New Compounds: Potential Antineoplastics VI: 2,4-Diamino-6-hydroxy-5-arylazopyrimidines and 1,3-Dimethyl-5-arylhydrazonoalloxans

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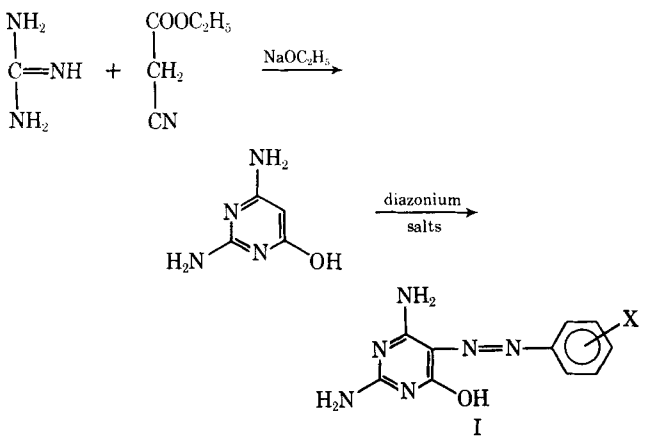
Abstract □ A series of 2,4-diamino-6-hydroxy-5-arylazopyrimidines and 1,3-dimethyl-5-arylhydrazonoalloxans has been synthesized by the coupling of aryldiazonium salts with 2,4-diamino-6-hydroxypyrimidine and 1,3-dimethylbarbituric acid, respectively. The former are also obtained by the cyclization of ethyl cyanoglyoxalate arylhydrazones and guanidine hydrochloride in the presence of sodium ethoxide.

Keyphrases □ 2,4 - Diamino - 6 - hydroxy - 5 - arylazopyrimidines—synthesis, potential antineoplastics □ 1,3-Dimethyl-5-arylhydrazonoalloxans—synthesis, potential antineoplastics □ Antineoplastics—2,4-diamino-6-hydroxy-5-arylazopyrimidines, 1,3-dimethyl-5-arylhydrazonoalloxans, synthesis

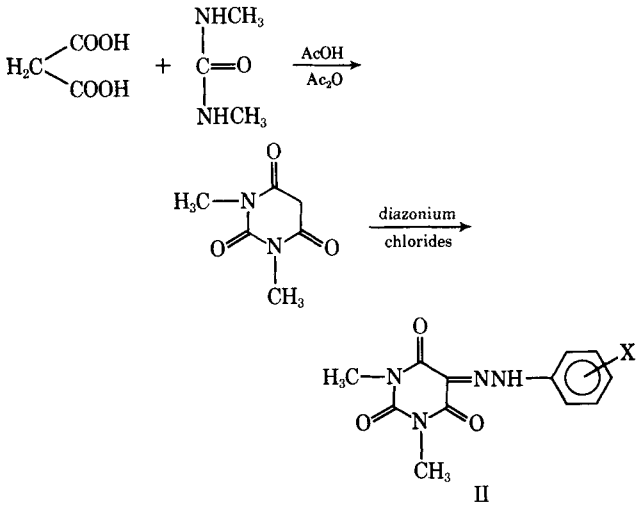
Several arylazopyrimidine analogs are known to possess considerable antitumor activity (1–3). Recently, the synthesis of a few 2-amino-4,6-dimethyl-5-arylazopyrimidines and related compounds has been reported from the authors' laboratories (4–8). Screening results encouraged the present authors to explore the anticancer activity of more congeners of pyrimidines. Interest in pyrimidines led to the extension of this study to include derivatives of 1,3-dimethylalloxan, because this ring constitutes one of the rings of the interesting antibiotic, fervenulin (9).

This paper describes the synthesis of 2,4-diamino-6-hydroxy-5-arylazopyrimidines (I, Scheme I) and 1,3-dimethyl-5-arylhydrazonoalloxans (II, Scheme II). These were prepared by the coupling of aryldiazonium salts with 2,4-diamino-6-hydroxypyrimidine (10) and 1,3-dimethylbarbituric acid (11), respectively.

