tartrate and treated with three-sevenths of its weight of *l*-tartaric acid as above. When the sparingly soluble ***l*-acid tartrate** was recrystallized from abs. ethanol it was obtained in fine colorless prisms which melted at 189° beginning to sinter at 184°. When this was admixed with a specimen of the *l*-tartrate of glaucentrine O-ethyl ether it melted at the same temperature. Found: C, 59.94; H, 6.60. A Dumas nitrogen determination on these tartrates gave consistent high values and this tendency was confirmed with an analysis on *d*-glaucine *l*-acid tartrate; $[\alpha]^{25}D$ +100° (*c* 0.25 in water).

Glaucentrine O-Ethyl Ether.—A small specimen of glaucentrine in ethanol was treated with an excess of an ether solution of diazoethane. The non-phenolic base which had been purified by solution in dilute oxalic acid was converted into its ***l*-acid tartrate**. This when recrystallized from abs. ethanol consisted of colorless fine prisms which melted at 189° sintering at 184°. The **methiodide** was prepared in ether solution containing a small amount of methanol. It crystallized in a short time and when recrystallized from methanol–ether melted at 225° either alone or in admixture with a specimen similarly prepared from the synthetic *l*-tartrate. Calcd. for $C_{23}H_{30}O_4NI$: C, 54.01; H, 5.87. Found: C, 54.01; H, 5.82.

GUELPH, ONTARIO, CANADA RECEIVED FEBRUARY 28, 1951

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

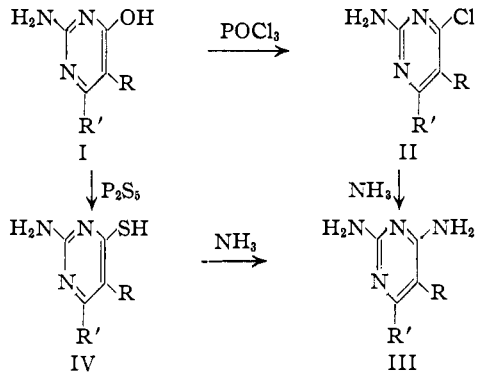
2,4-Diaminopyrimidines as Antimalarials. I.[1] 5-Aryloxyl and 5-Alkoxyl Derivatives

BY ELVIRA A. FALCO, PETER B. RUSSELL AND GEORGE H. HITCHINGS

The preparation of six 2,4-diamino-5-alkoxypyrimidines and forty-nine 2,4-diamino-5-aryloxypyrimidines *via* the corresponding 2-amino-4-hydroxy- and 2-amino-4-chloropyrimidines is described. Unsubstituted amino groups in the 2,4-diaminopyrimidine moiety appear essential to high antimalarial activity. This activity reaches a maximum in the phenoxy series with an electron-attractive substituent in the *para* position of the benzene ring and a methyl radical in the pyrimidine-6 position.

During the study of a series of pyrimidines as antagonists of nucleic acid derivatives,[2] 2,4-diaminopyrimidines and condensed systems containing this moiety were found generally to interfere with the utilization of folic acid by *Lactobacillus casei*.[3] A similarity in microbiological properties and a structural resemblance between chlorguanide (N_1-*p*-chlorophenyl-N_5-isopropylbiguanide) and certain 2,4-diamino-5-phenoxypyrimidines was noted.[4] The testing of 5-(4′-chlorophenoxy)-2,4-diaminopyrimidine[4] and its 6-methyl homolog[5] as antimalarials revealed activities of encouraging dimensions. Accordingly the preparation and testing for antimalarial properties of a considerable number of 2,4-diaminopyrimidines were undertaken.[6] The most fundamental structural requirement for antimalarial activity in this series appears to be the nature of the substituent in the 5-position. A considerable variety of 5-substituents may give rise to active antimalarials, for example, alkyl, alkoxyl, aralkyl, aryloxyl and aryl radicals, whereas the bromo and nitropyrimidines, amides of 2,4,5-triaminopyrimidine and 5-unsubstituted pyrimidines, are inactive.[6] The present paper deals primarily with the alkoxyl and aryloxyl derivatives. Succeeding papers will present the 5-aralkyl, 5-aryl and other diaminopyrimidines.

The preparations of the diamino alkoxy and aryloxypyrimidines (III) are readily carried out from the 2-amino-4-hydroxypyrimidine (I) *via* the 2-amino-4-chloropyrimidine (II) although an alternative route *via* the 2-amino-4-mercaptopyrimidine (IV)



may be used.[7,8] In the preparation of 2-amino-4-chloro-5-phenoxypyrimidine (II, R = OC_6H_5, R′ = H) Hull, *et al.*,[9] found that acetylation of the 2-amino-4-hydroxypyrimidine prior to treatment with phosphoryl chloride was necessary to avoid excessive losses. This was confirmed; however, the direct chlorination of the other 2-amino-4-hydroxy-5-aryloxypyrimidines to be reported proceeded smoothly and in most instances in excellent yield.

The 2-amino-4-hydroxypyrimidines were prepared by the condensation of an appropriately substituted α-formylacetic ester or β-ketoester with guanidine. The esters were obtained in the main along conventional lines, alkoxyacetic esters from chloroacetic acid[10,11] and a sodium alkoxide followed by esterification, aryloxyacetic esters from ethyl bromoacetate and a sodium phenoxide,[12] and

(1) Presented in part at the 119th Meeting of the American Chemical Society, April, 1950.

(2) G. H. Hitchings, G. B. Elion, E. A. Falco, P. B. Russell, M. B. Sherwood and H. VanderWerff, *J. Biol. Chem.*, **183**, 1 (1950).

(3) G. H. Hitchings, G. B. Elion, H. VanderWerff and E. A. Falco, *ibid.*, **174**, 765 (1948).

