at 3 mm. in a Claisen–Vigreux flask gave the results listed in Table II.

TABLE II

Fraction	Boiling range at 3 mm., °C.	Amt., g.	Sapn. equiv.	Butadiene units calcd.
1	68–75	3.1	214.8 208.1	1.13
2	110–120	1	259.6 263.0	2.05
3	132–140	1.4	246.8 260.0[a]	...
4	160–175	0.8	363.3 357.0	3.92
5	183–190	0.8	566	7.7
Residue above 190°		2	139.0	22.9

[a] Some methyl homoisophthalate obtained in this fraction.

The solid rubbery product isolated from this reaction absorbed oxygen and in time became hard and brittle. Analysis of one of these products which had stood for two months showed average values of 71.0% carbon, 8.9% hydrogen and 20.1% oxygen. The carbon–hydrogen ratio is 0.667 which approaches the value 0.670 for 100 butadiene units (50 units is 0.675). On this basis the absorbed oxygen would have been 0.86 atom per double bond. The true size of the molecule is probably larger than this value.

The residue likewise underwent thermal polymerization to a rubbery solid when heated at 230° for four days.

The Action of Phenylsodium, Furylsodium and *p*-Phenylphenylsodium (G. H. P.).—All attempts to prepare phenylsodium by addition of amyl chloride to a suspension of sodium in benzene or benzene–*n*-octane mixture, while stirred in the high speed stirring apparatus at 25–40°, resulted in the formation of solid gels. This result was unexpected because in previous work[8] with ordinary stirring this method of preparing phenylsodium served excellently. The compound was, however, prepared smoothly from chlorobenzene and sodium. Addition of butadiene to this product failed to produce any short chain acids. As many as five experiments were made. Variation of time and temperature yielded no isolable products of low molecular weight.

2-Furylsodium was prepared by metalation of 51 g. (0.75 mole) of furan with benzylsodium. Addition of 18.5 g. of butadiene in the customary manner led to no short chain acid products.

(8) Morton and Fallwell, THIS JOURNAL, **59**, 2387 (1937); **60**, 1429 (1938).

p-Phenylphenylsodium was prepared from chlorobiphenyl and one and a half equivalents of sodium under conditions which were demonstrated by carbonation to give a 78% yield of *p*-phenylphenylsodium. Addition of butadiene in the customary manner produced no short chain acid products, but yielded small amounts of sticky rubber-like products.

***p*-Dichlorobenzene and Sodium** (G. H. P.).—*p*-Dichlorobenzene (25.4 g.) was treated with 23 g. of sodium powder in 310 ml. of *n*-octane at 62°. (The reaction did not occur appreciably at 25°.) The total time for addition was one hundred minutes. The mixture was stirred for an additional hour and the black-colored product poured on carbon dioxide. A very small amount only of brown resinous acid was obtained. No terephthalic acid could be detected.

Summary

Under the conditions tried butadiene adds with amyl-, benzyl- and cyclohexyl-sodium. The sodium compounds are decomposed by carbon dioxide or by water and alcohol to give acids or hydrocarbons.

The acids and derived esters having saponification equivalents and double bonds which correspond to addition of one or two butadiene units can be isolated readily. Those which have three or more units show unsaturation lower than expected and an oxygen content which is abnormally high. Other properties of the esters suggest that oxygen is absorbed readily.

These compounds, whether as esters or the corresponding hydrocarbons, undergo thickening by a thermal polymerization at 230°. The residues and rubber-like products undergo a similar thermal polymerization.

Phenylsodium, furylsodium and *p*-phenylphenylsodium do not add readily to butadiene. Rubber-like products are formed by these reagents.

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(9) Original manuscript received December 30, 1942.

