SYNTHESIS OF 2,6-DIAMINO-8-ARYLPURINES USING AROMATIC ALDEHYDES

V. S. Kuznetsov and A. L. Remizov

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2,6-Diamino-8-arylpurines were obtained by condensation of 2,4,5,6-tetraaminopyrimidine with aromatic aldehydes with nitrobenzene as the oxidizing agent in the presence of p-toluenesulfonic acid or divalent copper.

2,6-Diamino-8-arylpurines are capable of inhibiting the growth of microbes [1, 2] owing to their interference in the metabolism of folic acid and purines, and they are of interest as potential antifolic and antitumorigenic preparations [3]. However, a relatively small number of 2,6-diamino-8-arylpurines have been studied in this respect [1, 2, 4].

8-Arylpurines are usually obtained by cyclization of the corresponding 4-amino-5-acylaminopyrimidines [2, 4, 5]. The oxidative condensation of 1,2-diamines with aldehydes, which is widely used for the synthesis of benzimidazoles [6, 7], has been previously used in the purine series only for the preparation of xanthine derivatives [7, 8]. In the present study this condensation was used for the synthesis of 2,6-diamino-8-arylpurines (IV and VI).

Starting from 2,4,5,6-tetraaminopyrimidine (I), obtained by catalytic hydrogenation of 2,4,6-triamino-5-nitrosopyrimidine [9], we synthesized azomethines (II and XI, Table 1) for conversion to purines (IV and VI). In the case of some 2,4,6-triamino-5-(N-benzylideneamino)pyrimidines (II), the oxidative cyclization occurs even under the influence of air oxygen in weakly acidic aqueous media (method A), but this method does not have preparative value because of the considerable amount of impurities formed. 2,6-Diamino-8-phenylpurine (IVa) was obtained in low yield in an attempt to oxidize azomethine IIa by heating with nitrobenzene (method in [7]).

Since acid catalysis might have proved useful in the transformation under consideration, the oxidative cyclization of azomethines II by nitrobenzene in the presence of acids was investigated. Passage of hydrogen chloride through the reaction medium proved to be ineffective, while the use of p-toluenesulfonic acid (2 moles per mole of azomethine) makes it possible to readily isolate products in the form of well-crystallized p-toluenesulfonates and leads to an accelerated reaction, a decrease in the temperature needed, and an increase in the purity and yields of 2,6-diamino-8-phenylpurines (IV) (Table 2, method B). Practically the same results were obtained when equimolar amounts of 2,4,5,6-tetraaminopyrimidine p-toluene sulfonate (Ia) and the corresponding aromatic aldehyde were used in place of azomethines II.

Method B proved to be unsuitable in the case of 1-methyl-2-formylpyridinium bromide (V), and a stronger oxidizing agent – Cu^{2+} ions in weakly acidic media (method C) – was therefore used in the preparation of 2,6-diamino-8-(1-methyl-2-pyridino)purine (VI). A number of other 2,6-diamino-8-arylpurines (Table 2) were similarly synthesized. The yields in this case usually did not differ substantially from those obtained via method B, but the purity of the products, which was monitored by means of thin-layer chromatography (TLC) on silica gel, was sometimes lower. On the whole, methods B and C are of about equal value, but the latter apparently may find more application.

N. N. Petrov Scientific-Research Institute of Oncology, Ministry of Health of the USSR, Leningrad.
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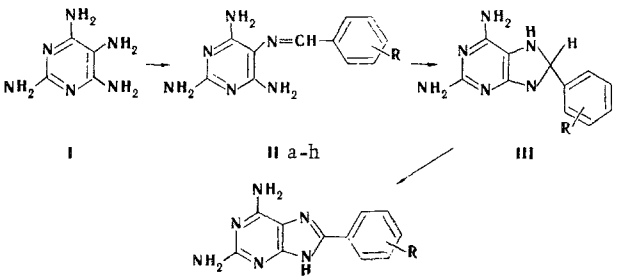
TABLE 1. 2,4,6-Triamino-5-(N-arylmethyleneamino)pyrimidines (IIa-h, XI)