(4) E. A. Falco, G. H. Hitchings, P. B. Russell and H. VanderWerff, *Nature* **164**, 107 (1949).

(5) L. G. Goodwin, *ibid.*, **164**, 1133 (1949).

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

(7) G. B. Elion and G. H. Hitchings, THIS JOURNAL, **69**, 2138 (1947).

(8) P. B. Russell, G. B. Elion, E. A. Falco and G. H. Hitchings, *ibid.*, **71**, 2279 (1949).

(9) R. Hull, B. J. Lovell, H. T. Openshaw and A. R. Todd, *J. Chem. Soc.*, 41 (1947).

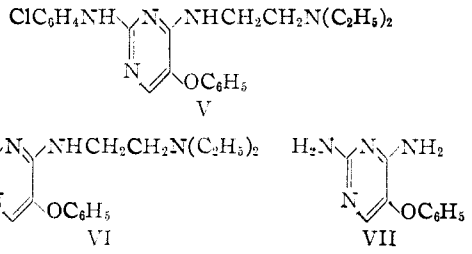
(10) H. G. Rule, W. Hay and J. Paul, *ibid.*, 1347 (1928).

(11) R. C. Fuson and B. H. Wojeck in "Organic Syntheses," Coll. Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 260.

(12) M. S. Newman, W. Fones and M. Renoll, THIS JOURNAL, **69**, 718 (1947).

α-aryloxy-β-ketoesters from the appropriate α-chloro-β-ketoester and a sodium phenoxide. The only record of the last method is the preparation of ethyl α-phenoxyacetoacetate by Hantzsch[13] who found this compound to cyclize during distillation to ethyl 3-methylcumaranone-2-carboxylate, consequently condensation with guanidine was carried out with the crude α-aryloxy-β-ketoesters.

In previous studies on pyrimidine antimalarials the presence of a dialkylaminoalkylamino side chain has been stated to be requisite to activity.[14] However, two types of pyrimidine antimalarials apparently can be distinguished, those (unsubstituted or bearing a relatively small group in the 5-position) in which the statement of Basford, *et al.*,[14] is borne out and a second group (carrying phenyl, phenoxyl, benzyl or alkoxyl groups in the 5-position) in which precisely the opposite is true. Thus a comparison of the antimalarial activities against *Plasmodium gallinaceum* in chicks of 2-*p*-chloroanilino-4-diethylaminoethylamino-5-phenoxypyrimidine[15] (V) (± at 160 mg. per kg.), 2-amino-4-diethylaminoethylamino-5-phenoxypyrimidine[9] (VI) (± at 60 mg. per kg.) and 2,4-diamino-5-phenoxypyrimidine (VII) (++ at 100 mg. per kg., *cf.* Table I, No. 8) indicates a stepwise increase in activity as the substituents are removed from the amino groups. A similar conclusion is indicated by the lower activity of 2-amino-4-methylamino-5-*p*-chlo-



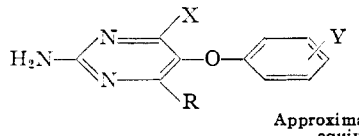
rophenoxypyrimidine as compared with the diamino derivative (Table I, No. 14). Also suggesting the optimal effect of the diamino structure are the lesser activities of the 2-amino-4-hydroxy- and 2-amino-4-mercaptopyrimidines (Table I, No. 12, 13).

Among the aryloxypyrimidines several (Table I, No. 2, 3, 7) have activities of dimensions in the range from 5 to 30 times that of quinine,[6] values suggesting the possible utility of one or more of these substances in the treatment of malarial infections. That the effects on the two plasmodia used in the screening tests may vary widely has been observed previously with representative antimalarials currently available.[5] Thus although the 4-chlorophenoxy derivatives are essentially equally active on the two plasmodia, the 3-chloro isomers are much more active on *P. gallinaceum* than on *P. berghei* (Table I, No. 2 *vs.* No. 3). When the effects on both microörganisms are taken into consideration maximal activity in this series is attained with an electron-attractive substituent in the para position of the benzene ring and a methyl group in the 6-position of the pyrimidine (*e.g.*, No. 2, 3, 7, Table I). When a para electron-attractive group is present the substitution of methyl for hydrogen in the 6-position results in a considerable increase in activity (*e.g.*, No. 2 *vs.* No. 1, Table I) but this activity drops off rapidly with a further increase in the length of the alkyl chain (No. 6 and 7, Table I). When the benzene nucleus is unsubstituted or substituted with an electron-donor group the introduction of a 6-alkyl group fails to increase the low activity (No. 8, 9, 10, 11, Table I). Aryl groups in the 6-position diminish activity in both types. Many of the aryloxypyrimidines have significant antibacterial activity especially against gram-positive organisms.[16] It is of some interest that this activity is in general enhanced by electron-donor substituents and diminished by electron-attractive substituents. In neither antibacterial nor antimalarial activity does the effect of the substituent appear to be primarily related to the pK_a value of the base since all the aryloxy diaminopyrimidines are only slightly ionized at *p*H values above 7.0.

Some of the alkoxy diaminopyrimidines have significant antimalarial activity, approximately of the order of quinine (No. 15 and 16, Table I). However, this group is not readily adaptable to the structural alterations which have given rise to the compounds of greatest activity in other groups.