The coupling reactions were carried out in different media: water, sodium hydroxide, sodium hydrogen carbonate, and ethanol containing sodium acetate. However, the reaction was found to proceed satisfactorily in the basic medium.



Scheme I



Scheme II

EXPERIMENTAL

Melting points were taken on a Kofler hot-stage apparatus and are uncorrected.

Ethyl Cyanoglyoxalate 4-Chlorophenylhydrazone—A solution of 4-chloroaniline (1.27 g., 0.01 mole) in concentrated hydrochloric acid (6 ml.) was cooled to 0°. Sodium nitrite (0.70 g., 0.01 mole) was gradually added. The diazonium salt solution was filtered into a well-cooled, stirred mixture of sodium acetate (6.0 g.) and ethyl cyanoacetate (1.13 g., 0.01 mole) in ethanol (30 ml.). After 1 hr., the precipitate was filtered off and washed with water; it gave pale-yellow needles (2.26 g., 90%), m.p. 145–146° (from ethanol).

Anal.—Calcd.: .... Found: Cl, 14.0; $C_{11}H_{10}ClN_3O_2$ requires Cl, 14.2%.

The details of other ethyl cyanoglyoxalate arylhydrazones which were prepared are given in Table I.

2,4-Diamino-6-hydroxypyrimidine—Ethyl cyanoacetate (22.6 g., 0.2 mole) was mixed with a solution of sodium ethoxide prepared from sodium (4.6 g., 0.2 g.-atom) and anhydrous ethanol (50 ml.). This mixture was allowed to stand while a second solution of sodium ethoxide of the same volume and concentration was prepared. To this solution was added guanidine hydrochloride (19.2 g., 0.2 mole). The sodium chloride was separated by filtration, and the clear filtrate containing guanidine was added to the solution of sodiocyanoacetate. The mixture was heated for 2 hr. under reflux and was then evaporated to dryness at ordinary pressure. The solid product thus obtained was dissolved in water (65 ml.) and acidified with glacial acetic acid (15 ml.). Upon cooling of the solution, 2,4-diamino-6-hydroxypyrimidine was obtained as light-yellow needles (22.16 g., 80%), m.p. 260–265° dec. [lit. (10) m.p. 260–270° dec.].

1,3-Dimethylbarbituric Acid—This was prepared by the procedure of Pfleiderer and Schundehutte (11) from *N,N'*-dimethylurea (17.6 g., 0.2 mole) and malonic acid (17.6 g., 0.2 mole). The product was obtained as colorless needles (21.84 g., 70%), m.p. 118–119° (from ethanol) [lit. (11) m.p. 124°].

2,4 - Diamino - 6 - hydroxy - 5 - (4 - chlorophenylazo)pyrimidine—*Method A*—A solution of 4-chlorobenzenediazonium chloride from

