associates for infrared and ultraviolet absorption measurements, and to G. Staffen and Miss I. N. Pratt for technical assistance.

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Pyrimidines. VII. 2-Amino-4-(substituted anilino)pyrimidines[1]

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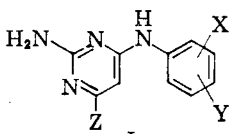
Received October 13, 1961

Arylaminopyrimidines of the general formula (I) have demonstrated a broad spectrum of pharmacological applications, including the antimalarials,[2] analgesic agents,[3] agents for the *Trypanosoma rhodesiense* infections,[4] antagonists to the folic-folinic acid system,[5] and bacteriostatic agents.[6-8] Rose and co-workers have suggested that this type of compound might act as a riboflavin antago-



I

nist.[2] Hence the synthesis of certain arylaminopyrimidines is logically incorporated in our general study of pyrimidines in the effort to obtain more information in the search for antitumor agents.

An extensive literature search indicated that very few of these 4-arylaminopyrimidines (I) where Z = CH_3, NH_2, OH, SH and Cl have been synthesized. In all cases the aniline-substitution is either at the *para* position or at the aniline nitrogen atom.

Existing methods for the preparation of these compounds are quite similar. Banks[3] has treated 2-amino-4-chloro-6-methylpyrimidine with aniline in aqueous ethanol, catalyzed by a trace of acid, to obtain 2-amino-4-anilino-6-methylpyrimidine. This general method of synthesis has been extended to include other 2-amino-4-(substituted anilino)-6-methylpyrimidines,[2,9,10] 2-amino-4-chloro-6-(substituted anilino)pyrimidines,[2,3] 2,4-diamino-6-(substituted anilino)pyrimidines,[4,9] and 2-amino-6-(substituted anilino)-4-pyrimidinols.[9]

When an *ortho* substituted aniline was used, according to the known procedures, the reaction failed to proceed. This prompted the investigation of a general method that could apply to all anilines. Peters and co-workers[11] have reported a fusion method for the preparation of 2-(methylthio)-4-(2',6'-dichloroanilino)-5-carbethoxypyrimidine. A modification of this procedure has been utilized for the preparation of arylaminopyrimidines (I), where Z = CH_3, NH_2, and Cl.

Since 2-amino-4-chloro-6-(substituted anilino)-pyrimidines can be prepared quite readily by fusion, we have used these chloro compounds for the preparation of the corresponding hydroxy and thio derivatives (I, Z = OH, SH). Various attempts to convert these chloro groups under mild conditions have failed, due to the fact that chloro compounds of this type are extremely unreactive towards nucleophilic substitution. In order to convert these chloro groups, it was necessary to use sodium hydroxide or sodium hydrosulfide heated in ethylene glycol at 150°. These reactions proceed readily in 65–85% yield. By this procedure all the arylaminopyrimidines (I, Z = SH, OH) have been synthesized.

The compounds have been submitted for general screening at the Cancer Chemotherapy National Service Center.

EXPERIMENTAL[12]

Preparation of arylaminopyrimidines (I, Z = NH_2, CH_3, Cl, SH, OH). *Method A.* (See Tables I, II, and III.) One milliliter of concentrated hydrochloric acid was added to a mixture of chloropyrimidine (0.1 mole) and aniline (0.1 mole) in a round-bottom flask. The flask was immersed in an oil bath preheated to 175°. When the internal temperature reached 120° a complete melt resulted. At 155° an exothermic reaction took place and the temperature rose spontaneously to 185°. This temperature was maintained for 20 min. and the melt cooled. The glass-like substance was dissolved in 200 ml. of dilute hydrochloric acid, treated with charcoal, and filtered. The clear filtrate was made alkaline with ammonia solution. The white crystalline arylaminopyrimidine deposited on cooling. The product was filtered, dried at 80°, and recrystallized from a mixture of water and ethanol.

Method B. (See Table IV). To 150 ml. of ethylene glycol,

(1) This investigation was supported by research contract SA-43-ph-3025 from the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service.

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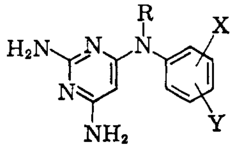
(12) All melting points were taken on a Thomas-Hoover melting point apparatus. The ultraviolet absorption spectra were determined with a Beckman DK-2.

