steam cone for one hour, 2,3-dihydroxyquinoxaline was obtained.

3-Amino-2-sulfanilamidoquinoxaline, XI.—A suspension of 6.4 g. (0.04 mole) of 2,3-diaminoquinoxaline in 125 ml. of dry pyridine was warmed to 35° and 9.2 g. (0.039 mole) of *p*-acetylaminobenzenesulfonyl chloride added gradually over forty-five minutes. The turbid mixture was warmed for one hour at 50°, treated with decolorizing charcoal, and concentrated *in vacuo* to a thick gum. By working with water a pale yellow granular precipitate was obtained which was twice dissolved in 3 *N* ammonium hydroxide, treated with decolorizing charcoal and precipitated with acetic acid. The product, 10.8 g. (75.6%), darkened at 250° and sintered and decomposed at 260°. An analytical sample recrystallized from glacial acetic acid behaved similarly.

Anal. Calcd. for 3-amino-2-(N⁴-acetylsulfanilamido)-quinoxaline, $C_{16}H_{15}N_5SO_3$: C, 53.77; H, 4.25; N, 19.60. Found: C, 53.75; H, 4.49; N, 19.75.

When two or more equivalents of *p*-acetylaminobenzenesulfonyl chloride were utilized, the same compound was obtained. Attempts to replace the amino group by hydroxyl by treatment with nitrous acid gave unidentifiable tars.

Hydrolysis of the acetyl group was effected by heating 8 g. of compound in 80 ml. of absolute ethanol and 40 ml. of concentrated hydrochloric acid for one hour at reflux. The reaction mixture was cooled and the precipitated white hydrochloride dissolved in 5 *N* ammonium hydroxide and precipitated with acetic acid. After two such purifications, the yield of pale yellow material was 5.0 g. (70.8%); it darkened at 260° and sintered and decomposed at 275–280°.

Anal. Calcd. for 3-amino-2-sulfanilamidoquinoxaline, $C_{14}H_{13}N_6SO_2$: C, 53.33; H, 4.15; N, 22.21. Found: C, 53.19; H, 4.10; N, 22.45.

Hydrolysis could also be accomplished by heating with 2.5 *N* sodium hydroxide but when 2.5 *N* hydrochloric acid was used only 2-amino-3-hydroxyquinoxaline was obtained.

Acknowledgment.—The authors are indebted to Dr. R. T. Major and Dr. Max Tishler for their kind encouragement, advice and criticism. Mr. R. M. Wilson, Jr., Mr. C. A. Robinson and Miss L. H. Falk assisted with the preparation of the compounds.

Summary

Material present in the kidneys of rats fed 2-sulfanilamidoquinoxaline was identified by synthesis as 3-hydroxy-2-sulfanilamidoquinoxaline. Efforts to synthesize this compound also led to the preparation of 3-methoxy-2-sulfanilamidoquinoxaline, 3-amino-2-sulfanilamidoquinoxaline, 2-chloro-3-methoxyquinoxaline, 2-amino-3-methoxyquinoxaline and 2,3-dimethoxyquinoxaline.

RAHWAY, N. J. RECEIVED FEBRUARY 8, 1946

[CONTRIBUTION FROM THE CHEMOTHERAPY DIVISION, STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID COMPANY]

Studies in Chemotherapy. XIV. Antimalarials. The Synthesis of Substituted Metanilamides and Related Compounds[1]

BY J. P. ENGLISH, J. H. CLARK, R. G. SHEPHERD, H. W. MARSON, J. KRAPCHO AND R. O. ROBLIN, JR.

2-Sulfanilamido-5-chloropyrimidine (Fig. 1, X = Cl) and its bromine analog (Fig. 1, X = Br) were prepared[2] in the course of attempts to obtain sulfanilamides more active than sulfadiazine (Fig. 1, X = H) in experimental malaria. These compounds proved to be unusual in that, unlike sulfadiazine and the other sulfanilamides tested, their antimalarial activity was only partially prevented by *p*-aminobenzoic acid.[3] Other sulfanilamidohalogen heterocycles did not show this behavior and we therefore explored other possibilities in attempting to develop this new antimalarial activity.

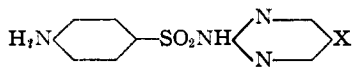
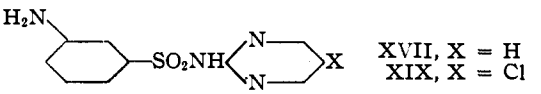


Fig. 1.—2-Sulfanilamidopyrimidines

To investigate the effects of isomerism, 2-metanilamidopyrimidine[4] (Fig. 2, XVII) and 2-metanilamido-5-chloropyrimidine (Fig. 2, XIX) were prepared. These compounds, isomers of



XVII, X = H
XIX, X = Cl

Fig. 2.—2-Metanilamidopyrimidines

sulfadiazine and its 5-chloro substitution product, proved to be highly active in sporozoite-induced *Plasmodium gallinaceum* infections in chickens,[5] and representative N¹-substituted metanilamides and orthanilamides, as well as variously substituted 2-phenylsulfonamidopyrimidines, were synthesized to study the relation of structure to activity in these series. The compounds prepared in this research are listed in Table I together with their antimalarial activities. Several known compounds are also included there for purposes of comparison.

The nitro compounds, from which the metanilamides and *m*-aminobenzamido compounds were prepared by reduction, are listed in Table II (see Experimental). These, with a few exceptions, were synthesized by the reaction of the appropriate acid chloride with the amine. The phenylsulfonamidoheterocycles in Table I were also prepared by this general procedure using benzenesulfonyl chloride. Anhydrous pyridine

(1) Presented in part before the Medicinal and Organic Sections of the American Chemical Society, Atlantic City, April 8–12, 1946.

(2) English, Clark, Clapp, Seeger and Ebel, THIS JOURNAL, **68**, 453 (1946).

(3) Waletzky and Brackett, unpublished results.

(4) The nomenclature is that proposed by Crossley, Northey and Hultquist, THIS JOURNAL, **60**, 2217 (1938).

(5) Brackett and Waletzky, in preparation.

