Anal. Calcd. for $C_6H_{11}O_2N$: N, 10.84. Found: N, 10.60.

Acid Hydrolysis: (A) *dl*-α-Aminononanoic Acid.—A solution of 22.2 g. of diethyl *n*-heptylacetamidomalonate in 100 ml. of concentrated hydrochloric acid was refluxed for seven hours and then cooled to 0°. There was thus precipitated a mass of shiny pearly plates. This material was collected by filtration and dried yielding 10.7 g. of amino acid hydrochloride. The crude product was dissolved in a mixture of ethanol and water (1:1) and the amino acid precipitated by the addition of 15 ml. of pyridine. The product was filtered, washed and air dried; yield 6.7 g. (55%). It was further purified with little or no loss by solution in 500 ml. of water containing 15 ml. of 10% sodium hydroxide, treating with charcoal, filtering and adding excess acetic acid to precipitate the amino acid. The pure compound melted at 270–273° (dec.).

Anal. Calcd. for $C_9H_{19}O_2N$: N, 8.08. Found: N, 7.83.

This amino acid could be isolated equally well by the use of ammonium hydroxide in place of pyridine since it is not very soluble in water. (Compare the isolation of *dl*-leucine.[4d]) Procedure (B) is preferable for lower molecular weight amino acids.

Acid Hydrolysis: (B) *dl*-α-Aminobutyric Acid.—A solution of 9.9 g. of ethyl ethylacetamidocyanoacetate in 40 ml. of 40% hydrobromic acid was refluxed for eight hours, treated with charcoal, cooled, filtered and concentrated *in vacuo* to dryness. The residue was extracted with four 10-ml. portions of absolute ethanol, diluted with ethanol and adjusted to *p*H 6 by addition of pyridine. There was thus obtained 4.24 g. (82.4%) of *dl*-α-aminobutyric acid identified by means of its benzoyl (Table I) and chloroacetyl derivatives.

Reduction of Ethyl Allylacetamidocyanoacetate.—To a solution of 6.3 g. of ethyl allylacetamidocyanoacetate (prepared by the method outlined for ethyl *n*-butylacetamidocyanoacetate) in 100 ml. of ethanol there was added 0.100 g. of palladium chloride and one gram of Nuchar. It required about one and one-half hours at room temperature and 40 pounds pressure to take up one equivalent of hydrogen. The reduction was then stopped and the catalyst and solvent were removed. The residue was dissolved in chloroform, washed with dilute hydrochloric acid and then with water, and the chloroform removed *in vacuo*. The residue was taken up in ethanol, treated with charcoal, filtered and diluted with water. Cooling gave 2.5 g. of white platelets melting at 76–79°. After two recrystallizations from water the product was shown by melting point and mixed melting point to be identical with ethyl *n*-propylacetamidocyanoacetate obtained from *n*-propyl bromide and acetamidocyanoacetic ester (Table I).

Reduction of Diethyl Allylacetamidomalonate.—Reduction of a solution of 2.2 g. of diethyl allylacetamidomalonate (see above) in 100 ml. of ethanol using Raney nickel catalyst was complete in one minute at room temperature and 40 pounds pressure. Upon removal of the catalyst and solvent the residue crystallized with the liberation of heat. The yield of product melting at 91–94° was quantitative. When mixed with diethyl *n*-propylacetamidomalonate, m. p. 93–95° (prepared from *n*-propyl bromide and acetamidomalonic ester by the method given for methyl iodide) the mixture melted at 93–94°.

Acetamidocyanoacetic Acid.—Seventeen grams of ethyl acetamidocyanoacetate was added to a solution of 5.6 g. of potassium hydroxide in 50 ml. of water and 100 ml. of ethanol and allowed to stand for forty-eight hours at room temperature. Most of the solvent was then removed *in vacuo*, and 50 ml. of water was added to the residue. Chloroform was added to dissolve the unreacted ester and the water layer was extracted with chloroform. Evaporation of the chloroform gave 8.0 g. of recovered acetamidocyanoacetic ester. The aqueous layer was cooled and acidified by the slow addition of concentrated hydrochloric acid to precipitate the product. The product was filtered and washed with ice water to give 6.0 g. of acetamidocyanoacetic acid, m. p. 117–118.5°. The yield was 80% based on the amount of acetamidocyanoacetic ester used. An analytical sample melted at 119–120.5°. The product evolved ammonia on warming with sodium hydroxide and lost carbon dioxide on heating an aqueous solution.

Anal. Calcd. for $C_5H_6O_3N_2$: N, 19.72. Found: N, 20.15.

Acknowledgment.—The author is indebted to Miss Audrey Fiescher and Mrs. Ruth Bachand for technical assistance, and to Miss Alice Rainey and Mr. Morris Auerbach for the nitrogen analyses.

Summary

Diethyl acetamidomalonate and ethyl acetamidocyanoacetate have been alkylated with all of the normal saturated alkyl halides up to and including nonyl, as well as with allyl, β-methylallyl and isobutyl halides. The resulting products have been hydrolyzed to amino acids which have been characterized through the benzoyl derivatives.