TABLE I

ANTIMALARIAL ACTIVITIES OF 2-AMINO-5-PHENOXYPYRIMIDINES



Compound number	X	R	Y	Approximate quinine equivalent *P. gallinaceum*	Approximate quinine equivalent *P. berghei*
1	NH_2	H	4-Cl	1	*ca.* 0.5
2	NH_2	CH_3	4-Cl	4.5	4.7
3	NH_2	CH_3	4-NO_2	30	*ca.* 5
4	NH_2	CH_3	3-Cl	7	*ca.* 0.5
5	NH_2	H	2-Cl	<1	<1
6	NH_2	C_2H_5	4-Cl	1	<0.5
7	NH_2	C_3H_7	4-Cl	<1	<0.5
8	NH_2	H	H	*ca.* 1	<0.5
9	NH_2	CH_3	H	<1	<0.5
10	NH_2	H	4-OCH_3	*ca.* 1	0
11	NH_2	CH_3	4-OCH_3	<1	0
12	OH	H	4-Cl	<0.5	*ca.* 0.1
13	SH	H	4-Cl	0	*ca.* 0.5
14	CH_3NH	H	4-Cl	*ca.* 0.5	<0.5
	2,4-Diamino-5-alkoxypyrimidines 5-Substituent				
15	C_2H_5O			1.2	<1
16	*n*-C_4H_9O			3	1.5

Experimental

Antimalarial Testing.—The methods employed in antimalarial testing have been described[5,6] and a general survey of the antimalarial properties of 2,4-diaminopyrimidines has been published.[6] The testing was carried out in the Wellcome Laboratories of Tropical Medicine (London) by L. G. Goodwin and I. M. Rollo. For the purposes of this paper selected results are presented here in terms of approximate quinine equivalents (Table I). In a number of instances

(13) A. Hantzsch, *Ber.*, **19**, 1292 (1886).

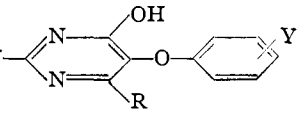
(14) F. R. Basford, F. H. S. Curd, E. Hoggarth and F. L. Rose, *J. Chem. Soc.*, 1354 (1947).

(15) F. H. S. Curd, D. N. Richardson and F. L. Rose, *ibid.*, 378 (1946).

(16) Unpublished observations with H. VanderWerff and S. R. M. Bushby.

TABLE II

2-AMINO-5-ARYLOXY-4-HYDROXYPYRIMIDINES

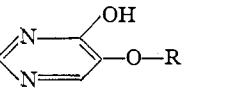


R	Y	M.p.,[b] °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	2-Cl	260–262	$C_{10}H_8ClN_3O_2$	50.5	3.4		50.2	3.3	
H	4-Cl	249	$C_{10}H_8ClN_3O_2$	50.5	3.4		50.6	3.3	
H	2,4-diCl	297	$C_{10}H_7Cl_2N_3O_2$	44.1	2.6		44.1	3.0	
H	2,4-diBr	290–296	$C_{10}H_7Br_2N_3O_2$	33.2	1.9	11.6	33.2	2.1	11.2
H	4-Cl, 3-CH_3	230–234	$C_{11}H_{10}ClN_3O_2.H_2O$			15.6			16.0
H	2-Cl, 4-$C(CH_3)_3$	280–284	$C_{14}H_{16}ClN_3O_2$			14.3			14.0
H	4-Cl, 2-$CH(CH_3)_2$, 5-CH_3	253–254	$C_{14}H_{15}ClN_3O_2.{}^1/_2H_2O$[a]	55.7	5.3	13.9	56.2	5.4	14.0
H	4-$C(CH_3)_3$	294–300	$C_{14}H_{17}N_3O_2$			16.2			15.9
H	4-$C(CH_3)_2CH_2C(CH_3)_3$	280–282	$C_{18}H_{25}N_3O_2$	68.6	7.9		69.0	7.9	
H	4-$CH_2C_6H_5$	267–270	$C_{17}H_{15}N_3O_2$			14.3		14.4	
H	2-$CH(CH_3)_2$, 5-CH_3	238–239	$C_{14}H_{17}N_3O_2$	64.9	6.6	16.2	65.0	6.8	15.8
H	4-CH(CH$_2$)CH$_2$—C_6H_4	250–300	$C_{19}H_{17}N_3O_2$	71.5	5.3	13.2	71.5	5.9	13.0
H	4-C_6H_5	>330	$C_{16}H_{13}N_3O_2$	68.8	4.7	15.1	68.7	4.9	15.2
H	4-$COOC_2H_5$	243–244	$C_{13}H_{13}N_3O_4$			15.3			15.0
H	3-OCH_3	223–228	$C_{11}H_{11}N_3O_3$			18.0			17.6
H	4-OCH_3	242–245	$C_{11}H_{11}N_3O_3$	56.7	4.7	18.0	56.7	5.0	18.5
H	4-$OCH_2C_6H_5$	288–289	$C_{17}H_{15}N_3O_2$	66.0	4.9	13.6	66.4	4.9	13.6
H	2,3-CH=CH—CH=CH—	>300	$C_{14}H_{11}N_3O_2$	66.4	4.3		66.9	4.0	
H	3,4-CH=CH—CH=CH—	280–282	$C_{14}H_{11}N_3O_2$	66.4	4.3		67.0	4.1	
H	3,4-CH=CBr—CH=CH—	>300	$C_{14}H_{10}BrN_3O_2$	50.6	3.0		50.9	3.1	
H	4,6-diCl-2,3-CH=CH—CH=CH—	300	$C_{14}H_9Cl_2N_3O_2$	52.2	2.8		51.9	2.9	
CH_3	H	*ca.* 300	$C_{11}H_{11}N_3O_2$	60.8	5.1		60.5	5.0	
CH_3	4-Cl	278–320	$C_{11}H_{10}ClN_3O_2$	52.5	4.0		52.7	4.0	
CH_3	4-$COCH_2CH_3$	.....	$C_{14}H_{15}N_3O_3$			15.4			14.9
CH_3	4-$SO_2C_6H_5$	.....	$C_{17}H_{15}N_3O_4S$			11.8			11.4
CH_3	4-OCH_3	283–284	$C_{12}H_{13}N_3O_3.CH_3COOH$			13.7			13.3
CH_3	4-$OCH_2C_6H_4Cl$-4′	289–293	$C_{18}H_{16}ClN_3O_2$			11.7			11.8
CH_3	3,4-CH=CH—CH=CH—	>310	$C_{15}H_{13}N_3O_2$			15.6			16.1
$CH_2CH_2CH_3$	3,4-CH=CH—CH=CH—	291–293	$C_{17}H_{17}N_3O_2$			14.2			14.3
C_6H_5	3,4-CH=CH—CH=CH—	250	$C_{20}H_{15}N_3O_2$	72.9	4.6		72.9	4.9	

[a] H_2O, calcd. 3.0; found, 3.3. [b] Melting points uncorrected. In all cases decomposition occurs.

