tate the crude aldehyde. Recrystallization from methanol gave 2.4 g. (8.6%) of the product as yellow crystals. Addition of phenylhydrazine to the filtrate from which the potassium salt of the aldehyde had precipitated gave an additional 4.3 g. (9.4%) of the phenylhydrazone of the aldehyde.

2,4-Dihydroxy-5-cyano-6-methylpyrimidine. A solution of 0.5 g. of the aldoxime and 10 ml. of acetic anhydride were heated under reflux for 30 min. The hot solution was filtered and cooled to room temperature to precipitate 0.15 g. of crystals, m.p. over 330°; ultraviolet, λ_{max} 273 mμ.

Anal. Calcd. for $C_6H_5N_3O_2$: N, 27.80. Found: N, 27.81. The same product was obtained by refluxing 0.5 g. of the aldoxime with 4.5 ml. phosphoryl chloride. The cooled reaction mixture was poured onto ice-water and the precipitate collected and recrystallized from ethanol to give 0.25 g. (56%) of product.

2,4-Dichloro-5-cyano-6-methylpyrimidine. Dimethylaniline (3 ml.) was added slowly and with cooling to a solution of 0.7 g. of 2,4-dihydroxy-6-methylpyrimidine-5-aldoxime in 6 ml. of phosphoryl chloride. The mixture was refluxed 0.5 hr., cooled, and poured onto ice water. The mixture was extracted with ether and the ether extracts washed with bicarbonate, dried, and evaporated to give a yellow crystalline residue. Recrystallization from petroleum ether (b.p. 60–80°) gave 0.45 g. (57%) of the product, m.p. 93–94°.

Anal. Calcd. for $C_6H_3N_3Cl_2$: N, 22.35. Found: N, 22.54.

2(4?)-Chloro-5-cyano-4(2?)-ethoxy-5-methylpyrimidine. On recrystallization of the 2,4-dichloro compound from ethanol, the 2(4?)-ethoxy compound was obtained as yellow plates, m.p. 134–136°.

Anal. Calcd. for $C_8H_8N_3OCl$: N, 21.27. Found: N, 21.20, 21.42.

Acknowledgment. This study was supported in part by grant CY-2457 from the National Cancer Institute of the National Institutes of Health and in part by grant G-1918 from the National Science Foundation. The authors wish to express their appreciation for this support to Dr. N. R. Smith for his advice and encouragement and to the State Department and the Conference Board of National Research Councils for a Fulbright Travel grant held by one of us (Yuzuru Yamamoto).

LOUISVILLE, KY.

[CONTRIBUTION FROM THE DEPARTMENT OF APPLIED CHEMISTRY, UNIVERSITY COLLEGE OF SCIENCE & TECHNOLOGY, CALCUTTA]

Syntheses of Some Arylamino- and Arylguanidinopyrimidines

DOLLY ROY, SUDHAMOY GHOSH, AND B. C. GUHA

Received February 8, 1960

A number of 6-hydroxy-5-unsubstituted pyrimidines having variously substituted arylamino, or arylguanidino groups at C-2 and/or C-4 positions were synthesized. It has been shown that the condensation of arylamines with 2-methylthio-4-amino-6-hydroxypyrimidine under mild condition yields 2-arylamino-4-amino-6-hydroxypyrimidines and under drastic conditions 2,4-bis(arylamino)-6-hydroxypyrimidines.

Curd and Rose[1] demonstrated that 5-unsubstituted 6-alkyl pyrimidines with amino or substituted amino groups at C-2 and C-4 positions were active as antimalarials. Hitchings,[2] *et al.* showed further that if 2,4-diamino-6-alkylpyrimidines have bulky substituents (for example phenyl, phenoxy, etc.) at the C-5 position, they prove to be strong antagonists of folic acid and some of them possess marked antimalarial[3] and antileukemic[4] properties. In connection with our studies of pyrimidines of potential chemotherapeutic value, it was considered of interest to investigate the biological properties of pyrimidines having hydroxyl group in the 6-position and which had variously substituted amino groups at C-2 and C-4 positions, while C-5 position was kept free. The synthesis of some arylamino- and arylguanidinopyrimidines of this type having various substituents at the *para* position of the benzene ring (I to IV) is being reported here. The pronounced inhibitory effects of some of these compounds on bacterial growth have already been reported in preliminary communications.[5,6]