TABLE I

PROPERTIES OF METANILAMIDES AND RELATED COMPOUNDS

Number	SN[a]	Name[i]	M. p., °C. (cor.)	D. equiv.[b]	Prepn.[c]	Yield, %[d]	Method of purification	Formula	Analyses, %[g] Calcd. C	H	N	Found[h] C	H	N
I	196	M		<0.02	j									
II	12,654	N[1]-Ethyl-M	90–91	<0.02	A	70	1	$C_9H_{12}N_2O_3S$	48.0	6.0	14.0	47.8	6.1	14.2
III	12,655	N[1],N[1]-Diethyl-M	90–91	<0.02	B	63	1	$C_{10}H_{14}N_2O_3S$	52.6	7.1	12.3	52.7	6.9	12.3
IV	12,661	N[1]-Phenyl-M	129–131	<0.02	k	73	5, 3	$C_{13}H_{12}N_2O_3S$						
V		N[1]-3,5-Dibromophenyl-M	179–180	<0.02	C	56	2	$C_{13}H_{10}Br_2N_2O_3S$	35.5	2.5	6.9	35.4	2.7	6.7
VI	12,646	N[1]-Phenyl-6-hydroxy-M	158–160	<0.02	l, m	57	6	$C_{13}H_{12}N_2O_4S$						
VII	12,651	Metanilylguanidine	187–189	<0.02	D	43	3	$C_7H_{10}N_4O_2S^n$	39.2	4.7	26.2	39.7	4.8	26.3
VIII		N[1]-(3,5-Dibromobenzoyl)-M	201–202	<0.02	E	71	4	$C_{14}H_{10}Br_2N_2O_4S^o$	36.0	2.3	6.4	36.4	2.5	6.2
IX	12,184	2-M-Py[j]	185–187	0.3	F	77	5	$C_{11}H_{11}N_3O_2S$	53.0	4.4	16.9	53.3	4.3	16.6
X	12,203	2-M-5-bromo-Py	196–198	0.75	G	70	5	$C_{11}H_{10}BrN_3O_2S$	40.2	3.1	12.8	40.2	3.2	12.8
XI	12,649	2-M-5-chloro-Py	187–189	0.25	H	45	5	$C_{11}H_{10}ClN_3O_2S$	46.6	3.6	14.8	46.5	3.6	14.8
XII	12,652	3-M-Py	198–199	0.	I	58	5	$C_{11}H_{11}N_3O_2S$	53.0	4.4	16.9	53.2	4.6	17.0
XIII	12,901	4-M-7-chloroquinoline	276–278	<0.02(d)	J	66	3, 5	$C_{16}H_{12}ClN_3O_2S$	54.0	3.6	12.6	53.9	3.7	12.5
XIV	12,201	2-M-thiazole	190–192	0.2	K	85	3, 5	$C_9H_9N_3O_2S_2$	42.3	3.6	16.5	42.5	3.7	16.4
XV	12,938	N[1]-2-Thiazolyl-6-hydroxy-M	230	<0.02	m	95	3	$C_9H_9N_3O_3S_2$	39.8	3.3	15.5	40.1	3.7	15.7
XVI		2-M-thiadiazole hydrate	ca. 60	<1	L, m	50	6	$C_9H_8N_4O_2S_2 \cdot H_2O^p$	35.0	3.7	20.4	35.4	3.6	20.5
XVII	11,435	2-M-P	250–252	3	M	70	3, 5	$C_{10}H_{10}N_4O_2S$	48.0	4.0	22.4	48.0	4.2	22.4
XVIII	12,653	2-M-5-bromo-P	238.5–240	4	N	63	5	$C_{10}H_9BrN_4O_2S^p$	36.5	2.8	17.0	36.6	3.0	16.6
XIX	11,437	2-M-5-chloro-P	230–232	6	O, m	84	5, 3	$C_{10}H_9ClN_4O_2S$	42.2	3.2	19.7	42.3	3.3	19.7
XX		2-M-5-iodo-P	250–251	4	P	48	5	$C_{10}H_9IN_4O_2S$	31.9	2.4		32.0	2.4	
XXI	12,202	2-M-4-methyl-P	210–213	0.05	R	73	5	$C_{11}H_{12}N_4O_2S$	50.0	4.6	21.2	49.9	4.7	21.1
XXII		2-M-5-bromo-4-methyl-P	197–198	1	S	56	2	$C_{11}H_{11}BrN_4O_2S$	38.5	3.2	16.3	38.8	3.5	16.0
XXIII	12,657	2-M-4-methoxy-P	228–230	<0.1	T	56	5	$C_{11}H_{12}N_4O_3S$	47.1	4.3	20.0	47.2	4.3	20.1
XXIV	12,662	2-M-5-bromo-4-methoxy-P	240–241	ca. 0.5	U	60	7, 2	$C_{11}H_{11}BrN_4O_3S$	36.8	3.1	15.6	37.0	3.2	15.6
XXV		N[1]-2-Pyrimidyl-6-chloro-M	250–252	1	W, m	74	5	$C_{10}H_9ClN_4O_2S$	42.2	3.2	19.7	42.4	3.4	19.4
XXVI	12,659	N[1]-Methyl-2-M-P	158.5–159.5	1	m	53	8	$C_{11}H_{12}N_4O_2S$	50.0	4.6	21.2	50.4	4.6	21.0
XXVII	12,658	N[1]-Methyl-5-chloro 2-M-P	130–131	ca. 1	m	40	8	$C_{11}H_{11}ClN_4O_2S$	44.2	3.7		44.2	3.9	
XXVIII	14,030	N[1]-2-Pyrimidyl-5-amino-M	283–285	<0.05(d)	X	81	3	$C_{10}H_{11}N_5O_2S$	45.3	4.2	26.4	45.5	4.4	26.5
XXIX	11,436	2-M-pyrazine	236–237	1	m	26	2	$C_{10}H_{10}N_4O_2S$	48.0	4.0	22.4	48.2	4.0	22.3
XXX		2-M-quinoxaline	231–232	<0.1	V	70	5	$C_{14}H_{12}N_4O_2S$	56.0	4.0	18.7	56.0	4.1	18.6
XXXI		2-O-P	225–227	<0.01	m	84	5	$C_{10}H_{10}N_4O_2S$	48.0	4.0		48.0	4.0	
XXXII	14,031	2-O-5-chloro-P	193.5–195	0.5(d)	m	32	2	$C_{10}H_9ClN_4O_2S$	42.2	3.2	19.7	42.3	3.2	19.7
XXXIII	14,029	2-O-pyrazine	229–231	<0.02	m	13	9, 5	$C_{10}H_{10}N_4O_2S$	48.0	4.0	22.4	48.3	4.1	22.5
XXXIV		2-B-5-chloro-Py	164.5–166	<0.1	v	87	5, 2	$C_{11}H_9ClN_2O_2S$	49.2	3.9		49.1	3.4	
XXXV	11,027	2-B-P	229–230	<0.02	q			$C_{10}H_9O_2N_3S$						
XXXVI	11,653	2-B-5-chloro-P	220–221	0.5(d)	v	80	10	$C_{10}H_8ClN_3O_2S^r$	44.5	3.0	15.6	45.0	3.1	15.6
XXXVII		2-B-5-bromo-4-methyl-P	205.5–207.5	<0.1(d)	m	32	4	$C_{11}H_{10}BrN_3O_2S$	40.2	3.0	12.8	40.4	3.3	12.8
XXXVIII	11,302	2-B-4-methyl-P	193–194	<0.02(d)	q			$C_{11}H_{11}N_3O_2S$						
XXXIX	12,647	2-(*p*-Bromo-B)-5-chloro-P	261–264	0.15(d)	v	33	9	$C_{10}H_7BrClN_3O_2S$	34.5	2.0	12.0	34.7	2.2	12.0
XL	12,650	2-(*p*-Bromo-B)-P	212–213.5	<0.02(d)	w	54	7	$C_{10}H_8BrN_3O_2S$	38.2	2.6	13.4	38.2	2.6	13.4
XLI	14,032	2-(3,5-Dibromo-B)-5-chloro-P	258–259	<0.1(d)	m	55	9	$C_{10}H_6Br_2ClN_3O_2S$			9.8			9.9
XLII		2-B-5-bromo-P	240–241	0.5(d)	v	74	5	$C_{10}H_8BrN_3O_2S$			13.4			13.2
XLIII		2-B-5-iodo-P	255–256	<0.5(d)	m	61	10	$C_{10}H_8IN_3O_2S^s$	33.3	2.2		33.3	2.2	
XLIV		2-B-5-cyano-P	226–227	<0.05(d)	m	63	2	$C_{11}H_8N_4O_2S$	50.8	3.1		50.7	3.3	
XLV	13,862	2-(*m*-Hydroxy-B)-P	212–214	<0.01(d)	m	61	6	$C_{10}H_9N_3O_3S$	47.8	3.6	16.7	47.9	3.7	16.8
XLVI	14,683	2-(*m*-Chloro-B)-P	187–190	<0.02(d)	m	31	7, 4	$C_{10}H_8ClN_3O_2S^t$	44.5	3.0	15.6	44.8	3.1	15.6
XLVII	1917	2-(*m*-Cyano-B-)-P	237–238	<0.02(d)	m	93	11	$C_{11}H_8N_4O_2S^u$	50.8	3.1	21.5	50.8	3.2	21.7
XLVIII	14,789	2-(*m*-Carboxy-B)-P	287–289	<0.02(d)	m	98	5	$C_{11}H_9N_3O_4S$	47.3	3.3	15.1	47.3	3.3	14.9
XLIX		2-(*m*-Carbamyl-B)-P	252–253	<0.02(d)	m	91	5	$C_{11}H_{10}N_4O_3S$	47.5	3.6	20.1	47.5	3.7	20.3
L	14,721	2-[*m*-(2-Pyrimidyl-carbamyl)-B]-P hydrate	254–255	<0.05(d)	m	56	11	$C_{15}H_{12}N_6O_3S \cdot H_2O$	48.1	3.8	22.4	48.0	3.9	22.2
LI		2-(*m*-Aminomethyl-B)-P hydrate	218–220	<0.05(d)	m	24	5, 6	$C_{11}H_{12}N_4O_3S \cdot H_2O$	46.8	5.0		46.8	5.1	
LII		2-(*m*-Aminobenzamido)-P	186–187.5	<0.01(d)	Y	55	6	$C_{11}H_{10}N_4O$	61.7	4.7		61.9	4.8	
LIII		2-(*m*-Aminobenzamido)-5-chloro-P	215–216.5	<0.03(d)	Z	60	3	$C_{11}H_9ClN_4O$	53.1	3.7		53.4	3.8	
LIV	13,872	*m,m'-bis*-(2-Pyrimidylsulfamyl)-carbanilide hydrate	ca. 315	<0.02(d)	m	59	5, 1	$C_{21}H_{18}N_8O_6S_2 \cdot H_2O^x$	46.3	3.7	20.6	46.4	3.8	20.5

[a] SN = Survey number, a number identifying compounds submitted to the Survey of Antimalarial Drugs and to appear in the forthcoming monograph, "A Survey of Antimalarial Drugs, 1941–1945," F. Y. Wiselogle, Editor. [b] Ratio, blood level sulfadiazine/blood level of compound giving an equal effect. Determined in these laboratories in sporozoite-induced *P. gallinaceum* infections of white leghorn chicks under the direction of Dr. S. Brackett, test O–2 of ref. (a). When the number is followed by a (d) the comparison was on a dosage basis, < shows the compound to be inactive at the dosage used. [c] Capital letters refer to the corresponding nitro compound in Table II. The reduction methods are discussed in the Experimental part. Small letters refer to footnotes. [d] Purified. [e] Symbols mean the following: 1, 50% alcohol; 2, abs. alcohol; 3, acid–charcoal; 4, ethylene chloride; 5, alkali–charcoal; 6, water; 7, 50% acetic acid; 8, methanol; 9, cellosolve; 10, glacial acetic acid; 11, ammonium salt (see exptl.). Purification was by crystallization from the boiling solvent or by reprecipitation, usually in the cold, from acid or alkali. [f] Microanalyses were carried out in these laboratories under the direction of Dr. J. A. Kuck. [g] Values given are the average of two determinations not differing by more than 0.3. [h] M = metanilamide or metanilamido (see footnote 4); Py = pyridine; P = pyrimidine; B = phenylsulfonamido; O = orthanilamido. [i] Footnote 31. [j] German Patent 226,240; *Frdl.*, 10, 807. [k] Williams, *J. Chem. Soc.*, 709 (1942). [l] See Experimental. [m] S: Calcd. 15.0. Found: 15.1. [n] Br: Calcd. 36.8. Found: 37.0. [o] S: Calcd. 9.7. Found: 9.7. [p] English, Chappell, Bell and Roblin, THIS JOURNAL, 64, 2516 (1942). [q] Cl: Calcd. 13.2. Found: 13.3. [r] S: Calcd. 8.9. Found: 8.9. [s] Calcd.: S, 11.9; Cl, 13.2. Found: S, 11.9; Cl, 13.1. [t] S: Calcd. 12.3. Found: 12.2. [u] Ref. *m*, Table II. [v] Ref. *p*, Table II. [w] S: Calcd. 11.8. Found: 11.6. [x] Prepared by Dr. G. W. Anderson. [y] S: Calcd. 23.4. Found: 23.4.

was used as a reaction medium for all of the heterocyclic amines except 4-amino-7-chloroquinoline; in this case the addition of triethylamine to the reaction mixture was necessary to obtain a satisfactory yield. The more basic medium was probably required because 4-aminoquinoline is a much stronger base than pyridine.[6] Both 2-(*m*-nitrophenylsulfonamido)-5-chloropyrimidine (O) and its bromine analog (N) were prepared via the acid chloride and also by the direct halogenation of 2-(*m*-nitrophenylsulfonamido)-pyrimidine (M). A similar bromination has been reported since this work was completed.[7] The corresponding iodo derivative (P) was prepared only by the latter method. In this case the presence of one mole of mercuric acetate was necessary for the reaction. These same reactions were also carried out with the 2-phenylsulfonamidopyrimidines.

