Potential Antineoplastics. 8. Synthesis and Pharmacology of 6-Methyl-2-thio-5-arylazouracils[1]

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The antitumor properties associated with various thio analogs of uracil[2-7] prompted us to synthesize new structural congeners of potential medicinal interest, which are reported in the present communication.

Preliminary evaluation of these derivatives in the leukemia 1210 system[8] by single and multiple-dose (400 mg/kg per day) injections indicated neither any appreciable activity nor toxicity.

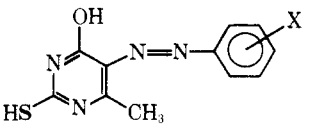
Experimental Section[9]

6-Methyl-2-thiouracil was prepd by a lit. route, mp 300–301° (lit.[10] mp 300°).

6-Methyl-2-thio-5-arylazouracil. Method A.—A soln of aryldiazonium salt from a substd aniline (0.01 mole) was slowly added to a well-cooled, stirred mixt of 6-methyl-2-thiouracil (0.01 mole) in 10% aq NaOH (10 ml) contg excess of AcONa. The mixt was kept at room temp for 2 days. The pptd solid was filtered off, washed (H_2O), and recrystd from EtOH–C_5H_5N (Table I).

Method B.—NH_2CSNH_2 (0.02 mole) was added to ethyl 2-arylhydrazone-2,3-dioxobutyrate (0.02 mole) contg EtONa prepd from 1.2 g of Na and anhyd EtOH (50 ml). The resulting mixt was refluxed for 3 hr and left overnight. The sepd ppt was collected by filtration, washed (H_2O), and recrystd from EtOH–C_5C_5N.

TABLE I
CHARACTERISTICS OF 6-METHYL-2-THIO-5-ARYLAZOURACILS



No.	X	Yield, %	Mp, °C	Color[a]	Formula	Analyses[b]
1	4-Cl	55	168–170 dec	BnN	$C_{11}H_9ClN_4OS$	N, Cl
2	2-Br	50	97–99 dec	DBnF	$C_{11}H_9BrN_4OS$	N, Br
3	2-OH	60	153–155 dec	RBnN	$C_{11}H_{10}N_4O_2S$	N, S
4	2,4-Cl_2	65	170–172	YN	$C_{11}H_8Cl_2N_4OS$	N, Cl
5	2,4-Br_2	50	190–191	YN	$C_{11}H_8Br_2N_4OS$	N, Br
6	2,5-Br_2	52	220–222 dec	YN	$C_{11}H_8Br_2N_4OS$	N, Br
7	2,3-Me_2	70	101–102	BnN	$C_{13}H_{14}N_4OS$	N, S
8	2,5-Me_2	65	100–101 dec	DRN	$C_{13}H_{14}N_4OS$	N, S
9	2,6-Me_2	55	104–105	ON	$C_{13}H_{14}N_4OS$	N, S
10	3,4-Me_2	60	167–168	RBnN	$C_{13}H_{24}N_4OS$	N, S
11	3,5-Me_2	60	227–228 dec	RBnN	$C_{13}H_{14}N_4OS$	N, S
12	2-Cl-6-Me	65	154–155 dec	OYN	$C_{12}H_{11}ClN_4OS$	N, Cl
13	2,5-Cl_2-4-NO_2	40	255–260 dec	YN	$C_{11}H_7Cl_2N_5O_3S$	N, Cl
14	4-Cl-2,5-$(MeO)_2$	55	204–205 dec	RBnP	$C_{13}H_{13}ClN_4O_3S$	N, S
15	5-Cl-2,4-$(MeO)_2$	55	248–249 dec	DRN	$C_{13}H_{13}ClN_4O_3S$	N, S

[a] B, bright; Bn, brown; D, deep; F, fibers; N, needle; O, orange; P, plates; R, red; Y, yellow. [b] Analytical data were within ±0.4% of the theoretical value.

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(8) Screening results were supplied by CCNSC of the National Institutes of Health, Bethesda, Md.

(9) Melting points were taken on a Kofler hot-stage type apparatus and are uncorrected.

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