ANTIMETABOLITE ACTIVITY OF 5-ARYLAZOPYRIMIDINES

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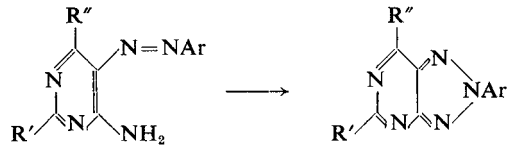
THE antimetabolite activity of a series of 5-arylazopyrimidines (I) has been observed in these laboratories. This type of compound, which is synthesised by the coupling of a diazotised arylamine with a 5-unsubstituted pyrimidine, has been described previously[1–4] but, although slight inhibition in certain bacterial systems was observed[2], no specific antimetabolite activity was reported. Compounds of structure I are converted on oxidation to 8-aryl-8-azapurines (II)[2–4], which proved to be essentially devoid of antimetabolite activity in our studies. This investigation began with the synthesis of new derivatives of structures I and II



(I) (II)

	R′	R″	Ar
a,	NH_2	SH	phenyl
b,	NH_2	OH	phenyl
c,	NH_2	OH	2′,6′-xylyl

containing the 6-mercaptopyrimido-moiety, common to the purine antagonists 6-mercaptopurine[5] and thioguanine[6], as potential antimetabolites and antitumor agents. During the course of these studies we learned of similar work at the Chester Beatty Research Institute in London on the antimetabolite activity of compounds of types I and II[7–9].

Certain compounds of structure I have now been found to display inhibitory activity in a previously described *Streptococcus faecalis* *8043-pteroylglutamic acid (PGA) bioassay system[10] and in a "maximum synthesis" system utilising *Escherichia coli* *6522[11], which in the former system is relieved by excess PGA and slightly by guanine, and in the latter system by adenine or guanine, but poorly by PGA (Table I). Inhibition in the *Str. faecalis* PGA system, which appears to be competitive over a narrow range, about 10 fold, of concentration, is also reversed by dihydro-PGA, 10-formyl-PGA, natural citrovorum factor (CF), or thymine. These compounds also are active in a previously described *Leuconostoc citrovorum* *8081-CF[12] bioassay system. The response of a guanineless mutant of *Aerobacter aerogenes* to guanine[13] is inhibited effectively by certain of the arylazopyrimidines.

Preliminary structure-activity correlation indicates that at least one

* American Type Culture Collection numbers.

TABLE I

50 PER CENT MINIMAL INHIBITING CONCENTRATIONS, μG./ML.

	Streptococcus faecalis				*Escherichia coli*		
Cpd.	Excess PGA 100 μg./ml.	PGA μg./ml. 0·1	0·01	0·001	Excess guanine, 100 μg./ml.	Medium alone	Excess PGA 100 μg./ml.	Excess purine* 50 μg./ml.
Ia	Complete reversal	34·0	2·8	2·8	2·2	9	20	70
Ib	,,	95·0	2·0	0·21	0·27	9	20	Complete reversal
Ic	,,	2·7	2·8	0·25	3·5	Inactive	Inactive	Inactive

* Adenine or guanine.

amino group *ortho* to the azo linkage is necessary for optimal activity of structure I. The aryl group (Ar) should be unsubstituted or contain electropositive substituents for maximum microbiological activity. Structure II, with few exceptions, has shown little activity.

Structure I is unusual in that it exhibits both anti-PGA and anti-purine activity. It is of interest that I exhibits this bivalent activity rather than II, which possesses the 8-azapurine nucleus of known antimetabolite properties[14,15]. Reduction of the azo linkage of I to the corresponding 5-aminopyrimidine results in a great decrease in microbiological activity.

Structural relationship of I to other similar antimetabolites[16–18] is evident. Further synthetic variations of both I and II are being made and studied, and further studies on the mechanism of action of these compounds and their activity in other biological systems are in progress[19].

SUMMARY

1. The discovery of both antipurine and antifolic activity is reported in certain 4-amino-5-arylazopyrimidines.

2. Details of the microbiological assays are indicated. Work on the 5-arylazopyrimidines and the chemically related 8-aryl-8-azapurines is being developed.

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