The pyrimidines of type I were synthesized by the reaction of 2-methylthio-4-amino-6-hydroxypyrimidine[7] (V) with the appropriate arylamines according to the method of Wheeler.[8] The reaction takes place with the elimination of methylthiol when an intimate mixture of equimolecular quantities of V and the corresponding arylamine is heated in an inert atmosphere at a temperature necessary for the mixture to go into solution. This type of displacement was not possible with the compound (VI) in which the C-4 and C-6 positions of pyrimidine ring were occupied by methyl groups (*Cf.* ref. 1). The lability of the methylthio group in compound V may be due to the possibility of tautomerism between V and Va as suggested by Curd and Rose.[1] Apparently this type of reaction does

(1) F. H. Curd and F. L. Rose, *J. Chem. Soc.*, 343 (1946).

(2) G. H. Hitchings, E. A. Falco, H. Vanderwerff, P. B. Russell, and G. B. Elion, *J. Biol. Chem.*, **199**, 43 (1952).

(3) E. A. Falco, L. G. Goodwin, G. H. Hitchings, I. M. Rollo, and P. B. Russel, *Brit. J. Pharmacol.*, 6, 185 (1951).

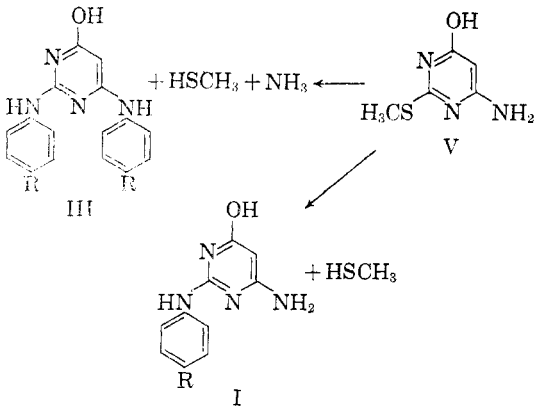
(4) J. H. Burchenal, S. K. Goetchins, C. C. Stock, and G. H. Hitchings, *Cancer Res.*, 12, 255 (1951).

(5) Sudhamoy Ghosh, Dolly Roy, and B. C. Guha, *Nature*, **182**, 187 (1958).

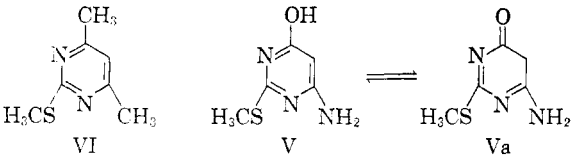
(6) Dolly Roy, S. Ghosh, and B. C. Guha, *Naturwissenschaften*, **45**, 392 (1958).

(7) B. T. Johnson and J. O. Carl, *Am. Chem. J.*, **34**, 175 (1905).

(8) H. L. Wheeler and G. S. Jamieson, *Am. Chem. J.*, **32**, 342 (1904).



not occur with 2-methylthio-4,6-dimethylpyrimidine (VI) as no such tautomerism is possible.



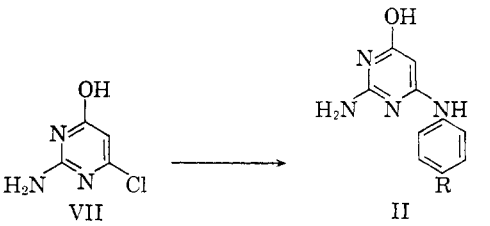
A study of the type of reaction of compound V with the different aromatic amines appears to indicate that a parallelism exists between the basicity of the amine and the yield obtained (Table I). It will be seen that the yields obtained from aniline, *p*-toluidine, and *p*-chloroaniline range in the order of their basicities. No reaction was possible with *p*-nitroaniline and α-naphthylamine apparently owing to their low basicity, the reactants being recoverable unchanged. The failure of reaction in the case of *p*-bromoaniline was due to the instability of this compound. *p*-Bromoaniline decomposed before the reaction could take place.

