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ANTINEOPLASTIC AGENTS. SYNTHESIS OF SOME 1-SUBSTITUTED 5-FLUOROURACIL DERIVATIVES

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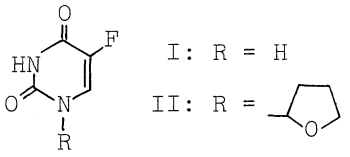
Reactions of 5-fluorouracil with various acyl chlorides, alkanesulfonyl chlorides, and arenesulfonyl chlorides in dioxane or dimethylformamide gave the 1-substituted derivatives. Some of these products showed markedly antitumor activity.

Since the introduction of 5-fluorouracil (I)[1] as antineoplastic agent, many 5-fluorouracil derivatives have been prepared in an effort to increase and to modify activity.[2] Recently, 1-(2-tetrahydrofuryl)-5-fluorouracil (FT-207) (II)[3] was employed as clinical drugs for certain solid tumors by oral administration, which shows minimal gastro-intestinal toxicity. However, II is much inferior to I in antitumor activity and is necessary to be improved in the aforesaid activity. The introduction of chemically simple groups into the 1-position of I might be useful to obtain the desired compounds. This paper describes the preparations of 1-acyl-, 1-alkanesulfonyl-, and 1-arenesulfonyl-5-fluorouracils.

When I was allowed to react with acyl, alkanesulfonyl, and arenesulfonyl chlorides in dioxane or dimethylformamide in the presence of tertiary amine or anhydrous pctassium carbonate, the corresponding 1-substituted 5-fluorouracil was produced. The structures of these products were established by microanalyses and by the spectral data.



I: R = H

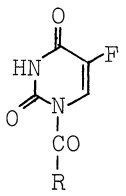
II: R =

The typical reaction procedure is described for the reaction of I with p-chlorobenzoyl chloride. To a suspension of I (2.6 g, 20 mmol) in dioxane (40 ml) and triethylamine (10 ml), p-chlorobenzoyl chloride (8.4 g, 40 mmol) was added. The mixture was stirred at 80°C for 6 hr, cooled to room temperature, and then filtered off. The filtrate was evaporated to dryness under reduced pressure and the residue was extracted with absolute ethanol. The extract was concentrated by evaporation. The resulting crystals which separated were recrystallized from ethanol to give 1-(p-chlorobenzoyl)-5-fluorouracil (1.18 g, 35%). In a similar manner, various 1-substituted compounds were obtained from I as shown in Table 1.

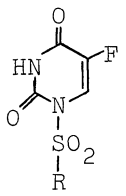
The above products have been submitted for animal testing. The results indicate that benzoyl and arenesulfonyl derivatives are more active and less toxic than II in Leukemia L-1210 system.[5]

The reactions of I with other acyl chlorides and arenesulfonyl chlorides are currently under investigation.

Table 1. 1-Substituted 5-Fluorouracil Derivatives



R	Mp[a] (°C)	Yield (%)
CH_3	126-127[b]	61
CH_3CH_2	124-125	52
C_6H_5	170-172	43
o-$CH_3C_6H_4$	180-181	36
p-$CH_3C_6H_4$	198-199	49
p-ClC_6H_4	185-186	35
2,4-$(Cl)_2C_6H_3$	175-177	69
p-$NO_2C_6H_4$	182-183	53
o-$CH_3OC_6H_4$	183-184	56
p-$CH_3OC_6H_4$	200-201	49
2-Furyl	165-166	71



R	Mp[a] (°C)	Yield (%)
CH_3	223-224	45
CH_3CH_2	214-215	23
d-10-Camphoryl	153-154	59
C_6H_5	256-257	55
o-$CH_3C_6H_4$	204-205	37
p-$CH_3C_6H_4$	241-242	62
2,4,6-$(CH_3)_3C_6H_2$	232-233	21
p-$CH_3CH_2C_6H_4$	215-216	43
p-BrC_6H_4	247-248	58
p-ClC_6H_4	237-238	45
p-IC_6H_4	253-254	50
p-$CH_3CONHC_6H_4$	240-241[c]	36
o-$NO_2C_6H_4$	229-231	59
1-Naphthyl	218-221	62
2-Thienyl	222-223	70
8-Quinolyl	272-273[c]	62

a) All melting points are uncorrected. b) Lit.,[4] mp 128-129°C. c) Decomp. point.

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References

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