Compound	Aryl group	Crystallization solvent	Empirical formula	Found, %		Calc., %		Yield, %
				N	E[a]	N	E	
IIa	C_6H_5	Alcohol	$C_{11}H_{12}N_6$	37,1	229	36,9	228	70
IIb	$3\text{-}HOC_6H_4$	Alcohol	$C_{11}H_{12}N_6O$	34,5	246	34,9	244	85
IIc	$4\text{-}HO\text{-}3\text{-}CH_3OC_6H_3$	Alcohol	$C_{12}H_{14}N_6O$	30,6	278	30,7	274	75
IId	$4\text{-}OHCC_6H_4$	Methyl cellosolve	$C_{12}H_{12}N_6O$	32,5	133	32,8	128	80
IIe	$4\text{-}O_2NC_6H_4$	DMF	$C_{11}H_{11}N_7O_2$	35,8	281	35,9	273	90
IIf	$4\text{-}(C_2H_5)_2NC_6H_4$	Alcohol	$C_{15}H_{21}N_7$	33,0	299	32,8	299	60
IIg	$4\text{-}(CH_3)_2NC_6H_4$	Alcohol	$C_{13}H_{17}N_7$	35,9	276	36,2	271	70
IIg dihydrochloride		Aqueous alcohol + NH_4Cl	$C_{13}H_{17}N_7 \cdot 2HCl \cdot H_2O$[b]	27,0	372	27,1	362	75
IIh dihydrochloride	$4\text{-}(CCH_2CH_2)_2C_6H_4$	Aqueous alcohol + LiCl	$C_{15}H_{19}Cl_2N_7 \cdot 2HCl \cdot H_2O$[c]	21,3	469	21,3	459	70
XI hydrobromide of the bromide		Methanol	$C_{11}H_{14}BrN_7 \cdot HBr \cdot H_2O$[d]	23,2	430[e]	23,2	423	65

a) From the results of volumetric determination of the aldehyde component by the method in [17].
b) Found: Cl 19.4%. Calculated: Cl 19.6%.
c) Found: Cl 31.5%. Calculated: Cl 31.0%.
d) Found: Br 38.3%. Calculated: Br 37.8%.
e) Determined by nitritometry.

We attempted to use method B as a modification of the method in [7] for the synthesis of benzimidazoles, but in this case acid catalysis to a great degree favors side transformation. Thus, 1-benzyl-2-phenylbenzimidazole (IX) and N-benzyl-o-phenylenediamine (X) were found in the reaction medium in addition to 2-phenylbenzimidazole (VIII) in the reaction of o-phenylenediamine (VII) with benzaldehyde in the presence of nitrobenzene and p-toluenesulfonic acid. The formation of X is an indirect indication of the occurrence of acid-catalyzed redox disproportionation of the intermediate 2-phenyl-1,2-dihydrobenzimidazole. A similar transformation is known for 1-substituted [10] and 1,3-disubstituted [11] 1,2-dihydrobenzimidazoles, but it has not been noted for compounds that do not contain substituents in the 1 and 3 positions.

A similar disproportionation of 2,6-diamino-7,8-dihydro-8-phenylpurines (III) does not occur under the conditions of method B; III are apparently completely protonated in the pyrimidine ring (the structurally similar 2,4,6-triaminopyrimidines have pK_a values of 6.8 [12]), and this hinders bimolecular (with respect to the imidazole derivatives [10]) disproportionation.



I II a-h III

IV a-g

II a R=H; b R=3-OH; c R=4-OH, R′=3-OCH_3; d R=4-CHO; e R=4-NO_2; f R=4-$N(C_2H_5)_2$; g R=4-$N(CH_3)_2$; h R=4-$N(CH_2CH_2Cl)_2$; IV a R=H; b R=4-NO_2; c R=3-NO_2; d R=2-NO_2; e R=4-$N(CH_3)_2$; f R=2-OH; g R=4-CHO

EXPERIMENTAL

2,4,5,6-Tetraaminopyrimidine p-Toluenesulfonate (Ia). 2,4,6-Triamino-5-nitrosopyrimidine, obtained via the method in [9], was hydrogenated in methyl cellosolve over Raney nickel at atmospheric pressure.