RENSSELAER, N. Y. RECEIVED OCTOBER 29, 1945

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

Studies in Chemotherapy. XIII. Antimalarials. Halogenated Sulfanilamidoheterocycles

BY J. P. ENGLISH, J. H. CLARK, J. W. CLAPP, DORIS SEEGER AND R. H. EBEL

In the course of the testing of sulfanilamides against sporozoite-induced infections of *Plasmodium gallinaceum* in the chicken it was found[1] that 2-sulfanilamido-5-bromopyrimidine and its chlorine analog showed an unusual property. This was demonstrated when an attempt was made to counteract the activity of these compounds by *p*-aminobenzoic acid which had previously prevented the activity of all the sulfanilamides against which it had been tested.[1,2] Contrary to expectations, the activity of these halogenated sulfadiazines was only partially reduced, rather than completely abolished, by *p*-aminobenzoic acid.

This unexpected observation led to the prepara-

(1) Special aspects of this subject will be discussed by Drs. S. Brackett and E. Waletzky of this Laboratory in a paper which is now in preparation. The routine testing of these compounds will be reported under Test 0-2 in the forthcoming monograph, "A Review of Antimalarial Drugs, 1941-1945," F. Y. Wiselogle, *Editor*.

(2) Marshall, Litchfield and White, *J. Pharmacol.*, **75**, 89 (1942); Seeler, Graessle and Dusenberry, *J. Bact.*, **45**, 205 (1943); Maier and Riley, *Proc. Soc. Exptl. Biol. Med.*, **50**, 152 (1942).

TABLE I

SULFANILAMIDOHETEROCYCLES

SN[a]	Compound[b]	M. p., °C.[c]	Max. blood level[d]	Chemotherapeutic activity[m] Bact.[e]	Mal.[f]
8607	2-S-5-Chloro P[n]		25	2	2
8605	2-S-5-Bromo P	229.8–230.3	33	2	2
9883	2-S-4-Amino-5-bromo P	260–262	10	0.3	0.5
5702	2-S-5-Bromo-4-methyl P[l]	233–235	15		.5
3517	2-S-5-Bromo-4,6-dimethyl P	250–252	2.5	0.5	.3
5286	2-S-5-(2,3-Dibromopropyl)-4,6-dimethyl P[k]	162–164	2	act	.5
12197	2-(2-Chloro S)-P	254–256	15	0.3	1.0
11048	2-S-5-Bromo T	*ca.* 200	20	.5	0.2
11051	2-S-5-Chloro T	*ca.* 225	20	.5	.25
4800	2-S-5-Bromo-4-methyl T	205-210	9	.1	.25
9657	2-S-5-Chloro-4-methyl T	*ca.* 218	17	.1	1.0
12200	2-S-5-Chloro Py	204–205	52	.3	<0.01[g]

tion of other similar compounds in the hope of extending this property and of preparing more active compounds. Since 2-sulfanilamido-5-halogenated-pyridines did not show this behavior,[1] attention was turned to the preparation of halogenated sulfanilamidothiazoles and of other halogenated sulfanilamidopyrimidines. Table I presents the properties of the compounds prepared in this study. 2-Sulfanilamido-5-bromo-4-methylpyrimidine had been previously prepared[3] and is listed for the sake of comparison.

The 2-amino-5-halogenpyrimidines were prepared by direct halogenation of 2-aminopyrimidine in aqueous solution.[4] 2-Amino-5-chloropyrimidine had been previously prepared[5] by the reaction of chloromalondialdehyde and guanidine. The present method is the more convenient but the earlier preparation serves to orient the product. Equal yields were obtained in some of the halogenations whether one or one-half molecular equivalent of halogen was used. The presence of amino and methyl substituents raised the yield over that obtained with the unsubstituted compound.

The reaction of acetylsulfanilyl chloride with 2-amino-5-chloropyrimidine has now been realized, contrary to an earlier report.[5] The ready reaction of 5-bromo-2,4-diaminopyrimidine with acetylsulfanilyl chloride is in contrast to the behavior of 2,4-diaminopyrimidine[6] and of 2-amino-5-bromopyrimidine, both of which react more sluggishly and in lower yield.

The stability of the halogen atoms in the 5-position of the pyrimidine ring to the drastic hydrolysis conditions used to remove the acetyl groups provides a striking confirmation of the difference in reactivity between halogens situated ortho and meta to ring nitrogen. Both 2- and 4-halogen pyrimidines are known to react readily with various alkaline reagents.[7]

(3) Sprague, Kissinger and Lincoln, THIS JOURNAL, **63**, 3028 (1941).

(4) Benary, *Ber.*, **63**, 2604 (1930).

(5) Roblin, Winnek and English, THIS JOURNAL, **64**, 567 (1942).

(6) Anderson, Faith, Marson, Winnek and Roblin, *ibid.*, **64**, 2902 (1942).