TABLE I

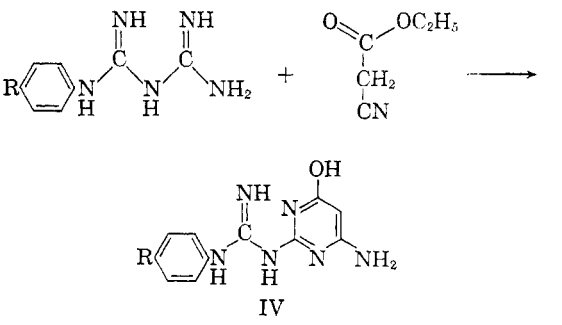
REACTION OF DIFFERENT AROMATIC AMINES WITH V TO PRODUCE COMPOUNDS OF THE TYPE I

Amine	Yield, %	Dissociation Constant (K) of Amine at 25°
p-Toluidine	80	1.5×10^{-9}
p-Bromoaniline	0	1.0×10^{-10}
p-Chloraniline	70	1.5×10^{-10}
Aniline	70	3.5×10^{-10}
p-Nitroaniline	0	3.45×10^{-11}
α-Naphthylamine	0	9.9×10^{-11}

When arylamines in excess were allowed to react with V under more drastic conditions (higher temperature and longer heating period), the formation of 2,4-bis(arylamino)-6-hydroxypyrimidines (type III) was favored. The treatment of 2,4-bis(*p*-chloroanilino)-6-hydroxypyrimidine (IIIc) with phosphorus oxychloride in the usual way gave rise to the corresponding 6-chloro compound (IIId). This shows that the 6-hydroxyl group in IIIc is free. The condensation of the second arylamine to produce compounds of type III is probably due to the presence of amidine structure $-N_{3}=C_{4}-NH_2$ in I involving N-3 and C-4 of the pyrimidine ring where the electronically deficient C-4 is vulnerable to nucleophilic attack by aromatic amines.



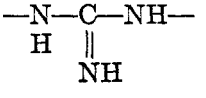
The pyrimidines of type II were synthesized by the condensation of 2-amino-4-chloro-6-hydroxypyrimidine[9] (VII) with the appropriate arylamine in presence of a mineral acid using a modification of the method of Banks.[10]



The compounds of type IV were prepared by the condensation of ethyl cyanoacetate with the corresponding arylbiguanide in absolute ethanol in presence of sodium ethoxide following a modified procedure of Curd and Rose.[1]

The C-5 position of these compounds is free because on treatment of an acidic solution of these pyrimidines with nitrous acid, they give rise to colored precipitates which show that nitrosation occurs in the 5-position. One such nitroso compound (IIIe) has been isolated.

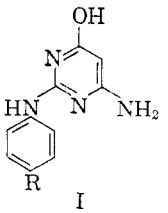
The ultraviolet absorption spectra of these compounds were determined in ethanol. The relevant data are given in Table III. It is known that the simple trisubstituted pyrimidines exhibit a maximum in the region 264 ± 6 mμ. However, in all the compounds listed below except in IVc the positions of the maxima are at higher wave length. This seems to be due to the presence of the phenyl ring near the pyrimidine nucleus. The fact that the compound IVc behaves differently is apparently because the phenyl group is separated from the pyrimidine nucleus by a chain of three atoms:



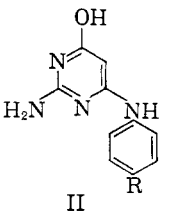
(9) S. Gabriel and J. Coleman, *Ber.*, **36**, 3381 (1903).
(10) C. K. Banks, *J. Am. Chem. Soc.*, **66**, 1127 (1944).