2-Amino-5-cyanopyrimidine did not react with *m*-nitrobenzenesulfonyl chloride, even under very drastic conditions.[8] The desired product (Q) was, therefore, prepared by the reaction of the iodo compound (P) with cuprous cyanide in boiling quinoline.[9] The corresponding benzenesulfonamide (XLIV) was also prepared from either the bromo derivative (XLII) or iodo derivative (XLIII). The structure of all of these compounds as 5-iodo or cyanopyrimidines was established by the preparation of the same cyano compound from both the bromo and iodo derivatives in either series. The bromo derivatives in both cases were prepared either by bromination of the sulfonamide or starting from 2-amino-5-bromopyrimidine.[2]

Yields in the reaction of substituted 2-aminopyrimidines with the sulfonyl chlorides were consistently lower than with 2-aminopyrimidine itself. This result was obtained with base strengthening groups (*e. g.*, 4-methyl or 4-methoxy) as well as with base weakening substituents such as halogens. The above observations made the direct halogenation of the sulfonamides the method of choice for the preparation of the halogenated phenylsulfonamidopyrimidines, especially as low yields were obtained in the halogenation of 2-aminopyrimidine.[2]

N-(*m*-Nitrophenylsulfonyl)-3,5-dibromobenzamide (E) was prepared by the reaction of 3,5-dibromobenzoyl chloride with *m*-nitrobenzenesulfonamide.[10] Some difficulty was encountered in working up N^1-(3,5-dibromobenzoyl)-metanilamide (VIII) due to its easy oxidative decomposition and N^3-rearrangement in alcoholic solution at 25°. Catalytic reduction gave a very satisfactory synthesis if the product was precipitated at once from the polar reduction solvent and recrystallized from a non-polar solvent such as ethylene chloride.

N^1-Methyl-2-metanilamidopyrimidines, XXVI and XXVII, were prepared by the reaction of the metanilamides, XVII and XIX, with diazomethane. N^1-Methylation was established by the hydrolysis of XXVII with sulfuric acid to give 2-methylamino-5-chloropyrimidine identical with that prepared from 2,5-dichloropyrimidine and methylamine. The point of methylation was shown to be the same in both cases by the dehalogenation of XXVII to XXVI using Raney nickel alloy in methanolic potassium hydroxide.[11] The absence of ring methylation was unexpected in view of the behavior of sulfapyridine and sulfathiazole in the same reaction.[12]

In the course of the synthesis of the 6-hydroxymetanilamides, VI and XV, by the method of Williams,[13] it was observed that the intermediate

(6) Albert and Goldacre, *Nature*, 153, 467–469 (1944).

(7) Price, Leonard and Whittle, *J. Org. Chem.*, 10, 327 (1945).

(8) A similar situation was encountered by Ellingson, Henry and McDonald (THIS JOURNAL, 67, 1711 (1945)) when they attempted the reaction of 2-amino-3-cyanopyrazine with acetylsulfanilyl chloride. They explain this failure to react on the basis of an unreactive imine tautomer. We prefer the explanation that the amine is so weakened by the cyano group that no reaction takes place. This is in accordance with the observation that sulfonyl chlorides do not react with carboxyamides under ordinary conditions (Crossley, Northey and Hultquist, *ibid.*, 61, 2950 (1939)). The postulation of a non-reactive tautomer also neglects the observation that 1-benzyl-2-pyridone imine reacts with acetylsulfanilyl chloride as readily as does 2-aminopyridine (Shepherd, Bratton and Blanchard, *ibid.*, 64, 2532 (1942)).

(9) Barber and Slack, *J. Chem. Soc.*, 613 (1944).

(10) Crossley, Northey and Hultquist, THIS JOURNAL, 61, 2950 (1939).

(11) Schwenk, Papa and Ginsberg, *Ind. Eng. Chem., Anal. Ed.*, 15, 576 (1943).

(12) Shepherd, Bratton and Blanchard, THIS JOURNAL, 64, 2532 (1942).

(13) Williams, *J. Chem. Soc.*, 709 (1942).

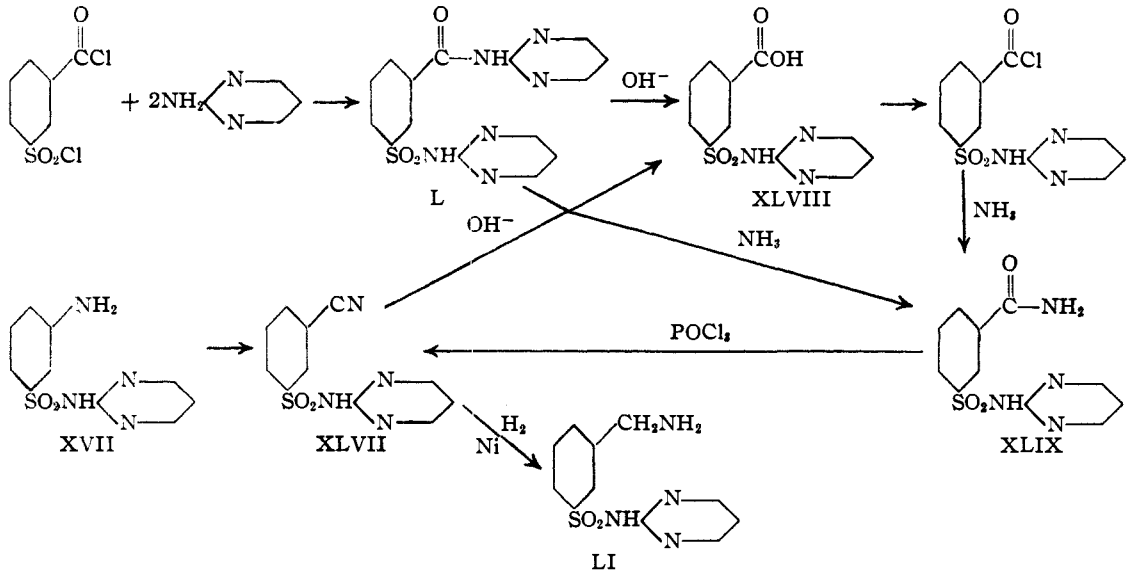


Fig. 3.—Preparation of 2-(*m*-cyanophenylsulfonamido)-pyrimidine.

6-acetoxy-N^8-acetylmetanilamides were smoothly converted to 6-hydroxy-N^8-acetylmetanilamides by aqueous ammonia. Hydrolysis with acid converted the diacetyl derivative directly to the hydroxy metanilamide.

Several of the compounds in Table I were prepared by the reaction of the corresponding 2-chloroheterocycle with sulfonamides. This reaction was carried out in nitrobenzene in the presence of potassium carbonate. The availability of 2-chloropyrazine[14] made this the method of choice for the synthesis of 2-metanilamidopyrazine (XXIX) and the isomeric orthanilamide (XXXIII). It was found possible to convert 2-amino-5-chloropyrimidine to 2-hydroxy-5-chloropyrimidine[15] by the action of nitrous acid and this was converted smoothly to 2,5-dichloropyrimidine by the action of phosphorus oxychloride. The dichloropyrimidine reacted with metanilamide and orthanilamide to give the respective N^1-(5-chloro-2-pyrimidyl) derivatives (XIX and XXXII).

2-Orthanilamidopyrimidine (XXXI) was prepared by the dehalogenation of 2-orthanilamido-5-chloropyrimidine (XXXII) after it had proved impossible to prepare it by the reaction of *o*-nitrobenzenesulfonyl chloride[16] and 2-aminopyrimidine. The only product which was isolated from the latter reaction was 2-(*o*-nitroanilino)-pyrimidine. This presumably arose from the initially formed but unstable 2-(*o*-nitrophenylsulfonamido)-pyrimidine by the loss of sulfur dioxide. A similar reaction has been reported[17] when N-(*p*-nitrophenylsulfonyl)-benzamidine was heated to 200°. Sulfur dioxide was evolved and N-(*p*-nitrophenyl)-benzamidine was formed.

(14) Sayward, U. S. Patent 2,391,745, December 25, 1945.

(15) We are indebted to Dr. R. Winterbottom for working out this procedure.

(16) "Organic Syntheses," Coll. Vol. 11, p. 471 (1943).

(17) Barber, *J. Chem. Soc.*, 102 (1943).

The three 3-substituted phenylsulfonamidopyrimidines, XLV–XLVII, were prepared by the application of the diazo reaction to 2-metanilamidopyrimidine (XVII). The cyano compound XLVII was also prepared by the series of reactions shown in Fig. 3 which was more satisfactory for the preparation of any quantity of this compound or its transformation products, XLVIII and LI.

In practice the direct reaction of L with ammonia under pressure to give XLIX was the more desirable procedure but the route through the acid permitted the demonstration of the identity of the acid, XLVIII, from the two different sources. L formed a hydrate when crystallized from water and the anhydrous compound was hygroscopic. The aminomethyl compound, LI, which also formed a hydrate, was prepared by Raney nickel reduction of the nitrile in alcoholic ammonia solution.

Of the compounds synthesized in this study, two general series, the N^1-heterocyclic metanilamides and the 2-phenylsulfonamido-5-chloro- and -bromopyrimidines have shown antimalarial activity. Several of the compounds fall into both classes and form a very interesting group which will be considered separately. In the metanilamidoheterocycles the effects of substituents in both the benzene and heterocyclic rings have been studied. In the benzene ring the introduction of a 6-hydroxy (*cf.* XIV with XV) or of a 5-amino (*cf.* XVII with XXVIII) inactivates the compound. The presence of a 6-chloro (XVII *vs.* XXV) seems to be without effect. The substitution of 4-methyl or of 4-methoxy in the pyrimidine ring of XVII lowers the activity markedly. Replacement of the sulfonyl group of the metanilamides with carbonyl leads to loss of activity (*cf.* LII and LIII with XVII and XIX).