(7) Gilman, "Organic Chemistry," John Wiley and Sons, New York, N. Y., 1938, p. 948.

The amino halogen thiazoles were prepared by two general procedures. By the first of these 2-aminothiazole or 2-amino-4-methylthiazole was halogenated directly by the method of Ochiai and Nagasawa.[8] This procedure, when carried out at room temperature, gave 2-amino-5-bromo-4-methylthiazole directly but an intermediate was isolated in the case of 2-aminothiazole which was converted to 2-amino-5-bromothiazole on heating. This recalls the behavior of pyridine[9] in the same type of reaction. An intermediate has also been isolated in the bromination of 2-amino-4,6-dimethylpyrimidine.[10]

In the second method an α,α-dihalogenated ketone or acetal reacted with thiourea to give a 2-amino-5-halogenthiazole. This method is reported in the patent[11] of Foldi, *et al.* 2-Amino-5-chlorothiazole was prepared by both methods. The preparation from dichloroacetal showed the position of the halogen but direct chlorination was a more satisfactory preparative method.

A study of the table of properties of these compounds reveals that, in general, they are well absorbed by mice. The two compounds showing the lowest maximum blood levels are those which are the most highly substituted. That there may be marked differences between the blood concentrations developed by different animal species was illustrated by 2-sulfanilamido-5-chloropyridine. This compound gave an excellent blood level in mice, but was very poorly absorbed by the chicken.

The compounds were all active as bacteriostatic agents for *E. coli* in a synthetic medium. 2-Sulfanilamido-5-bromopyrimidine and its chlorine analog were somewhat more active than sulfathiazole (used as the standard drug in this test). The activity of all the compounds against *E. coli* was prevented by the presence of *p*-aminobenzoic acid.

The members of this series of sulfanilamides were active against sporozoite-induced infections

(8) Ochiai and Nagasawa, *Ber.*, **72**, 1470 (1939).

(9) Englert and McElvain, THIS JOURNAL, **51**, 863 (1929).

(10) Huber and Hölscher, *Ber.*, **71B**, 87 (1938).

(11) U. S. P. 2,332,906; *C. A.*, **38**, 1752 (1944).

TABLE I
(*Continued*)

Formulas	Analyses,[h] % Calcd. C	H	N	X[i]	S	Found C	H	N	X[i]	S
$C_{10}H_9ClN_4O_2S$										
$C_{10}H_9BrN_4O_2S$	36.5	2.8	17.0	24.3	9.7	36.7	2.7	17.2	24.5	9.6
$C_{10}H_{10}BrN_5O_2S$	34.9	2.9	20.4			34.9	3.1	19.9		
$C_{11}H_{11}BrN_4O_2S$	38.5	3.2	16.3			38.6	3.1	16.6		
$C_{12}H_{13}BrN_4O_2S$	40.3	3.7	15.7	22.4	9.0	40.6	4.0	15.9	22.7	9.1
$C_{15}H_{18}Br_2N_4O_2S$	37.7	3.8	11.7	33.4	6.7	37.9	3.8	11.8	33.6	6.8
$C_{10}H_9ClN_4O_2S$	42.2	3.2	19.7	12.5	11.3	41.9	3.4	19.6	12.3	11.3
$C_9H_8BrN_3O_2S_2$	32.3	2.4	12.6		19.2	32.8	2.5	12.6		18.8
$C_9H_8ClN_3O_2S_2$	37.3	2.8	14.5	12.2	22.1	37.5	2.9	14.5	12.3	21.9
$C_{10}H_{10}BrN_3O_2S_2$	34.5	2.9	12.1	18.4		34.6	2.8	11.8	18.5	
$C_{10}H_{10}ClN_3O_2S_2$	39.5	3.3	13.8	11.7		39.7	3.3	13.7	11.8	
$C_{11}H_{10}ClN_3O_2S$	46.6	3.6	14.8	12.5		46.8	3.6	14.9	12.4	

[a] SN = Survey Number, an identifying number for compounds which will appear in a forthcoming monograph, entitled "A Survey of Antimalarial Drugs, 1941–1945," F. Y. Wiselogle, Editor. [b] S = sulfanilamido, P = pyrimidine, T = thiazole, Py = pyridine. [c] Cor., in most cases with decomposition and very dependent upon rate. [d] Mg.% following single oral dose of 0.5 g./kg. in white mice. Average of ten mice. Carried out by Miss D. Babbitt. [e] Against *E. coli* in synthetic medium. Figure is ratio minimum effective concentration sulfathiazole/MEC drug. Tests carried out in these Laboratories under the direction of Dr. H. J. White. [f] Figure is the sulfadiazine equivalent; *i. e.*, ratio of blood level of sulfadiazine/blood level of drug where the two give equal effect. Taken from test 0–2, ref. *a*. [g] Dosage equivalent: < shows that compound was inactive at this ratio. [h] Micro analyses carried out in these Laboratories under the direction of Dr. J. Kuck. [i] X = Cl or Br. [k] Prepared by Miss L. F. Pekrul. [l] Ref. 3. [m] Differences less than twofold in magnitude are probably not significant. [n] Ref. 5.