TABLE II

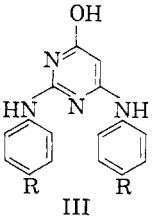
ARYLGUANIDINO- AND ARYLAMINOPYRIMIDINES



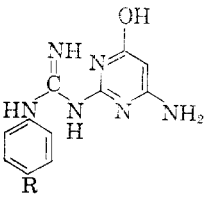
I



II



III



IV

Compounds	R	Yield, %	M.P.[a]	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Ia	—H	70	274–275	$C_{10}H_{10}N_4O$[b]	59.40	4.95	27.72	59.51	4.91	27.48
Ib	—CH_3	80	272–273	$C_{11}H_{12}N_4O$[b]	61.11	5.55	25.92	61.00	5.60	25.87
Ic	—Cl	70	269–270	$C_{10}H_9N_4OCl$[b]	50.73	3.80	23.67	50.65	3.77	23.71
IIa	—H	63	145	$C_{10}H_{10}N_4O$[c]	59.40	4.95	27.72	59.21	4.82	27.56
IIb	—CH_3	86	152–155	$C_{11}H_{12}N_4O$[d]	61.11	5.55	25.92	61.01	5.46	25.62
IIc	—Cl	95	168–169	$C_{10}H_9N_4OCl$[d]	50.73	3.80	23.67	51.00	3.75	23.67
IIIa	—H	46	214–216	$C_{16}H_{14}N_4O$[d]	69.06	5.03	20.14	69.20	5.03	20.14
IIIb	—CH_3	52	224–226	$C_{18}H_{18}N_4O$[d]	70.58	5.88	18.30	70.56	5.90	18.18
IIIc	—Cl	60	254	$C_{16}H_{12}N_4OCl_2$[b]	55.33	3.45	16.13	55.17	3.47	16.12
IVa	—H	42	151–152	$C_{11}H_{12}N_6O$[e]	54.04	4.91	34.40	54.02	4.88	34.45
IVb	—OCH_3	35	142	$C_{12}H_{14}N_6O_2$[c]	52.55	5.10	30.65	52.50	5.06	30.70
IVc	—CH_3	48	198	$C_{12}H_{14}N_6O$[d]	55.81	5.42	32.55	56.20	5.40	32.48
IVd	—NO_2	50	[f]	$C_{11}H_{11}N_7O_3$[g]	45.68	3.80	33.91	45.59	3.78	34.04
IVe	—Cl	34	221–222	$C_{11}H_{11}N_6OCl$[h]	47.39	3.94	30.16	47.35	4.02	29.88

[a] Melting points are uncorrected. [b] Recrystallized from 90% ethanol. [c] Recrystallized from water. [d] Recrystallized from 60% ethanol. [e] Recrystallized from aqueous acetone. [f] Decomposes above 310° without melting. [g] Recrystallized from *N,N*-dimethylformamide. [h] Recrystallized from acetone.

TABLE III

ULTRAVIOLET ABSORPTION DATA OF ARYLGUANIDINO- AND ARYLAMINOPYRIMIDINES IN ETHANOL

Compound	λ_{max} (mμ)		log ε	
2-(*p*-Chloroanilino)-4-amino-6-hydroxypyrimidine (Ic)	275		4.115	
2-Amino-4-(*p*-chloroanilino)-6-hydroxypyrimidine (IIc)	250	292	4.421	3.639
2,4-Bis(*p*-chloroanilino)-6-hydroxypyrimidine (IIIc)	243	279	4.224	4.510
2-(*p*-Chlorophenylguanidino)-4-amino-6-hydroxypyrimidine (IVc)	265		4.433	

The biological properties of these compounds are under detailed investigation and will be reported elsewhere.

EXPERIMENTAL[11]

2-(p-Chloroanilino)-4-amino-6-hydroxypyrimidine (Ic). 2-Methylthio-4-amino-6-hydroxypyrimidine (5.2 g., 0.033 mole) and *p*-chloroaniline (4.3 g., 0.033 mole) were thoroughly mixed and the mixture was slowly heated on an oil bath in an Erlenmeyer flask provided with an air condenser and an inlet tube through which nitrogen was passed to maintain an inert atmosphere. When the temperature of the bath reached about 160° the mixture started to melt. The reaction mixture was maintained at this temperature until no odor of methylmercaptan was perceptible (about 6 hr.). After cooling and dissolving the mixture in ethanol and subsequent decolorization with charcoal, the product was precipitated with water. The suspension was made acidic (*p*H 3) with hydrochloric acid to dissolve any unchanged starting materials. The precipitate was filtered and washed with water. The product (5.2 g.) was crystallized from 90% ethanol to yield silky white crystals.