TABLE III

5-ALKOXY-2-AMINO-4-HYDROXYPYRIMIDINES



R	M.p.,[a] °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	266–267	$C_5H_7N_3O_2.{}^1/_2H_2O$	40.0	5.3		40.5	5.0	
$(CH_2)_3CH_3$	236–239	$C_8H_{13}O_2N_3$			23.0			22.5
$(CH_2)_7CH_3$	212–214	$C_{12}H_{21}N_3O_2$			17.6			17.6
$CH_2C_6H_5$	247–248	$C_{11}H_{11}N_3O_2$			19.4			19.4

[a] Melting points uncorrected. In all cases decomposition occurs.

(as indicated) these are to be regarded as approximations only, but sufficiently accurate for comparative purposes.

Alkoxyacetic Esters.—The alkoxyacetic acids were prepared from sodium chloroacetate and the requisite sodium alkoxide[10,11] followed by acid-catalyzed esterification. Methoxy- and ethoxyacetates are well known,[11] methyl butoxyacetate was characterized by Palomaa,[17] ethyl benzyloxyacetate by Rothstein.[18] Methyl octyloxyacetate was prepared by the esterification of octyloxyacetic acid[10] (39 g.) in methanol (250 ml.) containing sulfuric acid (1 ml.). The boiling point at 15 mm. pressure was 127–132°. Methyl *n*-lauryloxyacetate, prepared in the same manner, boiled at 161–175° at 22 mm.

Aryloxyacetic acids and esters in wide variety have been reported in the literature and most of the substances employed in these studies have been characterized elsewhere. The method used here differed from that of Auwers[19] only in the use of ethyl bromoacetate[20] in place of ethyl chloroacetate.

Formylation of Substituted Acetic Esters.—The formylation of the substituted acetic esters was carried out essentially as described by Johnson[21] for ethyl α-formylphenoxyacetate.

β-Ketoesters.—The ethyl esters of acetoacetic, β-ketovaleric,[22] β-ketocaproic[22,23] and benzoylacetic acids were employed.

(17) M. H. Palomaa, *Ann. Acad. Sci. Fennicae (A)*, **4**, 1 (1913); *C. A.*, **8**, 1772 (1914).

(18) B. Rothstein, *Bull. soc. chim.*, **51**, 691 (1932).

(19) K. Auwers and K. Haymann, *Ber.*, **27**, 2795 (1894).

(20) L. Haskelberg, *J. Org. Chem.*, **12**, 426 (1947).

(21) T. B. Johnson and H. H. Guest, *Am. Chem. J.*, **42**, 271 (1909).

(22) C. W. Anderson, I. F. Halverstadt, W. H. Miller and R. O. Roblin, Jr., THIS JOURNAL, **67**, 2197 (1945).

(23) S. B. Soloway and F. B. LaForge, *ibid.*, **69**, 2677 (1947).

α-Chloro-β-ketoesters.—The α-chloro-β-ketoesters were prepared by the method employed by Allihn[24] for ethyl α-chloroacetoacetate, *i.e.*, treatment with 1 molecular proportion of sulfuryl chloride for 16 hours at room temperature followed by a slow distillation at atmospheric pressure, with eventual isolation of the required ester by distillation *in vacuo*. Ethyl α-chloro-β-ketovalerate, boiling at 100–111° at 21 mm., was obtained in 89% yield. Ethyl α-chloro-β-ketocaproate boiling at 93–98° at 8 mm. was obtained in 94% yield. Ethyl α-chlorobenzoylacetate was prepared according to Peratoner.[25]

α-Aryloxy-β-ketoesters.—Attempts to prepare ethyl α-aryloxyacetoacetates by the reaction of sodium phenoxide and ethyl α-chloroacetoacetate in ethanol resulted in the formation of ethyl aryloxyacetates and ethyl acetate. This reaction, which is an alternative method of preparation of aryloxyacetates, is similar to the reported cleavage which occurs with sodium ethoxide in alcohol giving ethyl ethoxyacetate, ethyl acetate with some ethyl chloroacetate.[13,26] However, the reaction proceeded smoothly in non-polar solvents usually toluene at reflux temperatures. The required sodium phenolate is obtained by heating the phenol with an equimolecular quantity of sodium in about 10 parts by weight of toluene. The esters are purified by shaking the toluene solution successively with water, very dilute aqueous acetic acid and water. The toluene is removed by distillation under reduced pressure (aspirator). Distillation of these esters was not attempted in view of their tendency to cyclize,[13] but the crude product was condensed directly with guanidine carbonate or free guanidine in ethanolic solution.

2-Amino-4-hydroxypyrimidines. General Method. A. Formyl Derivatives.—To the crude sodium derivative of the formyl ester is added absolute ethanol (about 500 ml. per mole) and the ether is removed by evaporation. A solution of guanidine in ethanol (prepared by mixing solutions of equimolar quantities of guanidine hydrochloride and sodium in ethanol followed by filtration of the precipitated sodium chloride) in amount equivalent to the original substituted acetic ester is added and the solution is refluxed for 16 hours. The reaction mixture is poured into water (3 volumes) and acidified with acetic acid (*p*H 6). The solid 2-amino-4-hydroxypyrimidine is collected by filtration, washed with water, sucked as dry as possible and washed with a little ether to remove any oily material. It is purified by solution in dilute sodium hydroxide solution (1 equivalent) followed by precipitation with acetic acid, or by recrystallization from acetic acid or aqueous alcohol.