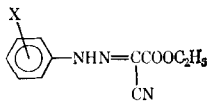


Table I—Characteristics of Ethyl Cyanoglyoxalate Arylhydrazones

No.	X	Yield, %	M.p.	Color[a]	Formula	Analysis, % Calcd.	Found
1	H	90	89–90°	PeYN	$C_{11}H_{11}N_3O_2$	N 19.4	N 19.2
2	2—Me	85	121–122°	BYN	$C_{12}H_{13}N_3O_2$	N 18.2	N 18.0
3	2—NO_2	85	114–115°	BYN	$C_{11}H_{10}N_4O_4$	N 21.4	N 21.3
4	3—NO_2	80	156–157°	OP	$C_{11}H_{10}N_4O_4$	N 21.4	N 21.1
5	4—NO_2	85	193–194°	PeYN	$C_{11}H_{10}N_4O_4$	N 21.4	N 21.2
6	2—Br	75	129–130°	PeYN	$C_{11}H_{10}BrN_3O_2$	Br 27.0	Br 26.8
7	2—Et	80	109–110°	YN	$C_{13}H_{15}N_3O_2$	N 17.1	N 17.3
8	2—MeO	75	135–136°	YN	$C_{12}H_{13}N_3O_3$	N 17.0	N 17.2
9	3—MeO	75	95–96°	BYN	$C_{12}H_{13}N_3O_3$	N 17.0	N 16.7
10	4—EtO	78	81–82°	BYN	$C_{13}H_{15}N_3O_3$	N 16.1	N 16.0
11	2,3—Me_2	80	100–101°	YN	$C_{13}H_{15}N_3O_2$	N 17.1	N 17.2
12	2,4—Me_2	85	157–158°	BYN	$C_{13}H_{15}N_3O_2$	N 17.1	N 16.8
13	2,5—Me_2	85	115–116°	YN	$C_{13}H_{15}N_3O_2$	N 17.1	N 17.0
14	2,6—Me_2	78	100–101°	PeYN	$C_{13}H_{15}N_3O_2$	N 17.1	N 17.0
15	3,4—Me_2	75	84–85°	PeYN	$C_{13}H_{15}N_5O_2$	N 17.1	N 16.9
16	3,5—Me_2	80	129–130°	OYN	$C_{13}H_{15}N_3O_2$	N 17.1	N 17.0
17	2,6—Et_2	85	101–102°	YP	$C_{15}H_{19}N_3O_2$	N 15.4	N 15.2
18	2,3—Cl_2	86	119–120°	OYN	$C_{11}H_9Cl_2N_3O_2$	Cl 24.8	Cl 24.6
19	2,4—Cl_2	85	168–169°	BYN	$C_{11}H_9Cl_2N_3O_2$	Cl 24.5	Cl 24.5
20	2,5—Br_2	70	165–166°	OYN	$C_{11}H_9Br_2N_3O_2$	Br 42.7	Br 42.6
21	2,5—$(MeO)_2$	75	102–103°	OP	$C_{13}H_{15}N_3O_4$	N 15.2	N 15.0
22	2—Cl—6—Me	90	107–108°	BYN	$C_{12}H_{12}ClN_3O_2$	Cl 13.4	Cl 13.2
23	2,5—Cl_2—4—NO_2	65	143–144°	BYN	$C_{11}H_8Cl_2N_4O_4$	Cl 21.5	Cl 21.1
24	4—Cl—2,5—$(MeO)_2$	80	164–165°	GYN	$C_{13}H_{14}ClN_3O_4$	Cl 11.4	Cl 11.2
25	5—Cl—2,4—$(MeO)_2$	85	176–177°	GYN	$C_{13}H_{14}ClN_2O_4$	Cl 11.4	Cl 11.1

[a] B, bright; Bn, brown; D, deep; Da, dark; F, fibers; G, golden; Gr, green; N, needles; O, orange; P, plates; Pe, pale; R, red; and Y, yellow.

4-chloroaniline (1.27 g., 0.01 mole) in concentrated hydrochloric acid (5 ml.) was slowly added to a well-cooled, stirred mixture of 2,4-diamino-6-hydroxypyrimidine (1.26 g., 0.01 mole) in 2 *N* sodium hydroxide (10 ml.) containing sodium acetate (5.0 g.). The precipitated solid was filtered off and washed with water; it gave bright-yellow needles (2.25 g., 85%), m.p. >300° [from ethanol–dimethylformamide (DMF)].

Anal.—Calcd.: .... Found: Cl, 13.2; $C_{10}H_9ClN_6O$ requires Cl, 13.5%.

Method B—Guanidine hydrochloride (1.92 g., 0.02 mole) was added to ethyl cyanoglyoxalate 4-chlorophenylhydrazone (5.02 g., 0.02 mole) dissolved in alcoholic sodium ethoxide (1.2 g. of sodium in 50 ml. anhydrous ethanol). After keeping for 1 hr., the mixture was refluxed for 2 hr. and left overnight. The solid, which separated, was collected and washed with water. It was obtained as bright-yellow needles (1.90 g., 70%), m.p. >300° (from ethanol–DMF). The melting point was not depressed upon admixture with the sample prepared by Method A.