2-(Anilino)-4-amino-6 hydroxypyrimidine (Ia) and *2 (p-toluidino)-4-amino-6-hydroxypyrimidine* (Ib) were prepared by the same general method as described for (Ic).

2,4-Bis(p-chloroanilino)-6-hydroxypyrimidine (IIIc). 2-Methylthio-4-amino-6-hydroxypyrimidine (5.2 g., 0.033 mole) and excess *p*-chloroaniline (15 g.) were thoroughly mixed and the mixture was heated on an oil bath in an atmosphere of nitrogen as described in the preparation of Ic. The temperature of the oil bath was slowly raised to 180–190° and maintained at that level until the solid completely melted (about 4 hr.). More *p*-chloroaniline was added at this stage to replenish any loss of it from the reaction mixture by evaporation. The temperature of the bath was lowered to 170–175° and the reaction mixture was further heated for another 4 hr. The mixture was then cooled and taken up in water and the aqueous medium acidified with dilute hydrochloric acid. The suspension was stirred for 2 hr. at room temperature to dissolve unchanged starting materials. This was then filtered and the residue washed well with water. The product was then purified by repeated crystallization from 90% ethanol.

2,4-Bis(anilino)-6-hydroxypyrimidine (IIIa) and *2,4-bis-(p-toluidino)-6-hydroxypyrimidine* (IIIb) were prepared by the same method as described for IIIc.

2,4-Bis(p-chloroanilino)-6-chloropyrimidine (IIId). Compound IIIc (1 g.) was finely powdered and treated with phosphorus oxychloride (15 ml.). When the initial vigor of the reaction subsided, the mixture was slowly heated over

(11) Before analysis the samples were dried *in vacuo* at 110° for about 8 hr. The solvents for crystallization, melting points, and analytical data are given in Table II.

boiling water-bath until all the solid went into solution. The excess oxychloride was removed by distillation under reduced pressure and the oily liquid was poured over crushed ice. A white precipitate appeared immediately which was filtered, washed with water and finally crystallized from aqueous acetone; yield 900 mg. IIId decomposes above 260°.

Anal. Calcd. for $C_{16}H_{11}N_4Cl_3$ C, 52.53; H, 3.00; N, 15.32. Found C, 52.49; H, 2.90; N, 15.26.

2,4-Bis(p-chloroanilino)-5-nitroso-6-hydroxypyrimidine (IIIe). Compound IIIc was finely pulverized and suspended in 30 ml. of 95% ethanol. Concentrated hydrochloric acid was added to this mixture until the *p*H went down to 3. Sodium nitrite (200 mg.) in 10 ml. of water was added drop by drop with stirring at room temperature maintaining the *p*H of the solution at about 3, until the nitrosation was complete. A deep brown colored precipitate was formed during nitrosation. The reaction mixture was cooled, filtered, and the residue washed thoroughly with water and then with cold alcohol. The product could not be satisfactorily crystallized; yield 850 mg. It does not melt below 310°.

Anal. Calcd. for $C_{16}H_{11}N_5O_2Cl_2$: C, 51.06; H, 2.92; N, 18.61. Found: C, 51.00; H, 2.86; N, 18.57.

2-(p-Nitrophenylguanidino)-4-amino-6-hydroxypyrimidine (IVd). *p*-Nitrophenylbiguanide (9 g., 0.04 mole) was added to a solution of sodium ethoxide (0.92 g., 0.04 mole of sodium in 100 ml. of absolute ethanol), and to this mixture was added slowly with stirring ethyl cyanoacetate (11.3 g., 0.1 mole) while the temperature was maintained below 20°. The mixture was heated under reflux for 16 hr. The mass became deep yellow and some precipitate appeared immediately on refluxing. The reaction mixture was cooled, filtered, and the precipitate washed first with water and then with alcohol. The product could be crystallized from *N,N*-dimethylformamide. The crystals appeared as fine yellow needles.

