POTENTIAL CARCINOSTATICS VI[1].

Biologically active 5-fluorouracil derivatives of 2-oxo-2,5-dihydrofuran.

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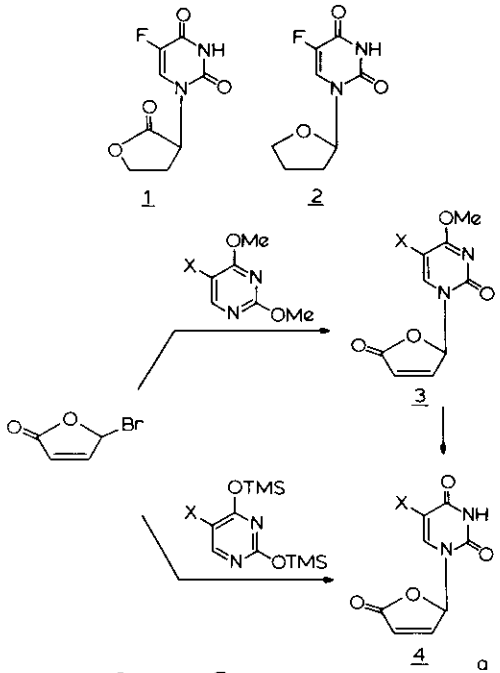
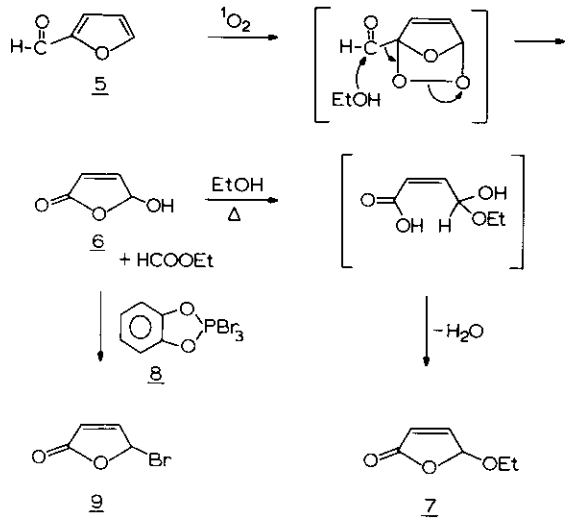
Abstract. 1-(2-Oxo-2,5-dihydro-5-furyl)-5-fluorouracil derivatives have been synthesized and shown to be active in the P-388 mouse leukemia test system.

As a part of a programme directed to the development of antineoplastic agents we have been interested in preparing non-glycosidic derivatives of 5-fluorouracil, which could either act as inhibitors of thymidylate synthetase or as pro-drugs that would be capable of releasing 5-fluorouracil at the target cell. In this connection the preparation of the 5-fluorouracil substituted butyrolactone 1 has been reported earlier[2] from this laboratory (Scheme I). The promising medical properties of Ftorafur 2[3,4,5] (1-tetrahydrofuran-2'-yl-5-fluorouracil, FT-207) stimulated us to undertake the preparation of 5-fluorouracil derivatives in which furanyl and pyranyl moieties were attached via N-3 of the pyrimidinyl system[6]. In this communication we report the synthesis and preliminary biological properties of the 5-fluorouracil non-glycosidic nucleoside analogues 3b and 4b. It should be mentioned that the corresponding uracil analogues 3a and 4a have been described in the literature[7]. The latter were synthesized by the reaction of 2,4-dimethoxypyrimidine with 5-bromo-2(5H)-furanone 9, which compound was obtained from furfural, in two steps. The first step comprises of the photoxidation of an ethanolic solution of furfural in the presence of eosin as a sensitizer. The product of this reaction has been reported to be variable.[7,10] We have observed that the course of the reduction is critically dependent upon the temperature at which it is carried out. If the irradiation is carried out without cooling the reaction flask, the solution starts to reflux, due to the heat of the light-source. After 45 h under these conditions, the aldehyde carbonyl absorption disappears (IR) and from the reaction-mixture 5-ethoxy-2(5H)-furanone 7 can be isolated in 50% yield. (B.p. 103°/15 mm) (Scheme II). This was also observed by Schenk et al.[8-10]. If, however, the reaction mixture is cooled with water or ice, during the irradiation, a considerably slower reaction



Scheme I



Scheme II

takes place and 5-hydroxy-2(5H)-furanone 6 is produced in 60% yield (m.p. 58-60°C). The rate of the reaction of furfural can be monitored via the disappearance of the UV-maximum (of furfural) at 276 nm. The aforementioned observations can be explained on the basis of the reaction mechanism outlined in Scheme II. Reaction of furfural with singlet oxygen - generated under the influence of the sensitizer - forms, initially, the corresponding ozonide. Nucleophilic attack on the carbonyl group by a molecule of ethanol would subsequently produce ethyl formate and the hydroxy compound 6 in a concomitant process. At elevated temperatures 6 would be expected to be converted into the ethoxy derivative 7 via the tautomeric formylacrylic acid. In a separate reaction we have shown that indeed, when hydroxy lactone 6 is refluxed in ethanol 7 is produced in good yield. 6 Could be conveniently converted into the corresponding bromide 9, in 50% yield, using catecholphosphorustribromide 8 in refluxing methylene chloride[7]. Reaction of 9 with 2,4-dimethoxy-5-fluoropyrimidine[11] (4 days, refluxing methanol) yielded 3b, which was converted into the furanone-substituted 5-fluorouracil 4b (m.p. 218-223°C), by treatment with HCl in methanol/water. When bromide 9 was allowed to react with 2,4-bis-(trimethylsilyl)-5-fluorouracil[3], in the presence of $SnCl_4$[12], the nucleoside analogue 4b was formed in one practical step. Both compounds exhibited considerable activity (Table 1) in the P-388 mouse leukemia test system on female CDF_1 mice.

TABLE 1

Activity of 5-fluorouracil derivatives 3b and 4b in P-388 mouse leukemia.
P-388 10^6 cells/mouse i.p.
Treatment i.p. days 1-9.

	doses	B.W.C.(g)[a]	Med.S.T.[b]	T/C(%)[c]
3b NSC no. 315844	60	-2.1	12.3	125
	40	-1.0	19.3	196
	20	+0.5	17.0	173
4b NSC no. 315845	80	-3.0	9.0	91
	60	-2.0	19.3	196
	40	-1.5	17.4	177
5-FU	40	-3.5	9.3	94
	20	+0.6	18.8	191
	10	+0.3	15.3	156
controls		+2.9	9.8	

[a]B.W.C. = body weight change on day 5.

[b]Med.S.T. = median survival time of 6 treated mice divided by that of the control group expressed as a percentage.

Inspection of Table 1 indicates that both 3b and 4b have biological activities (T/C % values) comparable to that of 5-fluorouracil. Further tests, particularly on solid tumours and studies aimed at elucidating the mode of action of these non-

glycosidic nucleoside analogues are currently in progress.

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