

Potential Antineoplastics. 8. Synthesis and Pharmacology of 6-Methyl-2-thio-5-arylazouracils¹

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The antitumor properties associated with various thio analogs of uracil²⁻⁷ prompted us to synthesize new

mg/kg per day) injections indicated neither any appreciable activity nor toxicity.

Experimental Section⁹

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 aryl-diazonium 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 (H₂O), and recrystd from EtOH–C₆H₅N (Table I).

Method B.—NH₂CSNH₂ (0.02 mole) was added to ethyl

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 ₉ ClN ₄ OS	N, Cl
2	2-Br	50	97–99 dec	DBnF	C ₁₁ H ₉ BrN ₄ OS	N, Br
3	2-OH	60	153–155 dec	RBnN	C ₁₁ H ₁₀ N ₄ O ₂ S	N, S
4	2,4-Cl ₂	65	170–172	YN	C ₁₁ H ₈ Cl ₂ N ₄ OS	N, Cl
5	2,4-Br ₂	50	190–191	YN	C ₁₁ H ₈ Br ₂ N ₄ OS	N, Br
6	2,5-Br ₂	52	220–222 dec	YN	C ₁₁ H ₈ Br ₂ N ₄ OS	N, Br
7	2,3-Me ₂	70	101–102	BnN	C ₁₃ H ₁₄ N ₄ OS	N, S
8	2,5-Me ₂	65	100–101 dec	DRN	C ₁₃ H ₁₄ N ₄ OS	N, S
9	2,6-Me ₂	55	104–105	ON	C ₁₃ H ₁₄ N ₄ OS	N, S
10	3,4-Me ₂	60	167–168	RBnN	C ₁₃ H ₁₄ N ₄ OS	N, S
11	3,5-Me ₂	60	227–228 dec	RBnN	C ₁₃ H ₁₄ N ₄ OS	N, S
12	2-Cl-6-Me	65	154–155 dec	OYN	C ₁₂ H ₁₁ ClN ₄ OS	N, Cl
13	2,5-Cl ₂ -4-NO ₂	40	255–260 dec	YN	C ₁₁ H ₇ Cl ₂ N ₄ O ₃ S	N, Cl
14	4-Cl-2,5-(MeO) ₂	55	204–205 dec	RBnP	C ₁₃ H ₁₃ ClN ₄ O ₃ S	N, S
15	5-Cl-2,4-(MeO) ₂	55	248–249 dec	DRN	C ₁₃ H ₁₃ ClN ₄ O ₃ S	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.

structural congeners of potential medicinal interest, which are reported in the present communication.

Preliminary evaluation of these derivatives in the leukemia 1210 system⁸ by single and multiple-dose (400

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 (H₂O), and recrystd from EtOH–C₆H₅N.

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

(10) G. W. Anderson, I. F. Halverstadt, W. H. Miller, and R. O. Roblin, Jr., *J. Amer. Chem. Soc.*, **67**, 2197 (1945).

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(1) (a) Abstracted in part from the thesis submitted by R.A.S. in fulfillment for the degree of Doctor of Philosophy, University of Roorkee, Roorkee, India (b) Part 7. H. G. Garg and R. A. Sharma, *Can. J. Pharm. Sci.*, **6**, 215 (1971).

(2) C. Heidelberger, *Annu. Rev. Pharmacol.*, **9**, 115 (1967).

(3) T. A. Khwaja and C. Heidelberger, *J. Med. Chem.*, **10**, 1066 (1967).

(4) V. Skaric and B. Gaspert, *J. Chem. Soc.*, 2631 (1969).

(5) V. Skaric and B. Gaspert, *Chem. Commun.*, 550 (1968).

(6) R. W. Holley, J. A. Apgar, G. A. Everet, J. T. Madison, M. Marquise, S. H. Merrill, J. R. Penswick, and A. Zamir, *Science*, **147**, 1642 (1965).

(7) M. N. Lippsett, *J. Biol. Chem.*, **240**, 3975 (1965).

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