B. **β-Ketoesters.**—Since the β-ketoesters usually condense well with guanidine carbonate, the latter is usually preferred although free guanidine, as above, may be used. For condensations with guanidine carbonate the quantity of solvent is unimportant; usually the ester is diluted with 3 to 4 volumes of absolute ethanol; the calculated equivalent (1/2 molar proportion) of guanidine carbonate is added and the mixture is refluxed for 16 hours. The 2-amino-4-hydroxypyrimidine is worked up as described above.

2-Amino-4-chloropyrimidines. General Method.—The dry 2-amino-4-hydroxypyrimidine from the previous step is added to 5 parts by weight (3 vol.) of phosphoryl chloride, the mixture is heated under a reflux condenser until the pyrimidine is completely dissolved and for an additional 20 minutes to complete the reaction (one to two hours in all). After cooling, the greater part of the phosphoryl chloride is removed by distillation under reduced pressure and the sirupy residue is poured over cracked ice (about 300 g. per 100 ml. of phosphoryl chloride taken) with stirring. Ammonium hydroxide is added and stirring is continued until the sirup has been transformed to a white solid and the supernatant is permanently alkaline (two hours). The 2-amino-4-chloropyrimidine is collected by filtration and dried *in vacuo* at a temperature below 45°.

With the exception of 2-amino-4-hydroxy-5-phenoxypyrimidine no particular difficulties were encountered in the chlorination of phenoxypyrimidines. With respect to this compound the work of Hull, *et al.*,[9] was confirmed.

2,4-Diaminopyrimidines. General Method.—The crude dry 2-amino-4-chloropyrimidine (above) is mixed with 5 parts of alcoholic ammonia (ethanol saturated with ammonia gas at 0–5°) in a bomb, closed and heated at 150 to 160° for 16 hours. After cooling, the contents of the bomb is evaporated to dryness, the residue is dissolved in dilute aqueous acetic acid, treated with carbon, filtered and the base is precipitated by the addition of an excess of sodium hydroxide solution, filtered and washed free of alcohol. The products may be recrystallized from hot ethanol. Alternatively further purification may be carried out by repetition of the solution in aqueous acid and precipitation by sodium hydroxide, or by conversion to the hydrochloride or sulfate in alcoholic solution.

2,4-Diamino-6-methyl-5-(4′-nitrophenoxy)-pyrimidine by Nitration of 2,4-Diamino-6-methyl-5-phenoxypyrimidine.—To a solution of 4 g. (0.019 mole) of 2,4-diamino-5-phenoxy-6-methylpyrimidine in 35 ml. of concentrated sulfuric acid at −5°, finely powdered potassium nitrate (1.9 g., 0.019 mole) was added portionwise with stirring over the course of an hour, the temperature being maintained below 5°. After stirring an additional hour in the cold the solution was poured over cracked ice and the mixture allowed to stand for two hours. The white sulfate was collected by filtration, suspended in water and an excess of sodium hydroxide was added (*p*H 10–11). The yellow base was recrystallized from absolute ethanol giving yellow plates (3.0 g., 60%) melting at 237–239° (dec.). Mixed with an authentic specimen of the *p*-nitro compound prepared from *p*-nitrophenol it melted undepressed at 238°. *Anal.* Calcd. for $C_{11}H_{11}O_3N_5$: C, 50.6; H, 4.2; N, 26.8. Found: C, 50.8; H, 4.0; N, 27.0.

5-(4′-Aminophenoxy)-2,4-diamino-6-methylpyrimidine.—Five grams of the above nitrophenoxypyrimidine in 100 ml. of absolute ethanol containing a slight excess of hydrogen chloride was reduced catalytically in the presence of Adams platinum catalyst at 30 lb. hydrogen pressure during five hours. The catalyst was removed by filtration and the filtrate taken to dryness *in vacuo*. The product was purified by solution in dilute aqueous acetic acid followed by precipitation with sodium hydroxide solution. The yield was 2.95 g. (67%) of material melting at 195–196°. *Anal.* Calcd. for $C_{11}H_{13}ON_5$: N, 30.3. Found: N, 30.0. The product gave a strong color reaction on diazotization and coupling with β-naphthol.

5-(4′-Acetamidophenoxy)-2,4-diamino-6-methylpyrimidine.—The *p*-aminophenoxypyrimidine (above) gave a diacetyl derivative on shaking for two hours with acetic anhydride in aqueous suspension with occasional addition of ammonium hydroxide to maintain neutrality. The product was negative to the coupling test for aromatic amino groups. The crude product was refluxed for one hour with 2 molecular proportions of 0.2 *N* sodium hydroxide, cooled and filtered. The solid was recrystallized by solution in dilute aqueous acid followed by precipitation with sodium hydroxide (*p*H 8). The product melted at 260° and gave a negative test for diazotizable amino groups. *Anal.* Calcd. for $C_{13}H_{15}N_5O_2$: C, 57.2; H, 5.5; N, 25.6. Found: C, 57.3; H, 5.4; N, 25.0.