of *P. gallinaceum* with the exception of 2-sulfanilamido-5-chloropyridine, the inactivity of which may be explained by its failure to reach effective blood concentrations in the chicken. The range of sulfadiazine equivalents displayed by most of these compounds was not unusual for sulfanilamides.[1] However, there was a real quantitative and a striking qualitative difference in the activities of both 2-sulfanilamido-5-bromopyrimidine and its chlorine analog with respect to the rest of the series. The antimalarial activity of these two compounds was only partially, while that of all the remaining compounds was completely, counteracted by *p*-aminobenzoic acid.

This fact indicates that the introduction of the 5-halogen atom into sulfadiazine has conferred new properties upon the molecule with respect to antimalarial activity. The behavior of the rest of the compounds in the series showed that the effect of this addition was nullified by further substitution of 2-sulfanilamido-5-halogenpyrimidines and that the introduction of the halogen into a side chain was without effect. The halogenation of sulfanilamidothiazoles did not produce this effect. Nothing definitive can be said about the one sulfanilamido halogen pyridine reported since it failed to exhibit a blood level in the test animal.

One interpretation of these results is that these molecules exhibit two modes of action. The presence of sulfanilamide activity is shown by the lowered effectiveness of 2-sulfanilamido-5-chloropyrimidine and its bromine analog in the presence of *p*-aminobenzoic acid. The activity which persists in the presence of this compound is evidence for a second mode of action. The number of compounds studied at present is too small to permit deduction of the exact relationship of structure to this new type of antiplasmodial activity.

A somewhat similar case has been found by Lawrence and Goetchius[12] in the investigation of the *p*-aminobenzoic acid reversal of various sulfanilamidoindazoles against *Brucella abortus in vitro*. These authors showed that the effectiveness of the sulfanilamides was lessened but not abolished by *p*-aminobenzoic acid. The situation reported by Kaplan and Leubner[13] does not appear to be the same. They report that *p*-aminobenzoic acid does not affect the antibacterial action of N[1]-(3,5-dibromophenyl)-sulfanilamide and that the desamino compound is as active as the sulfanilamide.

Experimental[14]

The following 2-amino-5-bromo- or chloro-pyrimidines were prepared by the reaction of the corresponding 2-aminopyrimidine in aqueous solution with an equimolar amount of bromine or chlorine at 70–80°. The solutions were then neutralized and the products collected and dried. In some cases the hydrochloride or hydrobromide crystallized from the cooled reaction solution but this usually did not offer any advantages in purification. The purification was usually by treatment of an acid solution of the compound with charcoal.

2-Amino-5-chloropyrimidine.—A yield of 41% based on 2-aminopyrimidine,[15] or 82% based on chlorine, was obtained when one-half mole of chlorine per mole of amine was used. The yield was not increased with the use of one mole of chlorine. A 35% recovery of starting material was realized. The product melted at 236–237° (sealed tube) and was identical, by mixed melting point, with that prepared previously from chloromalondialdehyde.[5]

(12) Lawrence and Goetchius, *Proc. Soc. Expil. Biol. Med.*, **58**, 356 (1945).

(13) Kaplan and Leubner, THIS JOURNAL, **67**, 1076 (1945); Goetchius and Lawrence, *J. Bact.*, **49**, 575 (1945).

(14) All melting points are corrected.

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

2-Amino-5-bromopyrimidine.—The same yields were obtained in the bromination as in the chlorination and an equal recovery. The product melted at 242–244° after purification.

5-Bromo-2,4-diaminopyrimidine.—A 74% yield of this product was obtained by the bromination of 2,4-diaminopyrimidine[16] with an equimolecular quantity of bromine at 55°. It was recrystallized from water; m. p. 217° (dec.).

Anal. Calcd. for $C_4H_5N_4Br$: N, 29.9. Found: N, 29.7.

2-Amino-5-bromo-4,6-dimethylpyrimidine.—This compound has been prepared by the treatment of the perbromide of 2-amino-4,6-dimethylpyrimidine with sulfur dioxide.[10] By the present process a yield of 47% was obtained; m. p. 187–188°, (dec.). The earlier workers[10] reported 183–184°.

2-Sulfanilamido-5-halogenpyrimidines.—The reactions with acetylsulfanilyl chloride were carried out in the general manner which was described previously.[17] The major modification was in the use of higher temperatures, usually 80–90°. The higher temperature was not necessary with 5-bromo-2,4-diaminopyrimidine. The yields were, as a whole, lower than those usually obtained in this type of reaction, being about 50%.[17a] The crude products were partially purified by one treatment with charcoal in alkaline solution before being hydrolyzed by refluxing with two and one-half moles of 10% sodium hydroxide solution for one hour. These products were then purified by treatment of their alkaline solutions with charcoal. In most cases it was also possible to prepare hydrochlorides, insoluble in excess hydrochloric acid, as a further aid to purification. The only satisfactory decolorization of 2-sulfanilamido-5-bromo-4,6-dimethylpyrimidine was achieved by the treatment of a solution of the compound in acetone with charcoal.