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

Studies in Chemotherapy. XII. Some Sulfanilamidoheterocycles

BY J. H. CLARK, J. P. ENGLISH, P. S. WINNEK,[1] H. W. MARSON, Q. P. COLE AND J. W. CLAPP

Since the original report of the synthesis and high antibacterial[1a] activity of sulfadiazine (2-sulfanilamidopyrimidine), numerous derivatives of the sulfanilamidopyrimidines have been prepared and described.[2] The compounds reported here have been prepared in the continuing search for compounds of higher intrinsic activity and with better pharmacological properties. In addition to the usual bacterial tests, some of these have been subjected to malarial screening using *Plasmodium gallinaceum* in chickens as a test infection.

Most of the required aminopyrimidines were prepared by known methods. 2-Amino-4-*t*-butylpyrimidine was synthesized from guanidine carbonate and the copper derivative of formylpinacolone (4,4-dimethyl-1,3-pentanedione).[3] The procedure was simpler and the yield better than when free formylpinacolone was used.

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(1a) R. O. Roblin, Jr., J. H. Williams, P. S. Winnek and J. P. English, THIS JOURNAL, **62**, 2002 (1940).

(2) *For instance:* (a) W. T. Caldwell, E. C. Kornfeld and C. K. Donnell, *ibid.*, **63**, 2188 (1941); (b) J. M. Sprague, L. W. Kissinger and R. M. Lincoln, *ibid.*, **63**, 3028 (1941); (c) K. Ganapathi, *Proc. Indian Acad. Sci.*, **13A**, 386 (1941); (d) R. O. Roblin, Jr., P. S. Winnek and J. P. English, THIS JOURNAL, **64**, 567 (1942); (e) G. W. Anderson, H. E. Faith, H. W. Marson, P. S. Winnek and R. O. Roblin, Jr., *ibid.*, **64**, 2902 (1942).

(3) Couturier and Vignon, *Compt. rend.*, **140**, 1696 (1905).

TABLE I

SULFANILAMIDOHETEROCYCLES

SN[a]	Compound	M. p., °C.[g] (cor.)	Max.[h] blood level	Chemotherapeutic activity Bact.[i]	Mal.[k]	Formula	Analyses,[l] % Calcd. C	Calcd. H	Calcd. N	Found[m] C	Found[m] H	Found[m] N
112	2-S[b]P[c]	255–256	20	1	1	$C_{10}H_{10}N_4O_2S$	..	...	..	..	...	...
5,284	2-S-4-*t*-butyl P	236–237	5	0.03	0.01d	$C_{14}H_{18}N_4O_2S$	54.9	5.9	18.3	54.8	5.8	18.3[n]
11,039	2-(2-Methyl S) P	243–246	22	.02	.15d	$C_{11}H_{12}N_4O_2S$[o]	50.0	4.6	21.2	50.3	4.7	20.8[n]
5,240	2-S-4,5,6-Trimethyl P[e]	242–244	19	.25	.3	$C_{13}H_{15}N_4O_2S$	53.4	5.5	19.2	53.6	5.4	19.3
7,512	2-S-4-Amino P[f]	269–270	1	.01	.3	$C_{10}H_{11}N_5O_2S$	..	...	..	..	...	..
723	2-S-4-Ethoxymethyl-6-methyl P	158–160	22	.02	..	$C_{14}H_{18}N_4O_3S$	52.2	5.6	17.4	52.4	5.9	17.4
5,137	2-S-4-(γ-Diethylaminopropylamino) P	230–232	1	.01i	.01i	$C_{17}H_{26}N_6O_2S$	53.9	6.9	22.2	53.9	6.9	22.1
818	2-S-4,6-Diphenyl P	266–268	..	.01i	..	$C_{22}H_{18}N_4O_2S$	65.7	4.5	13.9	65.6	4.6	13.7
863	2-S-4-(2,2-Dimethyl-1,3-dioxolane-4-methoxy) P	228–230	5	.01i	..	$C_{16}H_{20}N_4O_5S$	50.5	5.3	14.7	50.3	5.2	15.0
14,034	2-S-Thiazole-5-sulfonic acid	258	1	.01i	.01id	$C_9H_9N_3O_5S_3$	32.2	2.7	12.5	32.3	2.9	12.7
720	2-S-1,3,4-Thiadiazole-5-acetic acid	209–210	1	.02	..	$C_{10}H_{10}N_4O_4S_2$	38.2	3.2	17.8	38.0	3.4	17.8
768	2-S-1,3,4-Thiadiazole-5-butyric acid	185.5–6.5	..	.01i	..	$C_{12}H_{14}N_4O_4S_2$	42.1	4.1	16.4	42.3	4.0	16.3