2-(Phenylguanidino)-4-amino-6-hydroxypyrimidine (IVa). A solution of sodium ethoxide (3 g., 0.13 mole of sodium in 75 ml. of absolute ethanol) was treated with phenylbiguanide hydrochloride (10.7 g., 0.05 mole) in an ice bath. This was shaken well until the reaction was complete. The precipitated sodium chloride was filtered and to the filtrate ethyl cyanoacetate (11.3 g., 0.1 mole) was added with shaking, taking care that the temperature of the mixture did not rise above 30°. Some precipitate appeared immediately and the amount increased on standing. The mixture was left at room temperature (25–28°) for 24 hr. The heavy precipitate formed was filtered and washed with cold absolute alcohol. This was suspended in water when most of the precipitate went into solution. The mixture was acidified with hydrochloric acid, cooled to 2°, filtered, and the residue washed with cold water. The residue could be crystallized from aqueous acetone.

2-(p-Methoxyphenylguanidino)-4-amino 6-hydroxypyrimidine (IVb). A mixture of *p*-anisylbiguanide hydrochloride (12.2 g., 0.05 mole), sodium ethoxide (2.3 g. sodium in 50 ml. absolute ethanol), and ethyl cyanoacetate (5.7 g., 0.05 mole) was refluxed for about 2 hr. The precipitate obtained was washed with alcohol, suspended in water (50 ml.), and neutralized with hydrochloric acid. After cooling, the product was filtered, washed with cold water, and crystallized from water as white needles.

2-(p-Methylphenylguanidino)-4-amino-6-hydroxypyrimidine (IVc). A mixture of *p*-methylphenylbiguanide hydrochloride (11.4 g., 0.05 mole), ethyl cyanoacetate (11.3 g., 0.1 mole) and sodium ethoxide (3.5 g. of sodium in 100 ml. of absolute ethanol) was refluxed for 4 hr. The product obtained was isolated in the same way as described under IVb.

2-(p-Chlorophenylguanidino)-4-amino-6-hydroxypyrimidine (IVe). A mixture of *p*-chlorophenylbiguanide hydrochloride (12.5 g., 0.05 mole), ethyl cyanoacetate (5.7 g., 0.05 mole), and sodium ethoxide (1.3 g. of sodium in 50 ml. of absolute ethanol) was refluxed for 2 hr. The product was then isolated in the same way as described under IVb.

[Added in proof]

2-Amino-4-(p-chloroanilino)-6-hydroxypyrimidine (IIc). A mixture of 2-amino-4-chloro-6-hydroxypyrimidine (2.9 g., 0.02 mole), *p*-chloroaniline, (2.6 g., 0.02 mole), glacial acetic acid (30 ml.), and concentrated hydrochloric acid (0.4 ml.) was heated at refluxing temperature for about 4 hr. The resulting solution was treated with charcoal for decolorization and filtered hot. The desired product precipitated partially on cooling, but for complete precipitation the solution was diluted with 200 ml. of water and then neutralized partially with 20 ml. of 10*N* sodium hydroxide. The precipitate was filtered, thoroughly washed with water, and crystallized from 60% alcohol.

2-Amino-4-(p-toluidino)-6-hydroxypyrimidine (IIb) *and 2-amino-4-(anilino)-6-hydroxypyrimidine* (IIa) were prepared by the same general method as given for IIc.

Acknowledgment. We are grateful to the Council of Scientific & Industrial Research, Government of India, for financing this work. Our thanks are also due to Prof. J. C. Bardhan for valuable discussion.

CALCUTTA, INDIA

[CONTRIBUTION FROM BATTELLE MEMORIAL INSTITUTE AND THE UNIVERSITY OF ALABAMA MEDICAL SCHOOL]

Synthesis of Some Vicinal Trimethoxyphenyl Derivatives of Heterocyclic Nitrogen Bases

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Received March 22, 1960

A number of vicinal trimethoxy analogs of compounds possessing psychopharmacological activity were synthesized to examine the influence of vicinal trimethoxy groups on this type of activity.

In a continuation of our investigation of correlations between chemical structure and psychopharmacological activity, we have undertaken the synthesis of several new compounds in which vicinal trimethoxy groups are present on the phenyl rings of a number of useful synthetic drugs which affect mood and behavior of human subjects. It is well known that the presence of vicinal trimethoxy groups on a phenyl ring can alter pro-

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