The preparation of 2-metanilamido-5-cyano-

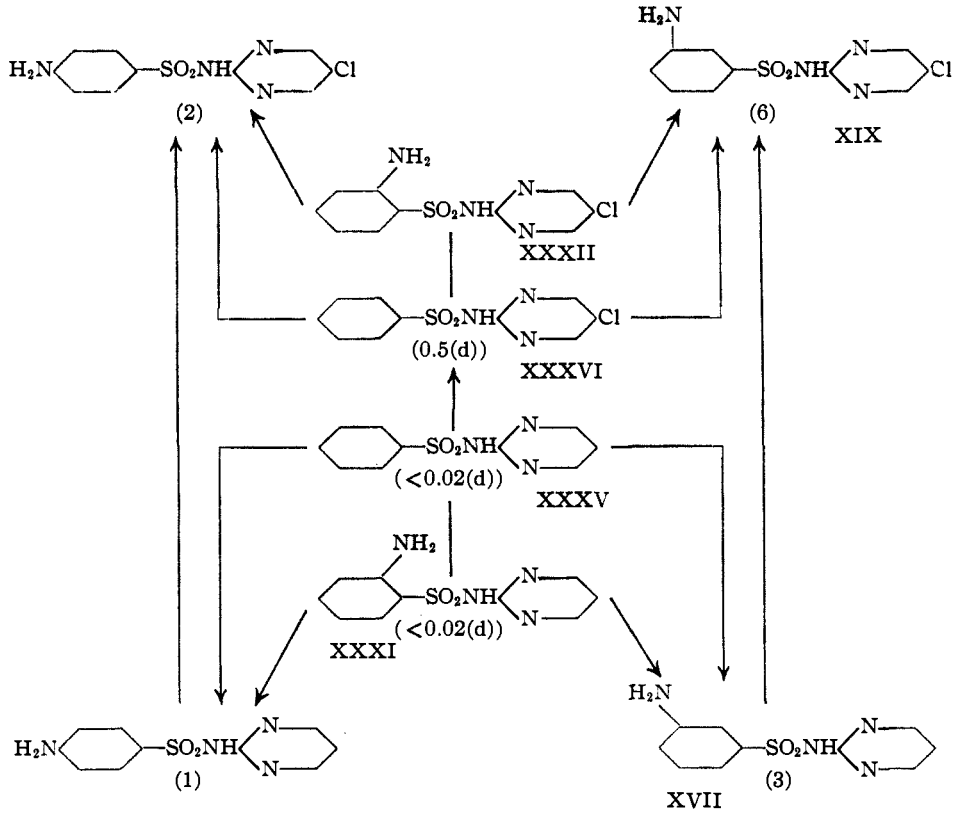


Fig. 4.—The relation of structure to antimalarial activity among 2-phenylsulfonamidopyrimidines. The lines represent a single transformation, either a substitution or an isomerization. The arrowhead points in the direction of increasing activity; where there is no head the compounds are equally active. The numbers in parentheses are sulfadiazine equivalents from Table I.

pyrimidine, which was of interest in the attempt to compare the influence of the cyano and chloro groups, was not achieved. (For a description of attempts to synthesize this compound, see the Experimental Section following the corresponding nitro compound, Q.) The administration of Q produced an appreciable antimalarial effect. That this was probably due to the metanilamide was indicated by the appearance of diazotizable amine in the blood. A similar situation was encountered previously in the case of 5-(*p*-nitrophenylsulfonamido)-tetrazole.[18] It should also be pointed out that activities proportional to blood level were found in the testing of 2-(*m*-nitrophenylsulfonamido)-5-chloropyrimidine, O, assuming the product in the blood to be the corresponding metanilamide (XIX).

The action of the 2-phenylsulfonamido-5-chloro and 5-bromopyrimidines (XXXVI and XLII) seems to be specific to the phenylsulfonamidohalopyrimidine system as 2-phenylsulfonamido-5-chloropyridine (XXXIV) is inactive. Moving the halogen to the benzene ring also destroys the activity (*cf.* XL with XLII). The 5-iodo compound (XLIII) in the pyrimidine series is essentially inactive as is the cyano compound. Again, 4-methyl in the pyrimidine ring has a depressing effect on the activity (*cf.* XXXVII with XXXVI).

The most active compounds have been found among those derivatives which belong to both of the above classes, namely, the 2-metanilamido-5-halogenopyrimidines (XVIII, XIX and XX). However, this combination effect is counteracted by the same substituents which lower the activity of metanilamidopyrimidine itself, *i. e.*, 4-methyl (XXII) and 4-methoxy (XXIV).

The increased effectiveness of the halogenated compounds over the non-halogenated ones is of interest when it is recalled that the same substitution increased the antimalarial activity of sulfadiazine.[2] In the earlier case, the enhanced activity of 2-sulfanilamido-5-chloropyrimidine (Fig. 1, X = Cl) was not completely prevented by *p*-aminobenzoic acid. Two modes of action in the same molecule were postulated to explain this observation. This hypothesis is reinforced by the present observation of the antimalarial activity of 2-phenylsulfonamido-5-chloropyrimidine (XXXVI). The activity of compound XXXVI, like the residual activity of 2-sulfanilamido-5-chloropyrimidine, is not counteracted by *p*-aminobenzoic acid. The presence of a second mode of action is also indicated by the increased activity of 2-metanilamido-5-chloropyrimidine (XIX) over the

(18) Roblin, Williams, Winnek and English, THIS JOURNAL, **62**, 2002 (1940).

unchlorinated compound (XVII). If the simplifying assumption is made that the metanilamido-heterocycles have the same mode of action, the activity of XIX would appear to be due to a combination of the mode of action found in XVII and that found in XXXVI. Similarly the activity of 2-sulfanilamido-5-chloropyrimidine would be due to the activity found in sulfadiazine plus that found in XXXVI. A résumé of these relationships among the 2-phenylsulfonamidopyrimidines is shown in Fig. 4.

Further evidence of the nature of the mode of action found in XXXVI is provided by the consistently unfavorable effect of a methyl group in the 4-position of the pyrimidine ring adjacent to the chlorine. In the sulfanilamide series the total activity is decreased, and that remaining is completely prevented by *p*-aminobenzoic acid. Similarly, 2-phenylsulfonamido-5-bromo-4-methylpyrimidine (XXXVII) is without activity and that of the corresponding metanilamide (XXII) is reduced. In the case of the most active compound in these series, 2-metanilamido-5-chloropyrimidine (XIX), there is, unfortunately, no clear-cut method for demonstrating a dual mode of action. Again, however, a reasonable assumption, on the basis of the present evidence, is the existence of two modes of antimalarial action in this molecule.

The metanilamides described here are in striking contrast to the sulfanilamides both in their lack of antibacterial action[19] and in the more restricted nature of the N^1-substituents associated with antimalarial activity. The former observation is in agreement with previous reports on the antibacterial activities of metanilamides.[20] It was probably this fact, together with the parallel nature of the antimalarial and antibacterial action of the sulfanilamides,[3] which discouraged an earlier examination of this field.

The antimalarial activity of the metanilamides has been studied in detail in these laboratories.[21] In addition to the action on sporozoite-induced infections of *P. gallinaceum* which has been discussed above, the N^1-heterocyclic metanilamides have been shown to have activity on blood-induced infections of this same species, 2-metanilamido-5-chloropyrimidine (XIX) being sixteen times as active as quinine[22] in this type of experimental malaria. It has also been shown to be active in preventing sporozoite-induced infections of *P. cathemerium* in the canary,[23] an infection against which the sulfanilamides are inactive. The pharmacology and toxicity of 2-metanilamido-5-chloropyrimidine (XIX) (metachloridine) has been investigated in these laboratories and will be reported elsewhere.[24] Studies on human malaria, under the auspices of the National Research Council and the Committee on Medical Research of the O.S.R.D. are in progress.

(19) White, Jackson and Alverson, unpublished results.
(20) Northey, *Chem. Rev.*, **27**, 182 (1940).
(21) See ref. 5.
(22) Table I, Footnote *a*, Test O-1.
(23) Hughes and Brackett, unpublished results.
(24) Robinson and Mayer, unpublished results.

Experimental[25]

Nitro Compounds.—Of the nitro compounds listed in Table II, the preparations of E, P and Q are described separately below. All the others were prepared by the reaction of the corresponding acid chloride with the appropriate amine. The preparations of A, B, C and D were carried out in acetone. Two moles of the amines were used in the cases of A and B, and three moles of pyridine in the case of C. The preparation of D was similar to that of acetylsulfanilylguanidine,[26] using 40% aqueous sodium hydroxide as the base. It was necessary to use two moles of guanidine to minimize the formation of the disulfonylguanidine. This impurity could, however, be removed by alkaline extraction. The other condensations of the amines with acid chlorides were carried out in pyridine at the temperatures indicated in the table under conditions similar to those previously described.[27] Compounds N and O were also prepared by the halogenation of M in hot acetic acid solution as described for XLII and XXXVI. The yields were 71% and 45%, respectively.

P was prepared from M, and Q from P, by the methods used for the corresponding benzenesulfonamides, XLIII and XLIV (*see below*). In the case of Q, the heating time was restricted to four minutes to minimize the formation of extensive quantities of by-products. Neither acid nor basic reduction methods were successful in the reduction of Q to the corresponding metanilamide due to changes brought about in the cyano group. 2-Amino-5-cyanopyrimidine did not react with *m*-nitrobenzenesulfonyl chloride even in boiling pyridine. After one and one-half hours the amine was completely unchanged.

N-(*m*-Nitrophenylsulfonyl)-3,5-dibromobenzamide (E).—A solution of 29.8 g. (0.15 mole) of *m*-nitrobenzenesulfonamide[28] in 36 cc. of pyridine at 80° was treated with 40 g. (0.13 mole) of 3,5-dibromobenzoyl chloride[29] in two portions with cooling to keep the temperature at 90–100°. The mixture was heated at 100–110° for fifteen minutes, diluted with 60 cc. of absolute ethanol, and added to 34 cc. of hydrochloric acid (d. 1.19) in 135 cc. of water. The product was purified by dissolving in 50% alcohol with a minimum amount of 10% sodium hydroxide, treatment with charcoal, and reprecipitation by addition of the solution to 50% alcoholic 1 *N* hydrochloric acid. The resulting precipitate was extracted with two 250-cc. portions of ether and recrystallized from 350 cc. of 1:1 methanol-cellosolve using charcoal. The yield was 37 g. and an additional 9 g. of purified material could be obtained by working up the filtrate.