TABLE 2. 2,6-Diamino-8-arylpurines (IVa-g, VI)

Compound	Aryl group	Crystallization or reprecipitation solvent	Empirical formula	Found, %			Calc., %			R_f (50% EtOH saturated with sodium tetraborate)	UV spectrum in 0.1 M HCl		Yield, % (method)		
				N	C (S)	H (E)[e]	N	C (S)	H (E)		λ_{max}, nm	lg ε	A	B	C
IVa	C_6H_5	—	$C_{11}H_{10}N_6$	37,0			37,2			0,72	226; 314	4,34; 4,41		90	
IVa p-toluenesulfonate		Methyl cellosolve	$C_{11}H_{10}N_6 \cdot C_7H_8O_3S$	21,1	(8,0)		21,2	(8,0)					70[a]	70	70[a]
IVb[b]	4-$O_2NC_6H_4$	0.1 N NaOH in 50% ethanol precipitation with CH_3COOH	$C_{11}H_9N_7O_2$	36,2			36,1			0,63	246; 350	4,20; 4,29		7[c]	70
IVc[b]	3-$O_2NC_6H_4$	Dimethylformamide – ether	$C_{11}H_9N_7O_2$	36,0			36,1			0,60	222; 268; 314	4,42; 4,19; 4,33		70[c]	
IVd	2-$O_2NC_6H_4$	0.1 N NaOH in 50% ethanol precipitation with CH_3COOH	$C_{11}H_9N_7O_2$	35,9	48,5	3,4	36,1	48,7	3,3	0,68	258; 286	4,16; 4,18		55[c]	35
IVe	4-$(CH_3)_2NC_6H_4$		$C_{13}H_{15}N_7 \cdot 0{,}5H_2O$	34,4	54,3	5,5	34,2	54,4	5,6	0,51	225; 319	4,40; 4,38		90	
IVd sulfate		3 *N* H_2SO_4	$C_{13}H_{15}N_7 \cdot H_2SO_4$	26,8	(8,7)		26,7	(8,7)						95[c]	55
IVf	2-HOC_6H_4	Methyl cellosolve – ether	$C_{11}H_{10}N_6O$	34,8	54,4	4,2	34,7	54,6	4,1	0,83[d]	256; 326	4,08; 4,36		85[c]	40
IVg sulfate	4-$OHCC_6H_4$	1 N H_2SO_4	$C_{11}H_{10}N_6O \cdot 0{,}5H_2SO_4 \cdot 0{,}5H_2O$	27,0	(5,0)	(311)	26,9	(5,1)	(312)	0,77	338	4,31	40		10
VI		Methanol – ether	$C_{11}H_{12}BrN_7 \cdot HBr \cdot H_2O$[f]	23,4			23,3			0,15[d] 0.50[g]	255; 350	4,06; 4,16		0	75

* This is the yield of sulfate (identified by comparison with a sample obtained via the method in [5]) with respect to thin-layer chromatography on silica gel and the UV spectra.

b) This compound was identified by comparison of the UV spectra with the data in [18]. The IR spectrum contains a system of bands of stretching vibrations of the NH_2 and NH groups (3050-3500 cm^{-1}), two characteristic intense bands of the scissors vibrations of the NH_2 groups near 1660 and 1620 cm^{-1}, and bands of the stretching vibrations of aromatic rings at 1590 and 1510 cm^{-1}. The band of asymmetrical stretching vibrations of the NO_2 group in the IR spectrum of m-isomer IVc is well resolved and is observed near 1540 cm^{-1}.

c) The yield of the corresponding p-toluenesulfonate is indicated.

d) In methanol–acetic acid–water (7 : 2 : 2).

e) This is the equivalent weight; the functional aldehyde group was determined volumetrically by the method in [17].

f) Found: Br 38.3%. Calculated: Br 38.0%.

g) In methanol–2 N HCl (7 : 3).

The catalyst was removed, and an equivalent amount of p-toluenesulfonic acid was added to the solution. The solvent was removed to a small volume by vacuum distillation, and the precipitate was removed by filtration, washed with alcohol, and dried to give 65-70% of a product containing 96% of the major substance* (suitable for preparative purposes without additional purification). Compound Ia was crystallized from water for elementary analysis. Found: N 26.9; S 10.3%. $C_4H_8N_6 \cdot C_7H_8O_3S$. Calculated: N 26.9; S 10.2%.

