0·1 Torr. UV spectrum (pH 7): λ_{max} 306 nm (ε_{max} 3620). R_F values: 0·45 (S_1) and 0·14 (S_2). For the yield, melting point, and analysis see Table I.

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