TABLE I

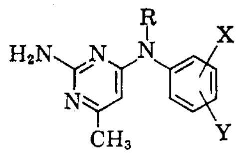
2,6-DIAMINO-4-(SUBSTITUTED ANILINO)PYRIMIDINES



X	Y	R	%, Yield	M.P.	U.V. Absorption pH 1 λ_{max}	pH 1 $\epsilon \times 10^{-3}$	pH 11 λ_{max}	pH 11 $\epsilon \times 10^{-3}$	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	H	H	78	172–174	288	21.3	234 287	15.2 19.1	59.7	5.5	34.8	59.5	5.3	34.6
H	H	CH_3	72	193–194	285	21.7	280	14.6	61.2	6.1	32.5	61.0	6.0	32.2
H	2-CH_3	H	79	182–183	281	21.5	277	15.5	61.2	6.1	32.5	60.8	6.1	32.5
H	3-CH_3	H	76	129–130	288	21.1	287	18.9	61.2	6.1	32.5	61.2	5.9	32.3
H	4-CH_3	H	84	172–173	287	22.8	233 285	16.6 20.0	61.2	6.1	32.5	61.4	6.0	32.3
H	4-CH_3O	H	87	179–180	285	24.4	283	20.3	57.3	5.7	30.3	57.1	6.0	30.4
H	4-HOC_2H_4	H	81	146–148	288	21.6	287	19.6	58.7	6.2	28.6	58.3	6.4	28.3
H	4-F	H	81	175–177	285	19.7	283	16.2	54.7	4.6	31.9	55.0	4.7	31.8
H	2-Cl	H	71	175–176	282	20.0	281	14.8	50.5	4.6	29.7	50.2	4.4	29.8
H	3-Cl	H	78	160–161	293	23.3	289	22.6	50.5	4.6	29.7	50.9	4.6	30.0
H	4-Br	H	90	175–176	293	25.2	291	24.4	42.9	3.6	25.0	42.6	3.5	25.0
3-CH_3	4-CH_3	H	83	163–164	287	22.2	285	19.4	62.6	6.6	30.4	62.4	6.4	30.2
4-CH_3	3-Cl	H	87	172–173	290	23.6	288	22.2	53.0	4.8	28.0	52.7	4.7	27.8
3-Cl	4-Cl	H	92	185–186	293	27.4	292	19.7	44.5	3.4	25.9	44.3	3.5	25.8

TABLE II

2-AMINO-6-METHYL-4-(SUBSTITUTED ANILINO)PYRIMIDINES



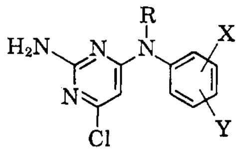
X	Y	R	% Yield	M.P.	U.V. Absorption pH 1 λ_{max}	pH 1 $\epsilon \times 10^{-3}$	pH 11 λ_{max}	pH 11 $\epsilon \times 10^{-3}$	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	H	CH_3	74	148–149	279	13.9	292	13.5	67.7	6.6	26.1	67.4	6.4	26.4
H	H	HOC_2H_4	67	162–163	278	13.9	291	12.9	63.9	6.6	22.9	63.7	6.2	22.9
H	3-CH_3	H	83	142–143	289	17.1	297	18.8	67.7	6.6	26.1	67.6	6.5	26.0
H	4-CH_3	H	91	224–225	289	17.1	297	17.9	67.7	6.6	26.1	68.0	6.5	25.9
H	4-CH_3O	H	89	222–223	288	15.7	295	16.3	62.7	6.1	24.3	62.8	6.0	24.3
H	3-C_2H_5O	H	64	159–160	289	16.1	300	18.3	63.9	6.6	22.9	63.9	6.4	23.0
H	4-HOC_2H_4	H	80	204–205	289	18.3	297	18.7	63.9	6.6	22.9	63.9	6.6	22.7
H	2-Cl	H	67	175–177	278	14.8	290	14.6	56.3	4.7	23.9	56.3	4.8	24.0
H	3-Cl	H	59	147–148	290	19.7	300	21.5	56.3	4.7	23.9	56.6	4.5	23.8
H	2-Br	H	78	172–173	280	15.1	291	15.1	47.4	4.0	20.2	47.2	3.8	20.2
H	4-Br	H	88	227–228	292	20.5	300	22.6	47.4	4.0	20.2	47.1	4.0	20.3
H	4-CN	H	53	215–216	303	32.8	309	38.6	63.9	4.9	31.1	63.6	4.6	31.0
2-CH_3	5-CH_3	H	67	191–192	275	12.8	289	13.4	68.3	7.0	24.5	68.0	6.8	24.6
3-CH_3	4-CH_3	H	88	213–214	289	16.0	297	17.1	68.3	7.0	24.5	68.2	6.8	24.3
4-CH_3	3-Cl	H	81	185–186	290	21.4	298	22.1	58.1	5.3	22.5	58.5	5.3	22.5
3-Cl	4-Cl	H	96	206–207	293	23.7	302	25.0	50.2	3.7	20.8	49.9	3.6	20.9