[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. [c] P = Pyrimidine. [e] Haworth and Rose, British Patent 552,887. [f] See ref. 2e. [g] With decomposition in most cases. [h] Mg.% following a single oral dose of 0.5 g. per kg. Determined on the pooled blood of ten mice by Miss Dorothea Babbitt in these Laboratories. [i] Bacteriostatic activity against *E. coli* in synthetic medium. This figure is the ratio, Minimum Effective Concentration of sulfathiazole/MEC of compound; i = inactive at this ratio. These values were determined in these Laboratories under the direction of Dr. H. J. White. [k] Antimalarial activities determined against sporozoite-induced infections of *P. gallinaceum* in white leghorn chicks in these laboratories. The figures are blood level (except when followed by "d" when the figure is based on dosage) sulfadiazine equivalents taken from (Ref. *a*, test 0–2); i = inactive at the ratio given. [l] Microanalyses were carried out in these laboratories under the direction of Dr. J. A. Kuck. [m] Average of two values not differing by more than 0.3%. [n] Nitrogen by macro Kjeldahl. [o] Calcd.: S, 12.1. Found: S, 12.0.

A more convenient synthesis and concomitant proof of structure of a compound which had been reported earlier from these laboratories has been achieved. 2-Sulfanilamido-4-aminopyrimidine[2e] had been prepared previously in very low yield by the reaction of acetylsulfanilyl chloride and 2,4-diaminopyrimidine with subsequent deacetylation. It was adduced at that time that the compound was the 2- and not the 4-sulfanilamido derivative because of its properties. This has now been proved by the preparation of the same compound by the ammonolysis of 2-sulfanilamido-4-methoxypyrimidine.[2d] The reaction of 4-alkoxypyrimidines with ammonia or amines does not seem to have been reported previously although the replacement of 2-alkylthio groups by the use of such reagents is well known.[4] The reaction is not unexpected in view of the similarity of a 4-alkoxypyrimidine to an imino ether in structure. This synthesis leaves no doubt as to the structure of the compound in question since the pyrimidine part of 2-sulfanilamido-4-methoxypyrimidine is derived originally from formylacetic acid and guanidine. 2-Sulfanilamido-4-(γ-diethylaminopropylamino)-pyrimidine was prepared by the same general method with the substitution of γ-diethylaminopropylamine for ammonia. The direct reaction of acetylsulfanilyl chloride and 2-amino-4-(γ-diethylaminopropylamino)-pyrimidine[5] was not successful. It is interesting that the reaction of 2-sulfanilamido-4-methoxypyrimidine and ammonia proceeds at a lower temperature than does that of 2-amino-4-methoxypyrimidine and the same reagent.

A study of the table and reference to earlier work[1,2d] reveals that simple alkyl substitution of the pyrimidine ring or of the sulfanilamide nucleus does not markedly affect the maximum blood level as compared with the parent sulfadiazine. However, more complicated substituents, such as the *t*-butyl or glycerolketal, do reduce this value somewhat. The value is still further reduced by amino substitution. The sulfonic acid group has reduced markedly the maximum blood level of sulfathiazole. These last observations are in general agreement with the work of Shannon and co-workers[6] who found that strongly ionic sulfanilamides, such as sulfanilylsulfanilic acid, were more rapidly excreted than were the parent compounds.