Compounds in Table I

1. **By Reduction of the Nitro Compound. Compounds II–V, VII–XIV, XVI–XXV, XXVIII, XXX, LII and LIII.**—These compounds were prepared by the reduction of the corresponding nitro compounds. II, III, V and VIII were obtained by catalytic reductions with Raney nickel in alcohol at 2–3 atmospheres of hydrogen pressure. VII was similarly prepared using Adams catalyst. Special handling was required by VIII (see below). XXII and XXV were obtained by an iron–acetic acid reduction (see below) and in all the other cases the nitro compound was reduced with ammonium sulfide.[30] The methods of purification are indicated in the table. Of the compounds prepared in this way, XIX was also prepared by the condensation of metanilamide with 2,5-dichloropyrimidine

(25) All melting points are corrected.
(26) Marshall, Bratton, White and Litchfield, *Bull. Johns Hopkins Hosp.*, **67**, 163 (1940).
(27) Roblin and Winnek, THIS JOURNAL, **62**, 2001 (1940).
(28) Obermiller, *J. prakt. Chem.*, (2) **89**, 86 (1914).
(29) Sudborough, *J. Chem. Soc.*, **67**, 593 (1895).
(30) "Organic Syntheses," Coll. Vol. 1, 52 (1941).

TABLE II

INTERMEDIATE NITRO COMPOUNDS

Cpd.	Name[a]	M. p., °C.[b] (cor.)	Intermediates[v]	Temp. of reaction, °C.	Purification Solvent[c]	Purification g./100 cc.[d]	Yield,[e] %	Formula	Analyses,/ % Calcd. C	Calcd. H	Calcd. N	Found[f] C	Found[f] H	Found[f] N
	m-Nitrophenylsulfonyl-													
A	-ethylamine[h]	80–81	..	35	1	20	80							
B	-diethylamine	66	..	60	1	20	85	$C_{10}H_{14}N_2O_4S$			10.8			10.8
C	-3,5-dibromoaniline	180–182	i	60	2	65	85	$C_{12}H_8Br_2N_2O_4S$			6.4			6.2
D	-guanidine	199–201	..	10	11	..	66	$C_7H_8N_4O_4S$[j]	34.4		22.9	34.3		22.8
E	-3,5-dibromobenzamide	221–222	..	90–110	3	15	77	$C_{13}H_8Br_2N_2O_5S$			6.0			6.0
F	-2-amino-Py	229–231	k	<70	9	3	60	$C_{11}H_9N_3O_4S$			15.1			15.1
G	-2-amino-5-bromo-Py	200–202	l	<45	4	..	70	$C_{11}H_8BrN_3O_4S$	36.9	2.3		37.2	2.3	
H	-2-amino-5-chloro-Py	195–197	m	35	4	..	77	$C_{11}H_8ClN_3O_4S$	42.1	2.6		42.3	2.8	
I	-3-amino-Py hydrochloride	248–249	n	40	5	2	73	$C_{11}H_9N_3O_4S\cdot HCl$	41.8	3.2	13.3	42.0	3.2	13.4
J	-4-amino-7-chloroquinoline	275–277	o	60	8	1.5	55	$C_{15}H_{10}ClN_3O_4S$			11.6			11.4
K	-2-aminothiazole	241–242	p	60–90	6	4	42	$C_9H_7N_3O_4S_2$			14.7			14.8
L	-2-aminothiadiazole	192–195	q	35	7	10	35	$C_8H_6N_4O_4S_2$	33.6	2.1		34.0	2.1	
M	-2-amino-P	217–219	p	80–90	8	10	70	$C_{10}H_8N_4O_4S$			20.0			19.7
N	-2-amino-5-bromo-P	245–247	m	120	8	5	40	$C_{10}H_7BrN_4O_4S$	33.4	2.0	15.6	33.8	2.1	15.7
O	-2-amino-5-chloro-P	234–237	m	120	8	5	40	$C_{10}H_7ClN_4O_4S$			17.8			17.7
P	-2-amino-5-iodo-P	256–257	r	...	8	6	67	$C_{10}H_7IN_4O_4S$	29.6	1.7		29.8	1.9	
Q	-2-amino-5-cyano-P	252–254	r	...	8	5	44	$C_{11}H_7N_5O_4S$	43.3	2.3		43.1	2.5	
R	-2-amino-4-methyl-P	227–229	p	35	4	..	42	$C_{11}H_{10}N_4O_4S$			19.0			19.1
S	-2-amino-5-bromo-4-methyl-P	227–228	m	60	8	75	8	$C_{11}H_9BrN_4O_4S$			15.0			14.5
T	-2-amino-4-methoxy-P	241–242	s	70	8	6	40	$C_{11}H_{10}N_4O_5S$			18.1			18.0
U	-2-amino-5-bromo-4-methoxy-P	272–273	r	65	8	1	30	$C_{11}H_9BrN_4O_5S$			14.4			14.3
V	-2-aminoquinoxaline	200–202	t	0	5	10	76	$C_{14}H_{10}N_4O_4S$			17.0			16.7
W	2-(2-Chloro-5-nitrophenylsulfonamido)-P	285	p	60–90	8	1	17	$C_{10}H_7ClN_4O_4S$[u]						
X	2-(3,5-Dinitrophenylsulfonamido)-P	290–293	p	80–90	4	..	52	$C_{10}H_7N_5O_8S$			21.5			21.5
Y	2-(*m*-Nitrobenzamido)-P	180–182	p	75	10	2	70	$C_{11}H_8N_4O_3$	54.1	3.3	22.9	54.2	3.6	22.6
Z	2-(*m*-Nitrobenzamido)-5-chloro-P	171–172	m	100	4	..	63	$C_{11}H_7ClN_4O_3$	47.4	2.5		47.6	2.7	

[a] Py = pyridine. P = pyrimidine. [b] Mostly with decomposition. [c] 1, Aqueous methanol; 2, abs. ethanol; 3, methanol–cellosolve; 4, alkali–charcoal; 5, 2% aqueous ammonia–charcoal; 6, 0.3 *N* alkali–charcoal; 7, 95% ethanol; 8, acetic acid; 9, dioxane; 10, ethylene chloride; 11, tetrachloroethane (used only for analytical sample, see Experimental). The alkali and ammonia were used at room temperature and the product was precipitated by acidification after filtration of the charcoal. The other solvents were used in the usual crystallization. [d] This amount was used with the indicated boiling solvent except for 4, 5 and 6, footnote (*c*). [e] The yield is of purified material. [f] Microanalyses were carried out in these laboratories under the direction of Dr. J. A. Kuck. [g] Average of two values not differing more than 0.3. [h] Chattaway, *J. Chem. Soc.*, **87**, 160 (1905). [i] Körner, *Jahresbericht*, 344 (1875). [j] S: Calcd. 13.1. Found: 13.2. [k] Pyridium Corp. [l] Chichibabin and Tyazhelova, *J. Russ. Phys.-Chem. Soc.*, **50**, 483 (1918); *C. A.*, **18**, 1495 (1924). [m] English, Clark, Clapp, Seeger and Ebel, THIS JOURNAL, **68**, 453 (1946). [n] Philips, *Chem. Zeit.*, **18**, 642 (1894). [o] Andersag, Breitner and Jung, U. S. Patent 2,233,970; *C. A.*, **35**, 3771 (1941). [p] Calco Chemical Division, American Cyanamid Co. [q] Freund and Meincke, *Ber.*, **29**, 2514 (1896). [r] See Experimental. [s] Hilbert and Johnson, THIS JOURNAL, **52**, 1152 (1930). [t] Weijlard, Tishler, Erickson, *ibid.*, **66**, 1957 (1944). [u] S: Calcd. 10.2. Found: 10.6. Cl: Calcd. 11.3. Found: 11.8. [v] References are to the amines. The sources of the acid chlorides are as follows: *m*-Nitrobenzenesulfonyl chloride, Gurdzhi, *Org. Chem. Ind.* (U. S. S. R.), **6**, 253 (1939); through *C. A.*, **34**, 2343 (1940); Hodgson and Whitehurst, *J. Chem. Soc.*, 482 (1944). 3,5-Dinitrobenzenesulfonyl chloride, Griffith, *ibid.*, **125**, 1401 (1924); Jackson and Earle, *Am. Chem. J.*, **29**, 218 (1903); the yield of sulfonic acid was increased appreciably by adding the fuming sulfuric acid in three portions. 2-Chloro-5-nitrobenzenesulfonyl chloride, Fischer, *Ber.*, **24**, 3194 (1891). *m*-Nitrobenzoyl chloride Eastman Kodak Co.

and XXV by the hydrolysis of its N^1-acetyl derivative. Both of these methods are described in more detail below.

XVI was obtained from the reduction in the form of the hydrate. On heating, this material began to lose water at 60° and took the form of a glassy solid. The anhydrous compound was obtained by recrystallization of the hydrate from chlorobenzene; m. p. 165–167.5°.

Anal. Calcd. for $C_6H_8N_4O_2S_2$: C, 37.5; H, 3.2; N, 21.9. Found: C, 37.6; H, 3.3; N, 22.1.

N^1-(3,5-Dibromobenzoyl)-metanilamide (VIII).—Because of the ready oxidative decomposition and rearrangement of this compound only analytically pure nitro compound was used in the reduction. This instability was illustrated by the immediate decomposition produced by charcoal treatment and also by the lowering of the melting point by 20° after an hour in alcoholic solution at room temperature. (That the material thus obtained is partially N^1-(3,5-dibromobenzoyl)-metanilamide is indicated by its separation into two fractions with methanol. The insoluble material melts at about 280°, is only slightly soluble in bicarbonate and shows a low content of diazotizable amine; *cf.* ref. 10 for a similar rearrangement in the sulfanilamide series.)

Catalytic reduction with platinum oxide (Baker Chemical Co.) gave a colorless reaction medium only if Raney nickel was also used. After three hours of shaking with hydrogen at an initial pressure of 35 lb. per sq. in. the mixture was filtered and precipitated *at once* with three volumes of water. After vacuum drying at 25° the product melted at 200–201°.

2. From the Amine and Sulfonyl Chlorides. Compounds XXXIV–XL and XLII.—These compounds were prepared by the condensation of either benzenesulfonyl chloride or *p*-bromobenzenesulfonyl chloride (Eastman Kodak Co.) with the appropriate amine from the source indicated in the table. The general method has been de-

scribed previously[27]; the yields and methods of purification are given in Table I. XXXVI and XLII were also prepared in better yields (80% *vs.* 63% and 74% *vs.* 48%, respectively) and in higher purity by the halogenation of XXXV by the method described below.