1-Methyl-2-formylpyridinium Bromide (V). A mixture of 25 mmole of 1-methyl-2-hydroxymethylpyridinium bromide [14] and 12.5 mmole of selenious acid in 50 ml of dioxane was heated at 100° for 6 h, after which hydrogen sulfide was bubbled through the mixture until the selenious acid had been completely reduced. The solvent was removed to dryness by vacuum distillation, and the residue was treated with 50 ml of warm water. The precipitated selenium and sulfur were removed by filtration, and the filtrate was evaporated to dryness in vacuo. The residue was dissolved in 10 ml of water, and the solution was filtered again and evaporated to dryness in vacuo. The resulting crystals were treated with 5 ml of methanol and removed by filtration to give a product in ~30% yield. Another 35% of product was obtained from the filtrate by precipitation with ether. The product turned yellow on heating to 110° and had mp 123-126° (dec., from methanol–ether). Found: Br 39.4%. C_7H_8BrNO. Calculated: Br 39.6%.

1-Methyl-2-formylpyridinium Chloride 2,4-Dinitrophenylhydrazone. A 2-g sample of KCl was added to 2.5 mmole of aldehyde V in 20 ml of a hot saturated solution of 2,4-dinitrophenylhydrazine in 2 N hydrochloric acid. The mixture was cooled, and the yellow crystals were removed by filtration and washed successively two times each with 1 ml of 2 N hydrochloric acid, 1 ml of methanol, and ether to give 30% of a product with mp 251-254° (dec., from 2 N hydrochloric acid). Found: N 19.9; Cl 10.1%. $C_{13}H_{14}ClN_5O_4 \cdot H_2O$. Calculated: N 19.7; Cl 10.0%.

2,4,6-Triamino-5-(N-arylmethyleneamino)pyrimidines (IIa-g, XI). A solution of 10 mmole of aromatic aldehyde in 10 ml of alcohol was added to a solution of 10 mmole of tetraaminopyrimidine hydrochloride (Ib) in 30 ml of 0.1 N hydrochloric acid. After 10 min the mixture was made alkaline to pH 8-9 with ammonia and cooled in an ice bath. The yellow or red crystalline precipitate was removed by filtration, washed with water and ether, and dried in a desiccator. As a rule, the substances did not have characteristic melting points (Table 1).

2,4,6-Triamino-5-[N-(4-dimethylamino)benzylideneamino]pyrimidine (IIg) Hydrochloride. A 20-mmole sample of p-dimethylaminobenzaldehyde and 6 ml of 6 N HCl were added to a solution of 20 mmole of tetraaminopyrimidine hydrochloride (Ib) in 60 ml of 0.1 N HCl, and the mixture was heated on a water bath until the aldehyde had dissolved. A 15-g sample of NH_4Cl was added to the hot solution, and the mixture was allowed to stand overnight. The precipitated yellow crystals were washed with ice water, alcohol, and ether (Table 1).

2,4,6-Triamino-5-{N-[4-di(2-chloroethyl)amino]benzylideneamino}pyrimidine (IIh) Hydrochloride. This compound was similarly obtained in aqueous alcohol and was salted out with lithium chloride.

2,4,6-Triamino-5-(1-methyl-2-pyridinomethyleneamino)pyrimidine Bromide Hydrobromide (XI). A 4-mmole sample of aldehyde V and 4 mmole of tetraaminopyrimidine hydrobromide (Ic) were dissolved by heating in 5 ml of water. The solution was cooled, and the orange precipitate was removed by filtration, washed twice with 1 ml of ice water and ether, and dried in a desiccator (Table 1).

2,6-Diamino-8-arylpurines (IVa-g, VI)

Method A. 2,6-Diamino-8-(4-formylphenyl)purine Sulfate (IVg). Air was bubbled for ~15 h through a solution of 10 mmole of azomethine IId and 0.01 g of $CuSO_4$ in 20 ml of 0.01 M acetate buffer with pH 4.5 and 5 ml of methyl cellosolve at 80-90°. The mixture was then cooled, and the orange precipitate was removed by filtration and washed with water and alcohol. Crystallization gave a colorless finely crystalline substance (Table 2).