Although in some cases water solubility seems to have little to do with the maximum blood level,

(4) T. B. Johnson and D. Hahn, *Chem. Rev.*, **13**, 223–224 (1933).

(5) R. R. Adams and F. C. Whitmore, THIS JOURNAL, **67**, 1159 (1945).

(6) S. H. Fisher, T. L. Troast, A. Waterhouse and J. A. Shannon *J. Pharmacol.*, **79**, 373 (1943).

for instance in the case of 2-sulfanilamido-5-chloropyrimidine,[2d] the extreme insolubility of 2-sulfanilamido-4,6-diphenylpyrimidine is the only obvious reason for its lack of a demonstrable blood level.

While such preliminary data do not present the entire picture with respect to absorption and excretion as do such studies as those of Van Dyke, *et al.*,[7] a rough comparison of the compounds on this basis is permissible.

Only the trimethyl derivative approaches the activity of sulfadiazine in this bacteriostatic test. The extremely low relative activities of the others serve to point out that other factors in addition to the acidity[8] of the compounds in question are important. That the relative anti-malarial and anti-bacterial activities may not be dependent upon the same properties is evident from a comparison of the two columns of data.

Experimental[9]

These sulfanilamides, with two exceptions, were prepared by the general methods which have been reported previously.[10] In most cases the N^4-acetyl compounds were not purified extensively but were submitted directly to alkaline hydrolysis.

2-Sulfanilamido-4-aminopyrimidine.—Forty grams of 2-sulfanilamido-4-methoxypyrimidine[2d] was heated with 400 cc. of methanol and 200 g. of anhydrous ammonia in an autoclave at 110° for one hour.[11] After the release of the excess ammonia the alcohol was evaporated in a stream of air and the residue was dissolved in dilute sodium hydroxide. This solution was treated twice with Norit and the colorless final filtrate was adjusted to *p*H 7. The precipitate was collected and dried; yield 23 g. (57%), m. p. 269–270°. This melting point was not depressed by mixture with the compound prepared earlier.[2a]

2-Amino-4-methoxypyrimidine[12] did not react with ammonia under these conditions. When the reaction was run at 200° for four hours 2,4-diaminopyrimidine[13] was formed.

2-Sulfanilamido-4-(γ-diethylaminopropylamino)-pyrimidine.—Eight grams of 2-sulfanilamido-4-methoxypyrimidine[2a] and 3.8 g. of γ-diethylaminopropylamine[14] were mixed and heated at 100–110° for forty-five minutes. The initial slurry evolved a gas (presumably methanol) and became solid. This was broken up, washed with water and crystallized three times from the same solvent; yield 5 g. (45%).

2-Amino-4-ethoxymethyl-6-methylpyrimidine.—Eighteen grams of guanidine carbonate was heated with 25 g. of 1-ethoxyacetyl acetone[15] for four hours on a steam-bath. The reaction mixture was extracted with hot carbon tetrachloride and the product was isolated by distilling the solvent. The product was crystallized from the same solvent; yield 20.2 g. (69%), m. p. 106–108°.

Anal. Calcd. for $C_8H_{13}N_3O$: C, 57.5; H, 7.8. Found: C, 57.6; H, 7.8.

2-Sulfanilamido-4-ethoxymethyl-6-methylpyrimidine.—The partially purified N^4-acetyl compound melted at 163–165°. The sulfanilamide was crystallized from alcohol; over-all yield 40%.

2-Amino-4,6-diphenylpyrimidine.—Forty-six and four-tenths grams of crude dibenzoylmethane[16] was heated with 25 g. of guanidine carbonate at 180–210° for three hours. The mixture was treated with 250 cc. of boiling chloroform, filtered and the chloroform distilled. Two cc. of alcohol was mixed with the residual oil and the solution was chilled to precipitate the product; yield 20 g. (39%), m. p. 132–133°. Crystallization from toluene raised this to 135–137°.