3-Allylacetylacetone.[18]—Fifty grams (0.5 mole) of acetylacetone (Carbide and Carbon, purified through the copper salt) was added to a solution of 11.5 g. (0.5 atom) of sodium in 250 cc. of absolute alcohol and, after about five minutes, 67.0 g. of allyl bromide[19] was added all at once. The mixture was stirred and refluxed gently overnight, cooled, diluted to 500 cc. with petroleum ether and filtered from the sodium bromide. The filtrate was distilled to the separation of solid, diluted with petroleum ether and the process repeated. After distilling the solvent the allylacetylacetone was distilled through a short, packed column. The yield was 55.0 g. (78%); b.p. 195–196°. This material was used directly in the next reaction without further characterization.

2-Amino-5-allyl-4,6-dimethylpyrimidine.—Forty grams (0.28 mole) of 3-allylacetylacetone and 27.0 g. (0.14 mole) of 97% guanidine carbonate were stirred and heated under reflux at 170° for one hour, then another 5.0 g. of guanidine carbonate was added and the heating was continued for five hours at 150°. The product was extracted with four 125-cc. portions of boiling carbon tetrachloride and the combined extracts were treated with Norit, concentrated to 150 cc. and cooled. The pyrimidine crystallized. A second crop was obtained by further concentration of the filtrate. The yield was 22.6 g. (48%), m.p. 122–128°. The melting point was raised to 131–134° by crystallization from ethyl acetate.

2-Amino-5-(2,3-dibromopropyl)-4,6-dimethylpyrimidine.—Thirty and one-half grams (0.19 mole) of the above pyrimidine was dissolved in a mixture of 350 cc. of chloroform and 300 cc. of carbon tetrachloride. To the refluxing solution was added 30.0 g. (0.19 mole) of bromine in 100 cc. of chloroform at such a rate that the reaction mixture never contained much free bromine. The solution was refluxed for two hours after all of the bromine had been added. Upon cooling, 34 g. of crude product separated. The chloroform was fractionated from the mother liquor and a second, darker, crop was collected. The second crop was partially purified by treatment with Norit in hydrochloric acid solution and precipitation by ammonia. The two crops were then combined, dissolved in 650 cc. of hot 95% alcohol, and the solution was treated with Norit. The filtrate was concentrated to 300 cc. and the precipitate was collected; yield 38.5 g. (63%), m.p. 190–193°. A sample melting at 196–198° was obtained by slow crystallization from a large volume of carbon tetrachloride.

Anal. Calcd. for $C_9H_{13}Br_2N_3$: C, 33.5; H, 4.1; N, 13.0. Found: C, 33.6; H, 3.9; N, 13.3.

2-(N^4-Acetylsulfanilamido)-5-(2,3-dibromopropyl)-4,6-dimethylpyrimidine.[19a]—Thirty-eight and one-half grams (0.12 mole) of the pyrimidine was treated with 29.3 g. (0.13 mole) of acetylsulfanilyl chloride (commercial, recrystallized from ethylene chloride) in 60 cc. of dry pyridine at 35–40° for two hours. The reaction mixture was drowned in 300 cc. of dilute hydrochloric acid, the solid collected, treated with Norit in alkaline solution, precipitated and air dried. This was dissolved in 250 cc. of chloroform. The water was separated and the chloroform solution was dried with calcium chloride. The solution was diluted with 65 cc. of acetic acid and the chloroform was removed by distillation. The product crystallized slowly from the acetic acid. After another crystallization from acetic acid, a yield of 44 g. (70%), m.p. 148–152°, was obtained. This was used directly in the next step.

2-Sulfanilamido-5-(2,3-dibromopropyl)-4,6-dimethylpyrimidine.[19a]—Forty-four grams of the above material was hydrolyzed by letting it stand with 400 cc. of 95% alcohol containing 88 cc. of concentrated hydrochloric acid for four days. The alcohol was distilled at reduced pressure and the residue was dissolved in 1:5 hydrochloric acid and precipitated with sodium acetate. The air-dried material was then dissolved in chloroform, the water separated and the chloroform distilled. The residue was poured into absolute alcohol, which caused crystallization. After two crystallizations from absolute alcohol, 11 g., m.p. 162–163°, was obtained. The same product could be obtained by refluxing ten minutes with 24% hydrobromic acid.

A less stable modification of the same compound was occasionally obtained in the course of the alcohol crystallizations, m.p. 127–130°.

Anal. Calcd. for $C_{15}H_{18}Br_2N_4O_2S$: C, 37.7; H, 3.8; N, 11.7; Br, 33.4. Found: C, 37.6; H, 3.7; N, 11.6; Br, 33.5.