3. From Sulfonamides and Chloroheterocycles. Compounds XIX, XXIX, XXXII and XXXIII.—These compounds were prepared by the condensation of metanilamide[31] or orthanilamide[32] with 2-chloropyrazine[14] or 2,5-dichloropyrimidine (see below). The preparation of 2-metanilamidopyrazine (XXIX) illustrates the conditions used. A mixture of 41 g. (0.36 mole) of 2-chloropyrazine, 62 g. (0.36 mole) of metanilamide and 55 g. (0.4 mole) of anhydrous potassium carbonate was refluxed with stirring on an oil-bath at 160–180° for five hours. The mixture was cooled below 100°, poured into about 400 cc. of water, and steam distilled to remove the unchanged chloropyrazine. The residual solution was acidified to *p*H 7.5–8 to precipitate the unchanged metanilamide. The mixture was chilled and filtered and the filtrate acidified with acetic acid to precipitate the product. This material was purified by repeated treatment with charcoal in acid and in alkaline solution until the filtrate was colorless. The melting point of the product obtained in this way was not raised by recrystallization from alcohol.

XXXIII was prepared in the same manner except that a better yield was obtained when somewhat less than an equimolecular amount of potassium carbonate was used. Recrystallization from cellosolve was necessary to remove a persistent impurity.

In the preparation of XXXII and XIX, it was found helpful to use nitrobenzene as a solvent for the reactants. XIX was also prepared more readily and in better yield (84% *vs.* 53%) by another method (see above).

4. From Diazotized 2-Metanilamidopyrimidine (XVII). Compounds XLV–XLVII.—A solution of 50 g. (0.2 mole) of 2-metanilamidopyrimidine (XVII) in 60 cc. of sulfuric acid and 100 cc. of water was poured into 500 cc. of water and 500 g. of ice with shaking. The sulfate of the amine separated in finely divided form. This mixture was cooled to 0–2° and a solution of 14.7 g. of sodium nitrite in 100 cc. of water was added all at once with vigorous shaking. The temperature rise was negligible. After about ten minutes a clear yellow solution had formed. To obtain **2-(*m*-hydroxyphenylsulfonamido)-pyrimidine (XLV)**, the above solution was added in a thin stream to a vigorously boiling solution of 50 cc. of sulfuric acid in 500 cc. of water over ten to fifteen minutes. Heating was continued for another fifteen minutes and the solution then treated with charcoal and chilled. The product was purified by two recrystallizations from water. **2-(*m*-Cyanophenylsulfonamido)-pyrimidine (XLVII)** was prepared from the above diazonium solution neutralized to about *p*H 5 by the method of Korczynski and Fandrich.[33] The purification was tedious. The crude product was extracted first with acetone and then with ethylene chloride to remove impurities insoluble in these solvents. The product thus obtained was recrystallized from acetone; yield 16%. A much more satisfactory preparation from 2-(*m*-carbamylphenylsulfonamido)-pyrimidine (XLIX) is described below. **2-(*m*-Chlorophenylsulfonamido)-pyrimidine (XLVI)** was prepared according to the method given in Organic Syntheses[34] from a diazonium solution prepared as described above, but using an equivalent amount of hydrochloric acid in place of the sulfuric acid.

2-[*m*-(2-Pyrimidylcarbamyl)-phenylsulfonamido]-pyrimidine Monohydrate (L).—In three runs of approximately equal size 315 g. (1.42 moles) of *m*-chlorosulfonylbenzoic acid[35] was treated with 315 g. (1.5 moles) of finely ground phosphorus pentachloride. There was an immediate reaction with vigorous evolution of hydrogen chloride and formation of a mobile oil. The phosphorus oxychloride was removed on the steam-bath at reduced pressure. One-third of the residue (115 g.) was added with stirring to 114 g. (1.2 moles) of 2-amino-pyrimidine[36] in 230 cc. of pyridine. The temperature rose rapidly to about 110°. When it had fallen to 85–90° the reaction mixture began to crystallize. The resulting mush was added to 5 liters of water. Three similar runs were combined (total 2-aminopyrimidine: 345 g., 3.6 moles) and the solid filtered. The product was dissolved in 3 liters of water by the rapid addition of 110 cc. of concd. ammonium hydroxide. After the solution had stood for a short time a heavy precipitate of the ammonium salt of the sulfonamide separated. This was filtered, dissolved in hot dilute ammonium hydroxide, and poured into dilute acetic acid. The precipitate which formed was filtered and the purification repeated. The product thus obtained was quite pure and melted sharply at 254–255° with slight shrinking at 232°. In other preparations, crystallization in the reaction mixture was not observed and the ammonium salt showed much less tendency to crystallize. The final product gave a satisfactory analysis but had a melting point quite dependent on the rate of heating. Rapid heating often gave a melt at 230° with flowing of the melt around 250°. The change at 230° is presumably due to the loss of a molecule of water of crystallization which can also be removed at 100° at reduced pressure. The anhydrous form is so hygroscopic, however, that analysis of the hydrate, crystallized from water and air dried, is more satisfactory.

2-(*m*-Carboxyphenylsulfonamido)-pyrimidine (XLVIII).—This compound was obtained by the action of boiling 10% sodium hydroxide for one hour on either L or XLVII. The yield was nearly quantitative in both cases. Acidification of the reaction mixture with hydrochloric acid gave a pure product. The greater availability of L made this the preferred source.

2-(*m*-Carbamylphenylsulfonamido)-pyrimidine (XLIX). (A) **From L.**—A solution of 100 g. of L in 600 g. of anhydrous ammonia was heated for two hours at 100° in an autoclave. The residue obtained when the ammonia had evaporated was taken up in water, treated with charcoal and the product reprecipitated with acetic acid. One more similar treatment gave a pure product; yield: 91%.

(B) **From XLVIII.**—A mixture of 40 g. of XLVIII, 200 cc. of thionyl chloride, and 4 cc. of pyridine (without which the reaction was very slow) was refluxed for about forty-five minutes until a perfectly clear solution was obtained. The excess thionyl chloride was distilled and the residue was digested with 200 cc. of ethylene chloride. Two more washings with hot ethylene chloride gave 33.2 g. (78%) of ***m*-(2-pyrimidylsulfamyl)-benzoyl chloride**, m. p. 197–201°. This was treated, without further purification, with 200 g. of anhydrous ammonia. This was allowed to evaporate to dryness and worked up as in (A) to give 93% of material having a less satisfactory melting point than that obtained in (A).

2-(*m*-Cyanophenylsulfonamido)-pyrimidine (XLVII).—A mixture of 17.1 g. (0.06 mole) of XLIX, 25.6 g. (0.17 mole) of phosphorus oxychloride and 50 cc. of ethylene chloride was refluxed for ten minutes after solution was complete. The mixture was chilled and the mother liquor decanted. The crystalline solid was treated with water and the resulting product purified through the ammonium salt as described for L. The yield of 93% combined with the other excellent yields in this series makes this preparation preferable to that through the diazotization of XVII described above.

N¹-Phenyl-6-hydroxymetanilamide (VI).—This compound was prepared by the method of Williams.[18] It was found that the intermediate, 6-acetoxy-N³-acetyl-N¹-phenylmetanilamide, was readily hydrolyzed by simple solution in dilute ammonium hydroxide to **N³-acetyl-6-hydroxy-N¹-phenylmetanilamide.** The product reprecipitated by acetic acid melted at 230–231° and had an analysis corresponding to the monoacetyl derivative.

Anal. Calcd. for $C_{14}H_{14}N_2O_4S$: N, 9.1. Found: N, 9.2.

(31) Jacobs and Heidelberger, THIS JOURNAL, **39**, 2428 (1917).

(32) Beilstein, 4th ed., Vol. XIV, p. 682.

(33) Korczynski and Fandrich, *Compt. rend.*, **171**, 182 (1920); **183**, 421 (1926); Albert and Magrath, *J. Chem. Soc.*, 678 (1944).

(34) "Organic Syntheses," Coll. Vol. 1, 162 (1941).

(35) Smiles and Stewart, *J. Chem. Soc.*, **119**, 1795 (1921).

(36) Footnote *p*, Table II.

N¹-2-Thiazolyl-6-hydroxymetanilamide (XV).—This compound was prepared from 2-aminothiazole and the same acid chloride as in VI, but using pyridine instead of an excess of the amine. Solution of the crude reaction product in ammonium hydroxide, followed by acidification of the solution with acetic acid, gave a product of m. p. 265–270°, presumably the monoacetyl derivative corresponding to that obtained above. Acid hydrolysis of this material gave XV in 95% yield.

***m,m'*-Bis-(2-pyrimidylsulfamyl)-carbanilide Hydrate (LIV).**—Phosgene was passed into a solution of 25 g. (0.1 mole) of 2-metanilamidopyrimidine (XVII) in 1 liter of water containing 124 g. (1 mole) of sodium carbonate monohydrate until the mixture became acid to congo red paper. The solid was collected and washed with 1:4 hydrochloric acid. It was purified by solution in water with a minimum amount of sodium hydroxide, dilution with two volumes of alcohol, treatment with charcoal, and reprecipitation with alcoholic acetic acid.

N¹-2-Pyrimidyl-6-chlorometanilamide (XXV), Method I.—A mixture of 4.8 g. of iron powder and 4 cc. of 5% acetic acid was heated until foaming stopped. To the mixture was then added 2.4 g. of 2-(2-chloro-5-nitrophenylsulfonamido)-pyrimidine (W, Table II) and 10 cc. of water. The mixture was warmed and filtered and the filtrate acidified with acetic acid. The resulting solid was filtered and purified by treatment with charcoal in ammoniacal solution; yield, 74%.