Anal. Calcd. for $C_{16}H_{13}N_3$: C, 77.7; H, 5.3. Found: C, 77.6; H, 5.1.

2-Sulfanilamido-4,6-diphenylpyrimidine.—The partially purified N^4-acetyl compound melted at 250–252°. The sodium salt of the hydrolyzed material is less soluble than that of the N^4-acetyl and separated during the hydrolysis. Purification was through the potassium salt which was precipitated from water by excess potassium hydroxide.

2-Amino-4-(2,2-dimethyl-1,3-dioxolane-4-methoxy)-pyrimidine.—The sodium salt of 2,2-dimethyl-1,3-dioxolane-4-methanol[17] (acetoneglycerol) was prepared from 3.5 g. of powdered sodium and 20 g. of the ketal by refluxing for two hours in 200 cc. of purified dioxane. This solution was placed in the flask of a Soxhlet apparatus containing 20 g. of 2-amino-4-chloropyrimidine[2a] in the cup and the dioxane was refluxed overnight to extract completely the chloro compound. The dioxane was distilled and hexane was added to the residue. The resultant solid was filtered and separated from salt by continuous extraction with ether followed by crystallization from hexane; yield 23.8 g. (70%), m. p. 105° (Block).

Anal. Calcd. for $C_{10}H_{15}N_3O_3$: C, 53.3; H, 6.7. Found C, 53.8; H, 6.7.

2-N^4-Acetylsulfanilamido-4-(2,2-dimethyl-1,3-dioxolane-4-methoxy)-pyrimidine.—The crude reaction product (51% yield) was purified by treatment with Norit in alkaline solution; m. p. 249–251°.

Anal. Calcd. for $C_{18}H_{22}N_4O_6S$: C, 51.2; H, 5.3; N 13.8. Found: C, 50.9; H, 5.5; N, 14.0.

2-Sulfanilamido-4-(2,2-dimethyl-1,3-dioxolane-4-methoxy)-pyrimidine.—The crude hydrolysis product contained sulfanilylisocytosine[2a] from which the desired compound was separated by its greater solubility in acetone.

2-Amino-4-*t*-butylpyrimidine.—Forty-three and two-tenths grams of the copper salt of 4,4-dimethyl-1,3-pentanedione,[4] 50 g. of guanidine carbonate and 100 cc. of alcohol were mixed and refluxed for one hour. The alcohol was distilled and the residue was heated with stirring at 150–170° for two hours. The cooled reaction mass was broken up under 500 cc. of 1:4 hydrochloric acid and the suspension was filtered. The filtrate was made basic with ammonia and the heavy precipitate was collected, washed with water and the process repeated. The air-dried product was refluxed with 600 cc. of hexane until all of the moisture had been driven into a trap, and the cloudy suspension was filtered. Eighteen and one-tenths grams (44%) of product crystallized from the cooled filtrate, m. p. 103–105.5°. The melting point was not raised by further crystallization from hexane or alcohol. When free 4,4-dimethyl-1,3-pentanedione was condensed with guanidine carbonate the yield was only 18%.

Anal. Calcd. for $C_8H_{13}N_3$: N, 27.8. Found: N, 27.6.

2-Sulfanilamido-4-*t*-butylpyrimidine.—A 63% yield of the N^4-acetyl derivative was obtained, m. p. 248–251°. This was raised to 250–252° by crystallization from alcohol. A 45% over-all yield of the sulfanilamide was obtained after hydrolysis and crystallization from alcohol and 1:1 acetic acid.

2-(2-Methylsulfanilamido)-pyrimidine.—Reaction of 2-aminopyrimidine[1] with 2-methylacetylsulfanilyl chloride[18]

(7) H. B. Van Dyke, N. A. Tupikova, B. F. Chow and H. A. Walker, *ibid.*, **88**, 203 (1945).