in a round bottom flask, was added 10 g. of 2-amino-6-chloro-4-(substituted anilino)pyrimidine and 10 g. of sodium hydroxide. The flask was immersed in an oil bath preheated to 160°. A complete solution resulted when the internal temperature reached 110°. At 150° an exothermic reaction took place and the temperature reached 175°. Heating was continued for 30 min. The yellow-brown solution was cooled and then added to 500 ml. of water, treated with charcoal, and filtered. The clear yellow filtrate was acidified while hot with glacial acetic acid to precipitate 2-amino-6-hydroxy-4-(substituted anilino)pyrimidine. The compound was filtered while hot, dried, and recrystallized from a mixture of water and ethanol.

Method C. (See Table V.) This method is the same as Method B, except that sodium hydrosulfide was used in place of sodium hydroxide.

TABLE III

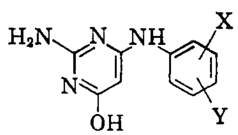
2-Amino-6-chloro-4-(substituted anilino)pyrimidines



X	Y	R	%, Yield	M.P.	U.V. Absorption Ethanol λ_{max}	$\epsilon \times 10^{-3}$	Calcd. C	H	N	Found C	H	N
H	H	CH_3	68	177–178	268	11.6	56.5	4.7	23.9	56.8	4.5	23.7
					300	20.1						
H	2-CH_3	H	54	230–231	292	12.2	56.5	4.7	23.9	56.1	4.9	23.5
H	3-CH_3	H	66	166–167	263	12.0	56.5	4.7	23.9	56.5	4.7	23.9
					302	21.6						
H	4-CH_3	H	78	236–238	264	13.2	56.5	4.7	23.9	56.2	4.6	23.5
					302	20.2						
H	4-CH_3O	H	74	213–215	258	12.0	52.7	4.4	22.3	52.4	4.2	22.2
					300	18.3						
H	2-C_2H_5O	H	77	153–154	253	10.7	55.5	4.9	21.2	55.7	5.1	21.2
					304	16.7						
H	4-HOC_2H_4	H	73	191–192	267	11.9	54.2	5.0	21.1	54.5	4.6	21.0
					302	19.9						
H	2-Cl	H	76	188–189	255	9.4	47.0	3.0	22.0	47.0	3.4	22.2
					297	14.8						
H	3-Cl	H	74	154–155	264	10.0	47.0	3.0	22.0	47.1	2.7	22.0
					303	18.9						
H	2-Br	H	63	194–195	296	14.7	40.1	3.7	18.7	40.4	3.4	18.4
H	4-Br	H	84	246–248	265	15.3	40.1	3.7	18.7	39.8	3.7	18.7
					304	28.2						
H	4-CN	H	52	279–281	245	10.3	53.9	3.3	28.5	54.2	3.1	28.3
					275	12.8						
					323	25.8						
3-CH_3	4-CH_3	H	78	227–229	267	14.7	57.8	5.3	22.5	57.6	5.0	22.1
					303	27.1						
4-CH_3	3-Cl	H	78	197–199	263	14.2	49.1	3.7	20.8	49.0	4.0	20.8
					304	25.0						
3-Cl	4-Cl	H	81	216–217	267	14.5	41.8	2.8	19.4	42.1	3.0	19.2
					304	28.9						