Method II.—6-Chlorometanilic acid[37] was converted to potassium 6-chloro-N-acetylmetanilate following the procedure of Jacobs and Heidelberger[31] for the unsubstituted metanilic acid; yield, 88%. A mixture of 10 g. of this material with 20 cc. of chlorosulfonic acid was heated for an hour on the steam-bath, chilled and poured over ice. The resulting gummy solid was extracted with chloroform, dried over anhydrous sodium sulfate, and the solvent distilled. To the gummy residue weighing 7.4 g. was added 10 cc. of pyridine and 2.6 g. of 2-aminopyrimidine. The mixture was heated at 55° for an hour, poured into water, and the gummy solid dissolved by the addition of ammonium hydroxide. The solution was treated with charcoal, filtered, and the product precipitated with acetic acid. The purification was repeated twice more to obtain 3.5 g. (39%) of **N¹-2-pyrimidyl-N⁴-acetyl-6-chlorometanilamide**; m. p. 300–305°.

Anal. Calcd. for $C_{12}H_{11}ClN_4O_3S$: N, 17.2. Found: N, 16.9.

Hydrolysis of a portion of this material with boiling 10% potassium hydroxide gave a product identical by mixed m. p. with that obtained by Method I.

N¹-Methyl-2-metanilamidopyrimidine (XXVI).—A suspension of 25 g. (0.1 mole) of 2-metanilamidopyrimidine (XVII) in 125 cc. of anhydrous ether and 15 cc. of absolute alcohol was treated with 0.1 mole of diazomethane in ether.[38] When nitrogen evolution ceased, the solid was extracted with 600 cc. of boiling 1:1 ether–alcohol. The residue was then extracted with cold alkali and the insoluble material combined with the residue obtained by evaporation of the ether–alcohol extract. The combined product was recrystallized from methanol and from 6 *N* acetic acid, yield, 53%.

To confirm its structure, this compound was also prepared by the dehalogenation of XXVII (see below) using a modification of the method of Schwenk, *et al.*[11] It was necessary to use methanolic potassium hydroxide rather than the recommended mixture of aqueous alkali and alcohol to obtain the necessary homogeneous reaction mixture and milder conditions. Catalytic dehalogenation using platinum and palladium on charcoal in alcoholic sodium hydroxide was not successful although the dehalogenation of 2-orthanilamido-5-chloropyrimidine proceeded smoothly under these conditions (see XXXI).

N¹-Methyl-2-metanilamido-5-chloropyrimidine (XXVII).—This compound was prepared by the action of diazomethane on XIX in the same manner as described above except that the alcohol was not necessary for rapid reaction and seemed to promote side reactions. The product from 0.1 mole of XIX was soluble in 300–600 cc. of 1:1 ether–alcohol, leaving unreacted material undissolved. After evaporation of the extract, the residue was recrystallized from methanol. The melting point was not raised by recrystallization from 25% acetic acid or ethylene chloride.

The structure of the compound was proved by hydrolysis with 64% sulfuric acid at 130–165° for one-half hour to give a 52% yield of 2-methylamino-5-chloropyrimidine identical by mixed melting point with that prepared from methylamine and 2,5-dichloropyrimidine (see below). On cooling the hydrolytic mixture, a crystalline salt separated. After filtration, this solid was treated with concd. ammonium hydroxide and then recrystallized from hot water to give 2-methylamino-5-chloropyrimidine.

2-Orthanilamidopyrimidine (XXXI).—A suspension of 11.4 g. of 2-orthanilamido-5-chloropyrimidine (XXXII, see above) and 1 g. each of 10% palladium–charcoal and 10% platinum–charcoal catalysts (Baker and Co.) in 40 cc. of water and 8 cc. of 40% sodium hydroxide was shaken at room temperature in an atmosphere of hydrogen at an initial pressure of 45 lb. per sq. in. One mole of hydrogen was absorbed in ten minutes. The mixture was diluted to 100 cc. and filtered and the product precipitated from the filtrate by acidification with acetic acid. The product was purified by two treatments with charcoal in ammonium hydroxide solution, followed by precipitation with acetic acid.

When reaction mixtures from the attempted condensation of 2-aminopyrimidine with *o*-nitrobenzenesulfonyl chloride[39] in pyridine were worked up by addition to water and acidification, a strong odor of sulfur dioxide was noticed. The solid obtained was insoluble in alkali and, after recrystallization from ether, had a melting point of 134–135.5°. The material gave a fairly satisfactory analysis for **2-(*o*-nitroanilino)-pyrimidine** and was identical by mixed melting point with the compound prepared from *o*-nitrochlorobenzene and 2-aminopyrimidine as described below.

Anal. Calcd. for $C_{10}H_8N_4O_2$: C, 55.6; H, 3.7; N, 25.9. Found: C, 56.1; H, 3.6; N, 25.2.

2-(*o*-Nitroanilino)-pyrimidine.—A mixture of 6.3 g. of *o*-nitrochlorobenzene (Eimer and Amend, redistilled, 0.04 mole), 9.5 g. (0.1 mole) of 2-aminopyrimidine, 25 cc. of *o*-dichlorobenzene (Eastman, T494), and a pinch of bronze powder was refluxed for twenty hours, cooled, and treated with water. The lower organic layer was separated and steam distilled to remove the solvent. The residue in the flask was extracted with ether. The extract was dried with potassium carbonate and the ether distilled. After crystallization from petroleum ether and ether a bright orange crystalline substance was obtained; m. p. 136–137.5°.

Anal. Calcd. for $C_{10}H_8N_4O_2$: N, 25.9. Found: N, 26.0.

2-(3,5-Dibromosulfanilamido)-5-chloropyrimidine.—To a stirred suspension of 45 g. (0.16 mole) of 2-sulfanilamido-5-chloropyrimidine[2] in 2.1 liters of glacial acetic acid at 65° was added a solution of 50 g. (0.31 mole) of bromine in 200 cc. of glacial acetic acid as rapidly as the reaction proceeded. When about half the bromine had been added, a precipitate formed and the reaction became much slower. The addition of 100 cc. of water allowed the reaction to proceed until half the remaining bromine had been added. At this point 100 cc. more of water was added and the precipitate filtered. The product was purified by solution in 300 cc. of warm 50% alcohol containing 12 g. of sodium hydroxide, treatment of the solution with charcoal, and reprecipitation with 200 cc. of concd. hydrochloric acid. The precipitate was filtered and washed with 700 cc. of hot alcohol; yield, 58.5 g. (84%); m. p. 264–265° (dec.).

Anal. Calcd. for $C_{10}H_7Br_2ClN_4O_2S$: N, 12.7. Found: N, 12.5.

(37) Suter and Weston, THIS JOURNAL, **62**, 605 (1940).

(38) "Organic Syntheses," Coll. Vol. 11, p. 166, Note 3 (1943).

(39) "Organic Syntheses," Coll. Vol. 11, p. 471 (1943).

2-(3,5-Dibromophenylsulfonamido)-5-chloropyrimidine (XLI).—To 20 cc. of glacial acetic acid, kept below 20°, was added with stirring 22 cc. of 2.5 *M* nitrosyl sulfuric acid[40] solution (10% excess), followed by a slurry of 22 g. (0.2 mole) of 2-(3,5-dibromosulfanilamido)-5-chloropyrimidine in 50 cc. of glacial acetic acid during five to ten minutes. Solution was complete in five minutes and, after stirring for thirty minutes, reduction was effected by rapid addition of the solution to a stirred mixture of 1 g. of red copper oxide and 140 cc. of absolute alcohol. The temperature rose to 65–70° and there was a brisk evolution of nitrogen which was complete in a few minutes. After standing for an hour, the product was filtered and washed with water, methanol and ether. The solid was dissolved in 200 cc. of hot methanol by the addition of 10 cc. of 10 *N* aqueous sodium hydroxide. The solution was treated with charcoal, filtered and chilled. The sodium salt which separated was filtered, redissolved in 80 cc. of 50% methanol and the solution treated with charcoal. The product was reprecipitated with acetic acid, filtered, washed with water, and recrystallized from cellosolve.

2-Phenylsulfonamido-5-iodopyrimidine (XLIII).—A refluxing mixture of 40 g. (0.17 mole) of 2-phenylsulfonamidopyrimidine,[41] 109 g. (0.34 mole) of mercuric acetate, and 500 cc. of glacial acetic acid was treated with 53 g. (0.21 mole) of iodine. There was immediate reaction with evolution of heat and formation of a precipitate. The iodine color was still present after fifteen minutes of heating. The slurry was added to 120 g. (0.7 mole) of potassium iodide and 25 g. of sodium sulfite in 700 cc. of water. The red and yellow mercury contamination was removed by washing the precipitate on the filter with potassium iodide solution, followed by sodium thiosulfate solution and water. The solid was dissolved in 1 liter of boiling acetic acid and filtered from a gelatinous gray material. The product crystallized from the colorless filtrate on cooling.

2-Phenylsulfonamido-5-bromo- and 5-chloropyrimidine (XLII and XXXVI).—A solution of 47 g. of 2-phenylsulfonamidopyrimidine (XXXV) in 350 cc. of boiling acetic acid was treated with 37 g. of bromine in 105 cc. of acetic acid. The mixture was refluxed for two hours and then chilled to precipitate the product. The solid was filtered and purified by precipitation from dilute ammonium hydroxide solution with acetic acid. Recrystallization from acetic acid did not raise the melting point.

The chloro compound was similarly prepared except that the chlorine was simply passed into the refluxing solution for five minutes and refluxing continued for five minutes more. There was no effort to determine the amount of chlorine used.

2-Phenylsulfonamido-5-cyanopyrimidine (XLIV).—A solution of 12 g. (0.03 mole) of 2-phenylsulfonamido-5-iodopyrimidine (XLIII) in 18 cc. of boiling synthetic quinoline (Eastman Kodak Co.) was treated with 3.8 g. (0.04 mole) of cuprous cyanide. After boiling for ten minutes, the greenish-black mixture was poured into a mixture of 72 cc. of concd. hydrochloric acid and 30 g. of ice. The resulting granular solid was dissolved in 60 cc. of concd. ammonium hydroxide and the copper removed by *very brief* treatment with zinc dust in the cold. The solution was then decolorized with charcoal and the product reprecipitated by addition to a mixture of 70 cc. of 6 *N* hydrochloric acid and 30 cc. of glacial acetic acid, with the occasional addition of ice. After recrystallization of the product from 275 cc. of absolute alcohol, the melting point was not further changed by recrystallization from acetic acid or ethylene chloride.