(8) Bell and Roblin, THIS JOURNAL, **64**, 2905 (1942).

(9) All melting points are corrected.

(10) R. O. Roblin, Jr., and P. S. Winnek, THIS JOURNAL, **62**, 1999 (1940).

(11) This reaction was carried out in these Laboratories under the direction of Dr. J. H. Paden.

(12) Hilbert and Johnson, THIS JOURNAL, **52**, 1152 (1930).

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

(14) F. C. Whitmore, H. S. Mosher, R. R. Adams, R. B. Taylor, E. C. Chapin, C. Weisel and W. Yanko, THIS JOURNAL, **66**, 725 (1944).

(15) Sommelet, *Bull. soc. chim.*, [4] **1**, 382 (1907).

(16) "Organic Syntheses," Coll. Vol. I, 199 (1932).

(17) Fischer and Pfähler, *Ber.*, **53**, 1606 (1920).

(18) Goldirev and Postovskii, *J. Applied Chem. (U. S. S. R.)*, **11**, 321 (1938).

gave a 50% yield of produc melting at 268° after decolorization in ammoniacal solution with Darco. The hydrolysis product was purified in the same manner.

2-Amino-4,5,6-trimethylpyrimidine.—A mixture of 13.5 g. of 3-methyl-2,4-pentanedione[19] and 10.6 g. of guanidine carbonate was heated at 150–160° for one and one-half hours. The cooled mass was dissolved in 50 cc. of 1:4 hydrochloric acid, the solution was treated with Norit, filtered and made basic with ammonia. The resulting precipitate weighed 9.9 g. (65% yield), m. p. 204–206°. After crystallization from water the m. p. was 206–207°.

Anal. Calcd. for $C_7H_{11}N_3$: N, 30.6. Found: N, 30.6.

2-Sulfanilamido-4,5,6-trimethylpyrimidine.—An 82% yield of N^4-acetyl derivative, m. p. 280–284°, was obtained. This melting point was raised to 286–288° by treatment of a solution of the compound in ammonia with Norit. The product was isolated from the cooled hydrolysis solution as the sodium salt by the addition of excess sodium hydroxide. Purification was effected by treatment of the alkaline solution with Norit and by crystallization from 10 parts of 90% acetic acid.

2-Amino-5 (or 4)-thiazolesulfonic Acid.—This compound was prepared by methods analogous to those reported by Ochiai and Nagasawa[20] to be effective for the preparation of the corresponding 4-methyl derivative. One hundred grams of 2-aminothiazole was added to 200 cc. of 20% oleum with cooling over a period of one hour. The mixture was heated on a steam-bath for two hours and then poured into 450 cc. of water. After standing two days the precipitate (136 g., 75% yield) was collected and crystallized from 500 cc. of water, decolorizing with Norit. The product was colorless and crystalline; yield 124 g. (69%), m. p. 248°. The barium salt was prepared in water.

Anal. Calcd. for $(C_3H_3N_2O_3S_2)_2Ba$: Ba, 27.0. Found: Ba, 27.7.

2-Sulfanilamido-5-thiazolesulfonic Acid.—The crude acetyl compound was hydrolyzed with boiling 2 *N* hydrochloric acid. The deacetylated compound crystallized from the hot acid. Norit did not decolorize a solution of the sodium salt but was effective on a hot aqueous solution of the free acid; yield (over-all) 7.1 g. (53%). 2-Amino-4-methyl-5-thiazolesulfonic acid[20] did not react with acetylsulfanilyl chloride under these conditions.

The two 2-amino-1,3,4-thiadiazole-5-aliphatic acids were prepared by the general method of Freund and Meincke[21] using the appropriate dicarboxylic acid chloride ester. The acetyl and ester groups were hydrolyzed simultaneously.