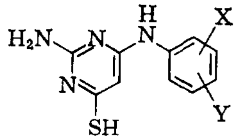
TABLE IV

2-Amino-6-hydroxy-4-(substituted anilino)pyrimidines



X	Y	%, Yield	M.P.	U.V. Absorption pH 1 λ_{max}	$\epsilon \times 10^{-3}$	pH 11 λ_{max}	$\epsilon \times 10^{-3}$	Calcd. C	H	N	Found C	H	N
H	2-CH_3	70	264–265	273	18.8	276	13.4	61.2	5.6	25.8	61.0	5.7	25.7
H	4-CH_3	83	262–263	278	19.7	286	17.7	61.2	5.6	25.8	61.5	5.8	25.6
H	4-CH_3O	80	295–297	277	18.5	234	14.8	56.8	5.2	24.1	56.9	5.3	23.8
						281	16.0						
H	2-Cl	71	273–274	275	20.3	282	15.8	50.9	3.6	23.6	50.7	4.0	23.6
H	3-Cl	73	259–260	283	18.1	289	21.6	50.9	3.6	23.6	50.9	4.0	23.6
H	4-Br	82	296–298	285	20.0	236	15.0	40.1	3.7	18.7	39.7	3.5	18.8
						290	24.0						
3-CH_3	4-CH_3	87	218–220	279	14.3	225	13.1	62.5	6.2	24.3	62.2	6.2	24.0
						285	14.3						
4-CH_3	3-Cl	81	307–309	281	18.6	224	17.5	49.1	4.9	20.8	48.9	4.8	21.0
						286	21.0						
3-Cl	4-Cl	85	258–259	288	19.0	260	12.7	44.0	3.0	20.6	43.6	3.3	20.4
						295	24.3						

TABLE V
2-AMINO-6-THIO-4-(SUBSTITUTED ANILINO)PYRIMIDINES



				U.V. Absorption									
				pH 1		pH 11		Calcd.			Found		
X	Y	%, Yield	M.P.	λ_{max}	$\epsilon \times 10^{-3}$	λ_{max}	$\epsilon \times 10^{-3}$	C	H	N	C	H	N
H	2-CH_3	63	259–260	237	13.0	243	17.6	56.6	5.2	24.1	56.4	5.0	24.0
				327	34.6	308	21.2						
H	3-CH_3	81	224–226	242	14.8	252	20.5	56.6	5.2	24.1	56.4	5.1	24.1
				326	32.0	314	26.5						
H	4-CH_3	85	284–285	244	12.8	252	17.6	56.6	5.2	24.1	56.5	5.2	24.0
				330	25.5	314	22.7						
H	4-CH_3O	79	238–239	241	12.6	251	17.6	53.1	4.9	22.5	53.1	4.9	22.3
				330	25.2	314	22.7						
H	2-Cl	67	237–238	322	23.6	252	18.0	47.5	3.6	22.0	47.8	3.3	22.0
						310	20.5						
H	3-Cl	80	285–286	240	13.9	253	22.7	47.5	3.6	22.0	47.4	3.3	21.9
				330	33.0	318	31.7						
3-CH_3	4-CH_3	83	220–222	224	38.6	252	15.5	57.3	5.7	22.7	57.6	5.7	22.8
			(dec.)	325	23.2	313	19.0						
4-CH_3	3-Cl	80	261–262	242	13.4	252	20.3	49.5	4.2	21.0	49.4	4.4	20.7
			(dec.)	326	30.4	315	26.2						
3-Cl	4-Cl	85	288–289	242	12.1	255	17.8	41.8	2.8	19.5	41.9	3.0	19.8
			(dec.)	268	10.9	320	26.4						
				332	30.7								

Acknowledgment. The authors wish to express their appreciation to Mr. Wayne H. Nyberg, Miss Phyllis G. Shaul, and Mrs. Carol R. Tuttle for their valuable assistance in performing analytical and instrumental measurements.

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A New Route to Glycosyl Phosphates

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Received October 16, 1961

Currently, there are very few methods available for the preparation of glycosyl phosphates. The direct phosphorylation of the glycosidic hydroxyl group of an otherwise protected sugar[1] has not been used extensively, because of the low yield obtained. The most widely used method, in fact the only practical one, is that involving the reaction of an acylglycosyl halide with some salt of either orthophosphoric acid or a diester thereof. The procedure of Cori, Colowick, and Cori[2] utilizing trisilver phosphate has been used for the preparation of a number of 1-phosphates; generally,[3] but not always,[3a,4] the anomer formed is that with the phosphate group *cis* to the hydroxyl group on carbon two of the sugar. The procedure using "monosilver phosphate"[3c,5] (the silver salt actually present is disilver phosphate[6]) appears to give, normally, the *trans*-anomer, as does the procedure using silver dibenzyl phosphate.[5,7] The use of silver diphenyl phosphate may result in the formation of either anomer, depending on the sugar employed.[1,4,8] Recently, certain improvements in the preparation of aldose 1-phosphates have been brought about by the use of tertiary amine salts, rather than silver salts, of phospho diesters.[9]

The present note describes the preparation of glycosyl phosphates by an entirely different procedure. The fully acetylated sugar is warmed *in vacuo* with anhydrous phosphoric acid; a vigor-

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