Method B. 2,6-Diamino-8-phenylpurine p-Toluenesulfonate (IVa). A mixture of 5 mmole of tetraaminopyrimidine p-toluenesulfonate (Ia), 5 mmole of p-toluenesulfonic acid, 5 mmole of benzaldehyde, 2 ml of isoamyl alcohol, and 5 ml of nitrobenzene was stirred and refluxed for 4 h. The completion of the reaction was monitored by testing with 2,4-dinitrophenylhydrazine. The mixture was allowed to stand over-

* The percentage of 2,4,5,6-tetraaminopyrimidine was determined by potentiometric titration with sodium nitrite solution; the percentage of acid was determined by a volumetric method after passing a solution of the salt through a column filled with KU-2 cation-exchange resin.

night, and the resulting colorless crystals were removed by filtration and washed with methanol and ether to give a product with mp 330° (dec.) (Table 2).

2,6-Diamino-8-phenylpurine (IVa). This compound was obtained by treatment of the p-toluenesulfonate with a warm dilute solution of ammonium hydroxide to pH 8. The product was a colorless finely crystalline substance. According to TLC and the UV spectrum, it was identical to a sample obtained via the method in [5].

2,6-Diamino-8-(p-, m-, o-nitrophenyl)purines (IVb-d) and 2,6-Diamino-8-(o-hydroxyphenyl)purine (IVf). These compounds were similarly obtained (Table 2).

Method C. 2,6-Diamino-8-(4-dimethylaminophenyl)purine Sulfate (IVe). A mixture of 10 mmole of tetraaminopyrimidine hydrochloride (Ib), 10 mmole of p-dimethylaminobenzaldehyde, and 60 ml of methyl cellosolve was stirred and refluxed for 1 h, after which 21 mmole of copper acetate was added, and the mixture was refluxed for 4 h. The precipitate was removed by filtration of the hot mixture and washed with methanol. It was then treated with 200 ml of 2N HCl until it had dissolved completely, and H_2S was bubbled through the mixture until the precipitation of copper sulfide was complete. The precipitate was separated, and the filtrate was vacuum-evaporated to dryness. The residue was dissolved in 50 ml of 6 N H_2SO_4, and the solution was treated with charcoal. The mixture was filtered, and the hot filtrate was diluted to twice its volume with water and cooled. The precipitated yellow crystals were removed by filtration and washed with water, methanol, and ether (Table 2).

2,6-Diamino-8-(1-methyl-2-pyridino)purine Bromide Hydrobromide (VI). A mixture of 4 mmole of azomethine (XI) and 8.4 mmole of copper acetate in 25 ml of methyl cellosolve was stirred and refluxed for 8 h. The brown precipitate was removed by filtration, washed with methanol, and dissolved by heating in 50 ml of 2 N HBr. Hydrogen sulfide was passed through the hot solution until the precipitation of copper sulfide was complete, and the precipitate was removed by filtration. The filtrate was vacuum-evaporated to dryness to give yellow crystals (Table 2).

Reaction of o-Phenylenediamine (VII) and Benzaldehyde under the Conditions of Method B. Benzaldehyde, VII, p-toluenesulfonic acid, and nitrobenzene in a molar ratio of 1 : 1 : 1 : 10 were dissolved in an organic solvent (isoamyl alcohol, methyl cellosolve, or chlorobenzene) or were mixed without a solvent and allowed to stand at a fixed temperature between 40 and 150°. In all cases, a test with 2,4-dinitrophenylhydrazine indicated rapid disappearance of the benzaldehyde. Compound VII (R_f 0.32), 2-phenylbenzimidazole (VIII) (R_f 0.25), 1-benzyl-2-phenylbenzimidazole (IX) (R_f 0.50), and N-benzyl-o-phenylenediamine (X) (R_f 0.54) were detected in the reaction medium by TLC on silica gel with benzene–methanol (10 : 1). In the cyclohexane–benzene (4 : 1) system, in which the other components of the mixture remain at the start, X has R_f 0.15. Compounds VIII, IX, and X were isolated and purified by crystallization, reprecipitation, and treatment of solutions of the p-toluene sulfonates and bases with adsorbents. The yield of VIII with mp 290-291° (291-292° [7]) was 40%, the yield of IX with mp 134-135° (134° [15]) was 15%, and the yield of X with mp 74-75° (75° [16]) was 2%. The identification of the substances was confirmed by mixed-melting-point determinations with authentic samples.

In all cases, the TLC was carried out on Silufol UV-254 chromatographic plates. The spots were detected by means of a UV lamp or in iodine vapors. The IR spectra of mineral-oil suspensions were recorded with a UR-10 spectrometer, while the UV spectra were recorded with an SF-4A spectrophotometer.

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