2-(*m*-Aminomethylphenylsulfonamido)-pyrimidine (LI).—A solution of 10 g. (0.04 mole) of 2-(*m*-cyanophenylsulfonamido)-pyrimidine (XLVII) in 40 cc. of aqueous ammonia and 160 cc. of absolute alcohol was treated with charcoal and the filtrate was shaken with three teaspoons of Raney nickel under 50 lb. initial hydrogen pressure. About 0.065 mole of hydrogen was absorbed in one hour and forty-five minutes and the reaction was stopped. The reduction mixture was filtered quickly and the filtrate was concentrated by boiling to obtain three crops of product. These were combined, dissolved in 300 cc. of dilute ammonia and treated with charcoal. The filtrate was concentrated to 50 cc. and cooled to precipitate the product (acidification was not a satisfactory method of precipitating the compound). The product was crystallized by extraction with large quantities of boiling water, treatment with charcoal, concentration and cooling. After several such treatments a yield of 2.4 g. (24%) was realized.

2-Amino-5-cyanopyrimidine.—A mixture of 8.7 g. (0.05 mole) of 2-amino-5-bromopyrimidine,[2] 5.0 g. (0.055 mole) of cuprous cyanide (Baker Chemical Co.) and 20 cc. of synthetic (practical quinoline gave a much lower yield) quinoline (Eastman Kodak Co.) was boiled for thirty minutes and added to 300 cc. of boiling glacial acetic acid and filtered hot. Four volumes of water were added to the cooled filtrate and the resulting precipitate (4–5 g.) was collected and purified by solution in 3 *N* acid (4 g./100 cc.) and reprecipitation with excess ammonia and by crystallization from acetic acid (20 cc./g.); dec. 300–310°; yield, 2.4 g. (40%).

Anal. Calcd. for $C_5H_4N_4$: C, 50.0; H, 3.4; N, 46.7. Found: C, 50.4; H, 3.6; N, 46.6.

2-Hydroxy-5-chloropyrimidine.—A finely divided precipitate of the sulfate of 2-amino-5-chloropyrimidine[2] was prepared by dissolving 20 g. (0.154 mole) of the amine in a hot mixture of 20 cc. of concd. sulfuric acid and 80 cc. of water and cooling the solution with stirring to below 10°. A solution of 10.7 g. (0.155 mole) of sodium nitrite in 30 cc. of water was then added at or below this temperature in one and one-half hours. After standing overnight the mixture was warmed on a steam-bath and treated with 70 cc. of ammonium hydroxide. When this solution was cooled the ammonium salt of 2-hydroxy-5-chloropyrimidine precipitated. This was dissolved in 80 cc. of hot water and the solution was treated with 11 cc. of glacial acetic acid to precipitate the product; yield, 12.8 g. (63%); m. p. 237–238° (dec.).

Anal. Calcd. for $C_4H_3ClN_2$: N, 21.5; Cl, 27.2. Found: N, 21.0; Cl, 27.3.

2,5-Dichloropyrimidine.—One hundred twenty-eight grams (0.98 mole) of 2-hydroxy-5-chloropyrimidine was added to 500 cc. of phosphorus oxychloride at room temperature with no evidence of reaction. The mixture was refluxed for one-half hour after solution had occurred. Four hundred cc. of phosphorus oxychoride was distilled at reduced pressure and the residue was poured onto ice and water and the resulting mixture was neutralized with about 300 g. of sodium carbonate. The mixture was steam distilled and all of the dichloro compound was collected with 600–800 cc. of distillate. The separated solid was collected, ground, and air-dried. The white solid weighed 81.5 g. (56%); m. p. 57–57.5°. This material is very soluble in organic solvents and may be crystallized by the slow addition of water to a methanol solution. It boils at 190° (atmos. press.). The compound appears to be non-irritating in marked contrast to 2,4-dichloropyrimidine.[42]

Anal. Calcd. for $C_4H_2Cl_2N_2$: Cl, 47.6. Found: Cl, 47.6.

5-Chloro-2-methylaminopyrimidine.—This compound was prepared by the reaction of one mole of 2,5-dichloropyrimidine with 2 moles of methylamine (33% aqueous) in 50% alcohol at 40–65° for one hour. Crystallization from water gave an 87% yield, m. p. 122–124°.

Anal. Calcd. for $C_5H_6ClN_3$: N, 29.3. Found: N, 29.2.

2-(N^3-Acetylmetanilamido)-pyrimidine.—A suspension of 5 g. of 2-metanilamidopyrimidine (XVII) in 15 cc. of acetic anhydride was refluxed for forty-five minutes without producing complete solution. The mixture was chilled and filtered and the solid extracted with 1:3 hydrochloric acid to remove unchanged amine. The product

(40) Hodgson and Turner, *J. Chem. Soc.*, 748 (1942).

(41) Footnote *q*, Table I.

(42) Footnote *s*, Table II.

was purified by solution in dilute ammonium hydroxide and reprecipitation after treatment with charcoal; m. p. 244–246°; yield, 4.3 g. (74%).

Anal. Calcd. for $C_{12}H_{12}N_4O_3S$: C, 49.3; H, 4.1. Found: C, 49.3; H, 4.2.

In another preparation, under quite similar conditions, complete solution was obtained during the reaction and the product appeared to contain a considerable amount of the diacetyl derivative. When this material was refluxed for ten minutes with dilute ammonium hydroxide the product obtained above resulted.

2-(N^8-Acetylmetanilamido)-5-chloropyrimidine.—The procedure was as above with the addition of two drops of sulfuric acid to the acetic anhydride; m. p. 258–260°; yield, 76%.

Anal. Calcd. for $C_{12}H_{11}ClN_4O_3S$: C, 44.1; H, 3.4. Found: C, 44.1; H, 3.3.

Sodium Salts of XVII and XIX.—The sodium salts of both of these compounds were best prepared by reaction with sodium ethoxide in boiling absolute alcohol. A solution of 1.5–2 equivalents of sodium in 10 parts of alcohol was used. The salts were quite soluble in aqueous alcohol and were prepared with difficulty by the usual method of diluting a concentrated aqueous solution of the salt with a large volume of alcohol.

2-Amino-5-bromo-4-methoxypyrimidine.—2-Amino-4-methoxypyrimidine was reacted with one mole of bromine in water over a period of one hour by the general directions of the preceding paper.[2] After neutralization with sodium hydroxide a 95.2% yield was obtained. After crystallization from benzene the m. p. was 125–126°.

Anal. Calcd. for $C_5H_6BrN_3O$: N, 20.6. Found: N, 20.0.

Acknowledgment.—The authors wish to express their appreciation to Drs. S. Brackett and E. Waletzky for many helpful discussions during the course of this work and for the antimalarial results quoted here.

Summary

1. The synthesis of twenty-seven new metanilamides, three new orthanilamides, and seventeen variously substituted 2-phenylsulfonamidopyrimidines has been described.

2. The antimalarial activities of these compounds in avian malaria have been reported and discussed with respect to their structure.

3. Among the metanilamides studied, a majority of the N^1-heterocyclic compounds showed antimalarial activity; other types of metanilamides were ineffective.

4. Of the benzenesulfonamides, only 2-phenylsulfonamido-5-halogenpyrimidines and their derivatives had antimalarial activity.

5. The most active compounds were 2-metanilamido-5-chloropyrimidine ("Metachloridine") and its bromine and iodine analogs. Metachloridine was six times as effective as sulfadiazine and sixteen times as active as quinine against *P. gallinaceum* in chicks.

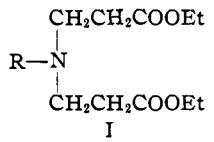
STAMFORD, CONNECTICUT RECEIVED FEBRUARY 28, 1946

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Piperidine Derivatives. XV. The Preparation of 1-Benzoyl-3-carbethoxy-4-piperidone. A Synthesis of Guvacine

BY S. M. MCELVAIN AND GILBERT STORK

Previous papers[1] from this Laboratory have reported the preparation of a number of 1-alkyl-3-carbethoxy-4-piperidones (II) by the Dieckmann cyclization of alkyl-di-(β-carbethoxyethyl)-amines (I)



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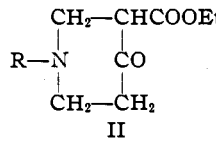

II

While this reaction produced compounds of structure II in quite satisfactory yields (63–78%) when R is an alkyl group,[1c] the yield of the piperidone (II) dropped to 11% when the reaction was applied to the diester (I) in which R is hydrogen.[2] This undoubtedly is due to the greater tendency of the secondary amino group of both this particular diester and the corresponding piperidone to become involved in other competitive reactions during and after the cyclization.

For the preparation of certain piperidine derivatives, however, it is desirable to have such a carbethoxypiperidone as II in which R is hydrogen or a group that may be readily replaced by hydrogen. Ruzicka and Fornasir[3] have reported the cyclization of N-benzoyl-di-(β-carbethoxyethyl)-amine (VI). While they did not isolate the carbethoxypiperidone (VIII), the oil they obtained from the reaction gave the characteristic test with ferric chloride and was hydrolyzed[4] to the hydrochloride of 4-piperidone, which was isolated as its dibenzylidene derivative. No yields were given for any of these products.

The work reported in the present paper was concerned with the development of satisfactory methods for the preparation of 1-benzoyl-3-carbethoxy-4-piperidone (VIII) and its immediate precursor N-benzoyl-di-(β-carbethoxyethyl)-amine (VI). The preparation of this latter compound, which is dependent upon the benzoylation of di-(β-carbethoxyethyl)-amine (IV), hitherto has been quite unsatisfactory because of the difficulties encountered in the preparation of this secondary amino ester. The interaction of ethyl β-iodopropionate and the ethyl ester of β-alanine,[3] and

(1) (a) McElvain, THIS JOURNAL, **46**, 1721 (1924); **48**, 2179 (1926); (b) Thayer and McElvain, *ibid.*, **49**, 2862 (1927); (c) Bolyard and McElvain, *ibid.*, **51**, 922 (1929).

(2) Kuettel and McElvain, THIS JOURNAL, **53**, 2692 (1931).

(3) Ruzicka and Fornasir, *Helv. Chim. Acta*, **3**, 806 (1920).

(4) Ruzicka and Seidel, *Helv. Chim. Acta*, **6**, 715 (1922).