2-(N^4-Acetylsulfanilamido)-4-amino-5-bromopyrimidine.—Thirty-eight and eight-tenths grams (0.20 mole) of the amino compound from above was allowed to react with 51.5 g. (0.22 mole) of acetylsulfanilyl chloride in 140 cc. of pyridine for one hour at 37–40° and precipitated by pouring into 450 cc. of water. The product was purified by treatment in alkaline solution with Norit to give 37 g. (48%). After crystallization from water the m.p. was 272° (dec.).

Anal. Calcd. for $C_{12}H_{12}BrN_5O_2S$: C, 37.3; H, 3.1; N, 18.1; Br, 20.8. Found: C, 37.4; H, 3.1; N, 18.5; Br, 20.9.

2-Sulfanilamido-4-amino-5-bromopyrimidine.—When boiling alcoholic hydrochloric acid was found not to effect the hydrolysis in twenty five minutes the following procedure was used.

(16) Johnson and Johns, *Am. Chem. J.*, **34**, 190 (1905).

(17) Roblin and Winnek, THIS JOURNAL, **62**, 1999 (1940).

(17a) The following preparation is reported in detail as other workers [Price, Leonard and Whittle, *J. Org. Chem.*, **10**, 327 (1945)] have reported a lack of success with it. A mixture of 25 g. (0.125 mole) of 2-amino-5-bromo-4,6-dimethylpyrimidine and 30 g. (0.13 mole) of acetylsulfanilyl chloride in 30 cc. of pyridine was stirred and heated at 60° for thirty minutes. The resulting oil was poured into 500 cc. of ice and water containing 40 cc. of hydrochloric acid. The solid which separated was purified by treatment with Darco in alkaline solution. The very light colored product weighed 31 g. (63% yield).

(18) The preparation of this compound has been reported [Beilstein, 4th ed., Vol. I, 804 (412)] but the details are not readily available.

(19) "Organic Syntheses," Coll. Vol. 1, 27 (1941).

(19a) Prepared by Miss Leota F. Pekrul.

Thirty-eight grams of the acetyl compound from the above preparation was boiled gently with four equivalents of 10% sodium hydroxide for one and one-quarter hours, diluted to 450 cc. and decolorized with Norit. The product was precipitated with acid and the treatment was repeated; yield 27.5 g. (80%). Crystallization from water gave material of m.p. 260–262°.

N-Acetyl-2-chlorosulfanilyl Chloride.—Twenty-one grams (0.12 mole) of *m*-chloroacetanilide (Eastman Kodak Co.) was chlorosulfonated with 40 cc. of chlorosulfonic acid by the procedure given for the preparation of N-acetylsulfanilyl chloride.[20] The product was partially purified by crystallization from benzene yielding 6 g. (18%) of material, m.p. (with evolution of gas) 120–126°. This was used without further purification.

2-(N⁴-Acetyl-2-chlorosulfanilamido)-pyrimidine.—A mixture of 6.7 g. (0.07 mole) of 2-aminopyrimidine[15] with 12.3 g. (0.046 mole) of the above sulfonyl chloride in 15 cc. of dry pyridine was heated at 75° for forty-five minutes. After precipitation by water the compound was purified by treatment with charcoal in alkaline solution; yield 8.2 g. (54%). Crystallization from alcohol gave a product of m.p. 279–280°.

2-(2-Chlorosulfanilamido)-pyrimidine.—Hydrolysis of 22 g. (0.07 mole) of the acetyl compound by boiling for 90 minutes with 100 cc. of 10% sodium hydroxide gave, after dilution and treatment with charcoal, 18 g. (94%) of white solid, m. p. 249–252°. Crystallization from a large volume of alcohol gave 14 g. of pure material. The ultraviolet absorption spectrum[21] was characteristic of sulfanilamides rather than of orthanilamides.

2-Amino-5-bromothiazole.—One hundred grams (1 mole) of freshly distilled 2-aminothiazole was dissolved in a mixture of 400 cc. of water and 125 cc. of 48% hydrobromic acid. The solution was treated with Norit, filtered and brominated by the aspiration of 160 g. (1 mole) of bromine into the solution in a stream of air at 15°. The bromine reacted instantaneously and the end of the reaction was indicated by the appearance of a yellow color. The reaction mixture was boiled for five minutes and cooled to give a heavy precipitate. This precipitate was collected, suspended in water in the presence of 600 cc. of chloroform and the whole was made alkaline by the addition of ammonia. The chloroform extract was decolorized with Norit, distilled to remove the water, concentrated to a thick mush and filtered. A second crop was recovered from the filtrate; yield 62 g. (35%), m.p. 105°. Crystallization from hexane raised the melting point to 108° (dec.).

If the original bromination solution was not boiled, a heavy white precipitate was obtained by concentrating the solution to one-half volume *in vacuo* and chilling. This material, dried *in vacuo* over flake sodium hydroxide, analyzed as the hydrate of 2-aminothiazole plus one molecule of bromine.