2-Amino-5-(4′-chlorophenoxy)-4-methylamino-6-methylpyrimidine.—The conversion of 2-amino-5-*p*-chlorophenoxy-4-chloro-6-methylpyrimidine to the 4-methylamino derivative followed the general procedure for amination given above with the substitution of 7 parts of ethanolic methylamine solution (saturated at 30°) for the alcoholic ammonia. After evaporation of the solvent the residue was dissolved in dilute aqueous acetic acid and precipitated wih sodium hydroxide solution. It was then converted to the hydrochloride by solution in cold methanol and addition of methanolic hydrogen chloride followed by ether. *Anal.* Calcd. for $C_{11}H_{11}ClN_4O\cdot HCl$: N, 19.5. Found: N, 19.1.

2,4-Diamino-5-(4′-hydroxyphenoxy)-pyrimidine.—5-Benzyloxyphenoxy-2,4-diaminopyrimidine was prepared by the general method from ethyl benzyloxyphenoxyacetate. This compound (2.5 g.) in glacial acetic acid (100 ml.) and palladium–charcoal[27] was shaken with hydrogen at low pressure[27] (maximum 35 lb.) for about two hours. The catalyst was removed by filtration and the solvent was removed by distillation under reduced pressure. The residue was dissolved in 75 ml. of warm methanol and an excess of methanolic hydrogen chloride was added. The resultant precipitate was recrystallized from hot methanol. The colorless crystals (1.25 g., 60%) melted at 273–275°. *Anal.* Calcd. for $C_{10}H_{10}N_4O_2\cdot HCl$: C, 47.2; H, 4.3; N, 22.0. Found: C, 47.5; H, 5.0; N, 21.9.

(24) F. Allihn, *Ber.*, **11**, 567 (1878).

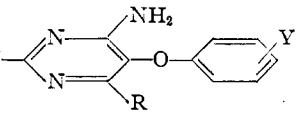
(25) A. Peratoner, *Gazz. chim. ital.*, **22** (II), 37 (1892).

(26) W. Mewes, *Ann.*, **245**, 58 (1888).

(27) R. Baltzly and J. S. Buck, THIS JOURNAL, **65**, 1984 (1943).

TABLE IV

5-ARYLOXY-2,4-DIAMINOPYRIMIDINES

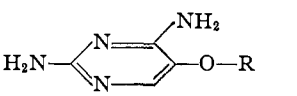


R	Y	M.p.,[a] °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	H	162–165	$C_{10}H_{10}N_4O$	59.4	5.0	27.7	59.4	4.8	27.8
H	2-Cl	142–145	$C_{10}H_9ClN_4O$	50.7	3.8		51.1	3.4	
H	3-Cl	180–181	$C_{10}H_9ClN_4O$	50.7	3.8		51.0	3.9	
H	4-Cl	173–175	$C_{10}H_9ClN_4O$	50.7	3.8		50.8	3.7	
H	4-Br	202–204	$C_{10}H_9BrN_4O$	42.7	3.2		42.7	2.9	
H	2,4-diCl	160–162	$C_{10}H_8Cl_2N_4O$	44.2	3.0	20.7	44.6	3.0	21.2
H	2,4-diBr	168–169	$C_{10}H_8Br_2N_4O$	33.3	2.2	15.6	33.3	2.4	15.2
H	2,4,5-triCl	228–230	$C_{10}H_7Cl_3N_4O$	39.3	2.3	18.3	39.3	2.1	18.7
H	4-Cl-3-CH_3	173–175	$C_{11}H_{11}ClN_4O$	52.7	4.4	22.4	52.9	4.1	21.8
H	2-Cl,4-C(CH_3)$_3$	238–240	$C_{14}H_{17}ClN_4O\cdot{}^1/_2H_2SO_4\cdot H_2O$	46.7	5.6		47.0	5.5	
H	4-Cl, 2CH(CH_3)$_2$-5-CH_3	205–208	$C_{14}H_{17}ClN_4O$	57.4	5.8	19.1	57.9	6.3	18.5
H	4-CH_3	272–273	$C_{11}H_{12}N_4O\cdot HCl$	52.3	5.2	22.2	52.6	5.0	22.1
H	4-C(CH_3)$_3$	157–160	$C_{14}H_{18}N_4O$	65.1	7.0	21.7	64.9	6.8	21.3
H	4-C(CH_3)$_2$$CH_2$C($CH_3$)$_3$	274–275	$C_{18}H_{26}N_4O\cdot HCl$	61.6	7.7	15.9	61.6	7.7	16.0
H	4-$CH_2C_6H_5$	186–187	$C_{17}H_{16}N_4O$	69.9	5.5	19.2	69.6	5.3	19.3
H	4-CH(—CH_2—)C_6H_4	190–200	$C_{19}H_{18}N_4O$	71.7	5.7	17.6	71.7	5.7	17.2
H	3,4-diCH_3	155–156	$C_{12}H_{14}N_4O\cdot H_2O$			22.6			22.8
H	2-CH(CH_3)$_2$,5-CH_3	163–165	$C_{14}H_{18}N_4O$	65.1	7.0	21.7	65.4	6.9	21.9
H	4-C_6H_5	246–248	$C_{16}H_{14}N_4O$	69.1	5.0	20.1	69.5	5.4	19.7
H	4-COOH	dec. 260–288	$C_{11}H_{10}N_4O_3$	53.7	4.1	22.8	53.8	4.3	22.4
H	4-$COOC_2H_5$	175–179	$C_{13}H_{14}N_4O_3$			20.4			20.7
H	4-OH	273–275	$C_{10}H_{10}N_4O_2\cdot HCl$	47.2	4.3	22.0	47.5	5.0	21.9
H	3-OCH_3	174–176	$C_{11}H_{12}N_4O_2$	56.9	5.2	24.1	56.9	4.9	24.2
H	4-OCH_3	147–150	$C_{11}H_{12}N_4O_2$	56.9	5.2		56.8	5.0	
H	4-$OCH_2C_6H_5$	269	$C_{17}H_{16}N_4O_2\cdot HCl\cdot C_2H_5OH$	58.5	5.6	14.3	57.9	5.9	14.3
H	4-$OCH_2C_6H_5$	185–189	$C_{17}H_{16}N_4O_2$			18.2			17.6
H	2,6-diOCH_3	200–203	$C_{12}H_{14}N_4O_3$			21.4			21.0
H	2,3-CH=CH—CH=CH—	195	$C_{14}H_{12}N_4O$	66.7	4.8		67.0	4.6	
H	3,4-CH=CH—CH=CH—	204–206	$C_{14}H_{12}N_4O$	66.7	4.8		66.5	4.9	
H	3,4-CH=CBr—CH=CH—	186–187	$C_{14}H_{11}BrN_4O$	50.8	3.3	16.9	50.7	3.3	16.7
H	4,6-diCl-2,3-CH=CH—CH=CH—	244	$C_{14}H_{10}Cl_2N_4O$	52.3	3.1	17.4	51.9	3.3	17.0
CH_3	H	180	$C_{11}H_{12}N_4O$	61.1	5.6	25.9	61.5	5.6	26.2
CH_3	3-Cl	270–273	$C_{11}H_{11}ClN_4O\cdot{}^1/_2H_2SO_4$	44.2	4.0	18.7	44.0	4.5	18.6
CH_3	4-Cl	205–207	$C_{11}H_{11}ClN_4O$	52.7	4.4	22.4	53.1	4.2	22.2
CH_3	4-NO_2	237–239	$C_{11}H_{11}N_5O_3$	50.6	4.2	26.8	50.8	4.0	27.0
CH_3	4-NH_2	195–196	$C_{11}H_{12}N_5O$			30.3			30.0
CH_3	4-NHCOCH_3	260	$C_{13}H_{16}N_5O_2$	57.2	5.5	25.6	57.3	5.4	25.0
CH_3	3,4-diCH_3	220–223	$C_{13}H_{16}N_4O$			23.0			22.8
CH_3	4-C_6H_5	328	$C_{17}H_{16}N_4O\cdot HCl$			17.8			17.6
CH_3	4-$COCH_2CH_3$	216–217	$C_{14}H_{16}N_4O_2$	61.8	5.9	20.6	61.8	5.8	20.2
CH_3	4-$SO_2C_6H_5$	274–276	$C_{17}H_{16}N_4O_3S\cdot HCl$	52.0	4.3	14.3	52.0	4.1	14.3
CH_3	4-OCH_3	211–213	$C_{12}H_{14}N_4O_2$	58.5	5.7	22.8	58.6	5.9	23.0
CH_3	4-$OCH_2C_6H_4Cl$-4′	179–183	$C_{16}H_{17}ClN_4O_2$			15.7			15.7
CH_3	3,4-CH=CH—CH=CH—	194–198	$C_{15}H_{14}N_4O$	67.7	5.3	21.1	67.4	5.3	21.1
CH_2CH_3	4-Cl	198–200	$C_{13}H_{15}ClN_4O$	61.8	5.9	21.3	61.6	5.6	21.0
$CH_2CH_2CH_3$	4-Cl	270–273	$C_{13}H_{15}ClN_4O\cdot HCl$			17.7			17.8
$CH_2CH_2CH_3$	3,4-CH=CH—CH=CH—	.....	$C_{17}H_{17}N_4O\cdot{}^1/_2H_2SO_4$	59.6	5.3	16.4	59.7	5.3	16.2
C_6H_5	4-Cl	187–188	$C_{16}H_{13}ClN_4O$	61.4	4.2	17.9	61.5	4.1	17.9
C_6H_5	3,4-CH=CH—CH=CH—	164–166	$C_{20}H_{16}N_4O$	73.2	4.9		72.9	4.9	