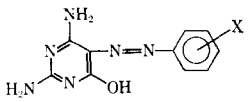


Table II—Characteristics of 2,4-Diamino-6-hydroxy-5-arylazopyrimidines

No.	X	Yield, %	M.p.	Color[a]	Formula	Analysis, % Calcd.	Found
1	H	85	>300°	OP	$C_{10}H_{10}N_6O$	N 36.5	N 36.3
2	2—Me	87	>300°	ORN	$C_{11}H_{12}N_6O$	N 34.4	N 34.2
3	2—NO_2	80	>300°	ORN	$C_{10}H_9N_7O_3$	N 35.6	N 35.5
4	3—NO_2	73	295° dec.	PeYN	$C_{10}H_9N_7O_3$	N 35.6	N 35.4
5	4—NO_2	75	>300°	DRN	$C_{10}H_9N_7O_3$	N 35.6	N 35.4
6	2—Br	75	>300°	ORN	$C_{10}H_9BrN_6O$	Br 26.0	Br 26.3
7	2—Et	80	>300°	ON	$C_{12}H_{14}N_6O$	N 32.6	N 32.3
8	2—MeO	77	270° dec.	DRN	$C_{11}H_{12}N_6O_2$	N 32.3	N 32.1
9	3—MeO	75	170° dec.	BnN	$C_{11}H_{12}N_6O_2$	N 32.3	N 32.4
10	4—EtO	70	>300°	RN	$C_{12}H_{14}N_6O_2$	N 30.6	N 30.4
11	2,3—Me_2	85	>300°	RN	$C_{12}H_{14}N_6O_2$	N 32.6	N 32.3
12	2,4—Me_2	80	>300°	RN	$C_{12}H_{14}N_6O$	N 32.6	N 32.5
13	2,5—Me_2	75	>300°	ORN	$C_{12}H_{14}N_6O$	N 32.6	N 32.4
14	2,6—Me_2	83	290° dec.	OYN	$C_{12}H_{14}N_6O$	N 32.6	N 32.5
15	3,4—Me_2	75	280° dec.	RN	$C_{12}H_{14}N_6O$	N 32.6	N 32.3
16	3,5—Me_2	77	295° dec.	YN	$C_{12}H_{14}N_6O$	N 32.6	N 32.7
17	2,6—Et_2	81	>300°	ON	$C_{14}H_{18}N_6O$	N 29.4	N 29.2
18	2,3—Cl_2	73	>300°	ON	$C_{10}H_8Cl_2N_6O$	Cl 23.7	Cl 23.5
19	2,4—Cl_2	75	>300°	DaBnN	$C_{10}H_8Cl_2N_6O$	Cl 23.7	Cl 23.4
20	3,5—Cl_2	85	>300°	BYN	$C_{10}H_8Cl_2N_6O$	Cl 23.7	Cl 23.5
21	2,5—Br_2	87	240° dec.	DRN	$C_{10}H_8Br_2N_6O$	Br 41.2	Br 41.0
22	2,5—$(MeO)_2$	76	>300°	RBnN	$C_{12}H_{14}N_6O_3$	N 29.0	N 29.2
23	2—Cl—6—Me	80	>300°	YN	$C_{11}H_{11}ClN_6O$	Cl 12.7	Cl 12.6
24	2,5—Cl_2—4—NO_2	85	285° dec.	YN	$C_{10}H_7Cl_2N_7O_3$	Cl 20.6	Cl 20.3
25	4—Cl—2,5—$(MeO)_2$	70	>300°	DRN	$C_{12}H_{13}ClN_6O_3$	Cl 10.9	Cl 10.7
26	5—Cl—2,4—$(MeO)_2$	75	277° dec.	DRN	$C_{12}H_{13}ClN_6O_3$	Cl 10.9	Cl 10.6

[a] See footnote [a] of Table I.