Anal. Calcd. for $C_3H_4Br_2N_2S\cdot H_2O$: C, 13.0; H, 2.2; N, 10.1; Br, 57.5. Found: C, 13.2; H, 2.3; N, 10.5; Br, 57.8.

Ten grams of this material was heated at 100° for one and one-half hours. The brown product was suspended in 20 cc. of water and 50 cc. of ether and made alkaline with ammonia. The ether was separated and the aqueous layer was extracted with 25 cc. more of ether. The ether was combined with the first portion and the solution was dried with sodium sulfate and distilled. There was obtained in this way 5.7 g. (82% calcd. on the formula above) of material identical with 2-amino-5-bromothiazole prepared above. When the addition product was made alkaline before heating, only an ether-insoluble, water-insoluble solid was obtained.

2-(N⁴-Acetylsulfanilamido)-5-bromothiazole.—A mixture of 10.5 g. (0.06 mole) of the above amine and 15 g. (0.064 mole) of acetylsulfanilyl chloride was ground, passed through a 20-mesh screen and then added to 15 cc. of pyridine at 10–15° with stirring. After standing for one hour at room temperature it was poured into 300 cc. of 1:12 hydrochloric acid. The material was treated once with Darco in alkaline solution and air dried; yield 14.2 g. (64%). It was not further purified.

2-Sulfanilamido-5-bromothiazole.—A suspension of 5 g. of the above, in 15 cc. of water, 15 cc. of concentrated hydrochloric acid and 10 cc. of 95% alcohol was refluxed for ten minutes after all of the solid had gone into solution. The hot solution was clarified with Norit, cooled and made alkaline with ammonia and then precipitated with acetic acid. It was finally purified by decolorization in cold acetone with Norit and crystallization from alcohol.

2-Amino-5-chlorothiazole: Method I.—Eighteen and seven-tenths grams (0.1 mole) of dichloroacetal,[22] 7.6 g. (0.1 mole) of thiourea, 20 cc. of hydrochloric acid and 40 cc. of water were refluxed for one and one-half hours. Another 3.8 g. of thiourea was added and the refluxing was continued for thirty minutes. The acidic solution was extracted with benzene, which was discarded. The aqueous solution was made alkaline with ammonia and extracted with benzene. The product was extracted from the benzene into aqueous acid, and, after making the solution alkaline, into ether, which was dried and decolorized with Norit. Distillation of the ether left a crystalline residue which, after crystallization from hexane, melted at 110–112° and was identical, by mixed melting point, with material prepared by Method II.

Method II.—A solution of 50 g. (0.5 mole) of 2-aminothiazole (distilled) in 100 cc. of 1:1 hydrochloric acid was decolorized with Norit and treated with 42 g. (0.59 mole) of chlorine in about twenty minutes. The solution was concentrated at atmospheric pressure to one-half of its original volume, chilled, and adjusted to *p*H 6 with ammonia. The precipitate was collected and dissolved in 400 cc. of warm benzene, from which solution the separated water was removed. The benzene was treated with Nuchar and chilled overnight to give 17.5 g. of light tan crystals, m.p. (dec.) 105–108°. Two such batches were worked up at the same time and gave 39.2 g. (42%). Repeated crystallization from benzene (Norit) gave a perfectly white product which melted at 111–115° on rapid heating. It colored quickly on standing in the air.

2-(N⁴-Acetylsulfanilamido)-5-chlorothiazole.—Eleven and one-half grams (0.085 mole) of the above amine and 20 g. (0.085 mole) of acetylsulfanilyl chloride were ground together and added to 25 cc. of pyridine in an ice-bath. The temperature rose to 55° and then fell to 30°. The mixture was removed from the ice-bath and kept at this temperature for one and one-half hours. The resulting oil was poured into 500 cc. of dilute hydrochloric acid. The precipitate was collected and partially purified by treatment in ammoniacal solution with Nuchar; yield 18.2 g. (64%); dec. *ca.* 240°.

2-Sulfanilamido-5-chlorothiazole.—A suspension of 19.9 g. (0.06 mole) of the above product in 60 cc. of water, 60 cc. of hydrochloric acid and 40 cc. of alcohol was refluxed for forty-five minutes and the hot solution treated with Norit. The solution was made alkaline with ammonia, decolorized with Nuchar, and precipitated by acidification with acetic acid. The product was dissolved in 600 cc. of hot alcohol, the solution treated with Norit, and cooled to give 7.6 g. melting at 223–225° (dec.). After several crystallizations from alcohol the decomposition point was 228°. By reworking the mother liquors 12.6 g. (71%) was obtained.

2-Amino-5-bromo-4-methylthiazole.—2-Amino-4-methylthiazole was brominated in 20% sulfuric acid by the method of Ochiai and Nagasawa.[8] Strict adherence to their conditions was necessary for satisfactory results.