[a] Melting points uncorrected. The compounds melt reversibly except as noted.

TABLE V

5-ALKOXY-2,4-DIAMINOPYRIMIDINES



R	M.p.,[a] °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	138–140	$C_5H_8N_4O$	42.9	5.7	40.0	42.6	5.9	39.7
CH_2CH_3	148–149	$C_6H_{10}N_4O$	46.8	6.5		47.1	6.3	
$(CH_2)_3CH_3$	234–236 dec.	$C_8H_{14}N_4O\cdot H_2SO_4\cdot H_2O$	32.2	6.0	18.8	32.6	5.7	18.9
$(CH_2)_7CH_3$	76–78	$C_{12}H_{22}N_4O$			23.5			23.7
$(CH_2)_{10}CH_3$	205–208	$C_{15}H_{28}N_4O\cdot HCl$[b]			17.7			17.3
$CH_2C_6H_5$	142–145	$C_{11}H_{12}N_4O\cdot H_2O$	56.4	6.0	23.9	56.0	5.8	23.9

[a] Melting points uncorrected. The compounds melt reversibly except as noted. [b] HCl, calcd., 11.5; found, 11.2.

2-Amino-5-(4′-chlorophenoxy)-4-mercaptopyrimidine.—To 10 g. of 2-amino-5-(4′-chlorophenoxy)-4-hydroxypyrimidine (prepared by the general method above) in 100 ml. of tetrahydronaphthalene was added 30 g. of phosphorus pentasulfide and the mixture was heated for two hours at 150–160° with continuous stirring.[7] After cooling, the solvent was decanted and the residue was heated with 100 ml. of approximately 1.5 *N* ammonium hydroxide. The solution was