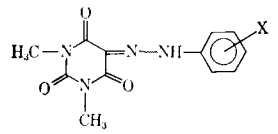


Table III—Characteristics of 1,3-Dimethyl-5-arylhydrazonoalloxan Derivatives

No.	X	Yield, %	M.p.	Color[a]	Formula	Analysis, % Calcd.	Found
1	H	75	255–256°	YN	$C_{12}H_{12}N_4O_3$	N 21.5	N 21.2
2	2—NO_2	65	244–245°	ON	$C_{12}H_{11}N_5O_5$	N 23.0	N 23.2
3	3—NO_2	75	232–233°	ON	$C_{12}H_{11}N_5O_5$	N 23.0	N 23.3
4	4—Cl	75	245–246°	YN	$C_{12}H_{11}ClN_4O_3$	Cl 12.1	Cl 12.0
5	2—Me	70	238–239°	PeYN	$C_{13}H_{14}N_4O_3$	N 20.4	N 20.2
6	2—Et	80	200–201°	BYN	$C_{14}H_{16}N_4O_3$	N 19.4	N 19.5
7	3—MeO	78	151–152°	BGrN	$C_{13}H_{14}N_4O_4$	N 19.3	N 19.1
8	4—MeO	85	195–196°	YP	$C_{13}H_{14}N_4O_4$	N 19.3	N 19.0
9	2,3—Cl_2	70	260–265° dec.	PeYN	$C_{12}H_{10}Cl_2N_4O_3$	Cl 21.6	Cl 21.3
10	2,4—Cl_2	90	244–245°	YN	$C_{12}H_{10}Cl_2N_4O_3$	Cl 21.6	Cl 21.5
11	3,5—Cl_2	85	254–255° dec.	ON	$C_{12}H_{10}Cl_2N_4O_3$	Cl 21.6	Cl 21.2
12	2,4—Br_2	75	247–248°	YGrN	$C_{12}H_{10}Br_2N_4O_3$	Br 38.3	Br 38.0
13	2,3—Me_2	80	203–204°	PeYN	$C_{14}H_{16}N_4O_3$	N 19.4	N 19.2
14	2,5—Me_2	80	246–247°	YN	$C_{14}H_{16}N_4O_3$	N 19.4	N 19.1
15	2,6—Me_2	75	225–226°	PeYP	$C_{14}H_{16}N_4O_3$	N 19.4	N 19.0
16	3,4—Me_2	85	240–241°	GrN	$C_{14}H_{16}N_4O_3$	N 19.4	N 19.6
17	2,5—Cl_2—4—NO_2	65	278–279°	PeYF	$C_{12}H_9Cl_2N_5O_5$	Cl 19.0	Cl 19.2
18	4—Cl—2,5—$(MeO)_2$	75	288–289°	ORN	$C_{14}H_{15}ClN_4O_5$	Cl 10.0	Cl 9.7
19	5—Cl—2,4—$(MeO)_2$	80	245–246°	ORN	$C_{14}H_{15}ClN_4O_5$	Cl 10.0	Cl 9.8

[a] See footnote [a] of Table I.

The details of other 2,4-diamino-6-hydroxy-5-arylazopyrimidines are given in Table II.

1,3 - Dimethyl - 5 - (4 - nitrophenylhydrazono)alloxan—1,3 - Dimethylbarbituric acid (1.56 g., 0.01 mole) was dissolved in water (20 ml.) and cooled to 0°. This was then treated with a stirred solution of 4-nitrobenzenediazonium chloride obtained from 4-nitroaniline (1.38 g., 0.01 mole) in concentrated hydrochloric acid (5 ml.) containing sodium acetate (5.0 g.). The solid, which separated, was collected, washed well with water, and obtained as yellow needles (2.75 g., 90%), m.p. 303–304° (from ethanol–DMF).

Anal.—Calcd.: .... Found: N, 22.8; $C_{12}H_{11}N_5O_5$ requires N, 23.0%.

The details of other 1,3-dimethyl-5-arylhydrazonoalloxans are given in Table III.

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