Ethyl 2-Amino-1,3,4-thiadiazole-5-acetate.—A mixture of 4.6 g. (0.05 mole) of powdered thiosemicarbazide and 12.7 g. (0.084 mole; a smaller excess gave a lower yield) of carbethoxyacetyl chloride[22] was warmed to 60° to start the vigorous reaction. When the initial reaction was over, the reaction mixture was heated at 60–70° for thirty minutes, cooled, and diluted to 75 cc. with ice and water. The insoluble material was filtered off and the filtrate was adjusted to a *p*H of *ca.* 5. The precipitated product was collected and crystallized from 65 cc. of water, decolorizing with Norit; yield 3.6 g. (37%); m. p. 158–160°.

Anal. Calcd. for $C_6H_9N_3O_2S$: N, 22.5. Found: N, 22.4.

2-Sulfanilamido-1,3,4-thiadiazole-5-acetic Acid.—The crude coupling product was hydrolyzed directly with an excess of 10% sodium hydroxide at the boiling point. The hydrolyzed material was recrystallized from water.

Ethyl Potassium Glutarate.—A solution of 9.9 g. (0.15 mole) of 85% potassium hydroxide in 100 cc. of absolute alcohol was added with stirring in one and one-half hours to 28.2 g. (0.15 mole) of diethyl glutarate (Eastman Kodak Co.) in 100 cc. of absolute alcohol. The resulting solution was refluxed for five minutes and filtered from a small amount of insoluble material. The filtrate was concentrated *in vacuo* to 50 cc. and chilled to precipitate the product. A second crop was obtained by further concentration and dilution with ether. After washing with ether and drying, the product weighed 18 g. (63% yield).

γ-Carbethoxybutyryl Chloride.[23]—A suspension of 18 g. of ethyl potassium glutarate in 100 cc. of dry ether was chilled in an ice–salt-bath and treated with a solution of 13.6 g. of thionyl chloride in 50 cc. of dry ether over a period of three and one-half hours. The mixture was refluxed for three hours, filtered and fractionated; yield 12.7 g. (75%), b. p. 52–57° (1 mm.).

Ethyl 2-Amino-1,3,4-thiadiazole-5-butyrate.—A mixture of 3.3 g. (0.37 mole) of powdered thiosemicarbazide and 10.5 g. (0.059 mole) of γ-carbethoxybutyryl chloride was heated at 70–75° with stirring for thirty minutes. The reaction was vigorous. The mixture was cooled, diluted to 50 cc. with ice and water, and decolorized with Norit. The filtrate was adjusted to a *p*H of *ca.* 5 and the product was collected and crystallized from water; yield 3.3 g. (41%), m. p. 153–154°.

2-Sulfanilamido-1,3,4-thiadiazole-5-butyric Acid.—To obtain a crystalline condensation product it was necessary to wash the initial gum with several changes of water. After decolorizing with Norit in alkaline solution a 75% yield of product of m. p. 225–226° was obtained. The hydrolyzed product crystallized only after standing under water for several weeks. It was then satisfactorily crystallized from water.

Acknowledgment.—We are indebted to Drs. S. Brackett and E. Waletzky for permission to quote their antimalarial results and for much helpful discussion. The assistance of Miss Margaret Baker in the determination of these values is gratefully acknowledged.

Summary

1. The synthesis of a number of new sulfanilamidoheterocycles has been described.

2. The antibacterial and antimalarial activities of these compounds have been presented and discussed with respect to the effects of structure on activity.

STAMFORD, CONN. RECEIVED SEPTEMBER 12, 1945

(19) Salkind, *J. Russ. Phys.-Chem. Soc.*, **37**, 486–492 (1905); "Beilstein," 4th Ed., 1, 791.

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

(21) Freund and Meincke, *ibid.*, **29**, 2516 (1896).

(22) Staudinger and Becker, *ibid.*, **50**, 1019 (1917).

(23) *Cf.* "Organic Syntheses," **25**, 19 (1945), for a general method of preparing the ester acid chlorides of dibasic acids from the monoesters.