TABLE VI

ULTRAVIOLET ABSORPTION SPECTRA

Compound, pyrimidine	pH 1 Maximum λ, mμ	pH 1 Maximum E_m	pH 1 Minimum λ, mμ	pH 1 Minimum E_m	pH 11 Maxima λ, mμ	pH 11 Maxima E_m	pH 11 Minimum λ, mμ	pH 11 Minimum E_m
2-Amino-5-(4′-bromophenoxy)-4-hydroxy					233	14,500		
	270	7100	255	6350	280	6,600	260	3240
2-Amino-5-(4′-chlorophenoxy)-4-hydroxy-6-methyl					233	15,400		
	268	9550	253	8400	280	8,850	255	4650
5-(4′-Bromophenoxy)-2,4-diamino-					233	19,000		
	275	4500	265	3930	287	6,900	263	3500
5-(4′-Chlorophenoxy)-2,4-diamino-6-methyl-					233	17,800	259	2760
	277	8150	258	5000	286	8,500		

treated with carbon, filtered, neutralized with acetic acid, and allowed to stand while a yellow precipitate slowly formed. The precipitate was recrystallized from 75% ethanol, giving 6.2 g. (56.5%) of bright yellow crystals melting at 249–250°. *Anal.* Calcd. for $C_{10}H_8ClN_3OS$: C, 47.4; H, 3.2. Found: C, 47.7; H, 3.3.

5-(4′-Chlorophenoxy)-2,4-diaminopyrimidine.—The amination of the 2-amino-4-mercaptopyrimidine above was investigated at several temperatures using a ten-fold proportion of concentrated ammonium hydroxide and heating for 16 hours.[8] The yields of diamino compound increased with rising temperature, a maximum of 42.5% being obtained at 180–185°. Longer treatment (70 hours) at 145° gave a 49% yield. The replacement of the mercapto by an amino group is thus much more difficult in this instance than with the dimercaptopyrimidines previously studied.[8] Attention was then turned to alcoholic ammonia. This gave obviously superior results; a yield of 51% of the diaminopyrimidine was obtained in 16 hours treatment at 155°. In each instance the diaminopyrimidine was compared with an authentic specimen prepared by the general method above. Mixed melting points were undepressed, falling in the range 172–175°.

Ultraviolet Absorption Spectra.—Ultraviolet absorption spectra were determined using the Beckman model DU spectrophotometer, in aqueous solutions at a concentration of 10 mg. per l. in 0.1 *N* hydrochloric acid and Sørensen glycine–sodium hydroxide buffer at *p*H 11. Representative spectra are shown in Table VI.

Acknowledgments.—We are indebted to Samuel W. Blackman and N. Martinez, Jr., for microanalyses, Phoebe Lee Graham for absorption spectra and Shirley DuBreuil for technical assistance. We wish to express our gratitude to Dr. Charles H. Kellaway for advice and encouragement and for the correlation of the efforts of the two laboratories involved.

TUCKAHOE, N. Y. RECEIVED FEBRUARY 2, 1951

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

2,4-Diaminopyrimidines as Antimalarials. II. 5-Benzyl Derivatives

BY ELVIRA A. FALCO, SHIRLEY DUBREUIL AND GEORGE H. HITCHINGS

2-Amino-5-benzyl-4-hydroxypyrimidines are prepared by the condensation of α-formyl-β-phenylpropionic esters or α-benzyl-β-ketoesters with guanidine. The conversion of these to 2,4-diaminopyrimidines *via* the 2-amino-4-chloro derivatives is described. Maximal antimalarial activity in this series is found when an electron-attractive substituent is present in the *para* position of the benzene ring and a methyl group is present in the pyrimidine-6 position.

The discovery of antimalarial activity in 5-(4′-chlorophenoxy)-2,4-diaminopyrimidine[1] and its 6-methyl homolog[2,3] indicated the desirability of the preparation and testing of various related structures. The oxygen atom of the phenoxypyrimidine was viewed as a connecting group of unknown importance between the pyrimidine and benzene nuclei. The preparation of similar substances with various atoms and groups, including nitrogen, sulfur and carbon in this position was therefore proposed for further investigation. The most readily accessible of these appeared to be the compounds with a methylene group in this position. Kast[4] had reported the preparation of 5-benzyl-2,4-diaminopyrimidine[5] by a rather roundabout and unfruitful method. However, Johnson and Ambelang[6] had formylated ethyl hydrocinnamate and condensed the resulting α-formyl derivative (I, R = H) with thiourea to give 5-benzyl-2-thiouracil. It seemed probable that α-formyl-β-phenylpropionic esters in general would condense with guanidine to give 2-amino-5-benzyl-4-hydroxypyrimidines (II, R = H) which could be converted to the diamino derivatives (IV, R = H) *via* the 4-chloropyrimidines (III, R = H) in the same manner as the 5-aryloxypyrimidines.

The available precedents were closer to the desired 5-benzyl-2,4-diamino-6-substituted pyrimidines, which were regarded as the more important series. Wheeler and McFarland[7] had prepared 5-benzyl-2-ethylmercapto-4-hydroxy-6-methylpyrimidine, and Curd, *et al.*,[8] had used this as an intermediate for the preparation of a series of 2-anilino-5-

(1) E. A. Falco, G. H. Hitchings, P. B. Russell and H. VanderWerff, *Nature*, **164**, 107 (1949).

(2) L. G. Goodwin, *ibid.*, **164**, 1133 (1949).

(3) E. A. Falco, P. B. Russell and G. H. Hitchings, THIS JOURNAL, **73**, 3753 (1951).

(4) H. Kast, *Ber.*, **45**, 3124 (1912).

(5) The identity of Kast's substance is an open question since the melting point which he reports is about 50° lower than that of an authentic sample prepared from 2-amino-5-benzyl-4-hydroxypyrimidine (*cf.* Table V).

(6) T. B. Johnson and J. C. Ambelang, THIS JOURNAL, **60**, 2941 (1938).

(7) H. E. Wheeler and D. F. McFarland, *Am. Chem. J.*, **42**, 101 (1909).

(8) F. H. S. Curd, D. N. Richardson and F. L. Rose, *J. Chem. Soc.*, 382 (1946).