2-(N⁴-Acetylsulfanilamido)-5-bromo-4-methylthiazole.—A mixture of 5.75 g. (0.03 mole) of this amine and 7.65 g. (0.33 mole) of acetylsulfanilyl chloride in 10 cc. of pyridine was kept at 37–40° for one-half hour and then for two hours at room temperature. The mixture was poured into

(20) "Organic Syntheses," Coll. Vol. I, 8 (1941).

(21) Carried out by Mr. J. F. Bone in these Laboratories.

(22) Prepared by the method of Mangani and McElvain, THIS JOURNAL, **60**, 2212 (1938), but using chloroacetal (Niacet) rather than acetal.

100 cc. of dilute hydrochloric acid and the solid was collected and purified by treatment with Darco in alkaline solution. It was found helpful to pour the clarified alkaline solution into dilute acid when precipitating the product, rather than the reverse; yield 9.6 g. (82%); dec. 223°. This was used in the next step without further purification.

2-Sulfanilamido-5-bromo-4-methylthiazole.—Eleven and nine-tenths grams of the above product was refluxed for two hours with 120 cc. of 10% potassium hydroxide, cooled and neutralized by pouring into dilute acetic acid. A solution of the precipitate in 400 cc. of acetone and 300 cc. of ether was purified by treatment with Norit. The product was precipitated by the addition of 150 cc. of water and distillation of the organic solvent; yield 6.2 g. (58%).

2-Amino-5-chloro-4-methylthiazole.—Eleven and one-half grams (0.15 mole) of thiourea was refluxed with 12.7 g. (0.1 mole) of 1,1-dichloroacetone[23] in 25 cc. of alcohol for thirty minutes. The mixture was poured into 150 cc. of water containing 10 cc. of hydrochloric acid and the solution was decolorized with Norit. The product was precipitated by neutralization with ammonia. It was dried and recrystallized from heptane; yield 5.4 g. (36%); m.p. 104–108°.

2-(N^4-Acetylsulfanilamido)-5-chloro-4-methylthiazole.—Four and three-tenths grams (0.03 mole) of the above amine reacted with 7 g. (0.03 mole) of acetylsulfanilyl chloride in 7 cc. of pyridine at such a rate that the temperature remained at 20–40°. After the solution had stood at room temperature for one hour, the product was precipitated by pouring the mixture into 100 cc. of water containing 10 cc. of hydrochloric acid. After purification by treatment in alkaline solution with charcoal 8.2 g. (82%) of white solid decomposing at 248° was obtained. After another such treatment in alkaline solution with charcoal the material was colorless and decomposed at 256–257°.[24]

Anal. Calcd. for $C_{12}H_{12}ClN_3O_3S_2$: C, 41.7; H, 3.5. Found: C, 41.6; H, 3.6.

2-Sulfanilamido-5-chloro-4-methylthiazole.—Eighteen grams of the acetyl compound was dissolved in 300 cc. of 10% potassium hydroxide and the solution was refluxed for two hours. The solution was then poured into enough 1:100 acetic acid to precipitate the product which was purified by several treatments in acetone solution with Darco. The solution was diluted with water and the acetone distilled to recover the material.

2-Amino-5-chloropyridine.—The chlorination of 2-aminopyridine in 20% sulfuric acid at 25° was much more satisfactory than the chlorination in alcoholic solution as described by Chichibabin.[25] The 2-amino-5-chloropyridine was separated from the more highly chlorinated side products by its greater insolubility in carbon tetrachloride. The product from the chlorination of 47 g. of 2-aminopyridine was extracted with 200 cc. of carbon tetrachloride and the residue was reprecipitated from solution in dilute hydrochloric acid, after Norit treatment, to give a 54% yield of 2-amino-5-chloropyridine, m.p. 136–137°. Chichibabin obtained a 68% yield, which we could not duplicate.

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Summary

1. The preparation of a number of new halogenated sulfanilamidoheterocycles has been described. Certain observations on the ease of halogenation of the intermediate aminoheterocycles have been made.

2. Of the compounds prepared, only 2-sulfanilamido-5-chloropyrimidine and its bromine analog were found to have increased activity over sulfadiazine against sporozoite-induced *P. gallinaceum* malaria in the chick.

3. This activity was qualitatively as well as quantitatively different from that of sulfadiazine since it was not completely counteracted by *p*-aminobenzoic acid. This behavior has been interpreted as the exhibition of two modes of antiplasmodial action by one molecule.

(23) Borsche and Fittig, *Ann.*, **133**, 113 (1865).

(24) Foldi, Gerecs, Demjen and Konig[11] report the preparation of this compound by the reaction of acetylsulfanilyl thiourea and 1,1-dichloroacetone but give the melting point as 217° and report the m.p. of the hydrolyzed compound to be about 260°. They have apparently reversed the two temperatures as we have repeated their preparation and find the product to agree with ours as reported.

(25) Chichibabin and Egorov, *J. Russ. Phys.-Chem. Soc.*, **60**, 683 (1928); [*Chem. Zentr.*, **99**, II, 1670 (1928)].

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