Pharmacological data: Topical anesthetic activity, 5 × cocaine; infiltration anesthetic activity, 5 × procaine, LD_{50}, 475 mg./kg.

The corresponding free base, 1-[4-(2,6-dimethylheptyl)-amino]-2-propanol *p*-aminobenzoate was prepared and recrystallized from pentane; m. p. 49.5–50.5°.

Anal. Calcd. for $C_{19}H_{32}O_2N$: N, 8.74. Found: N, 8.81.

1-(8-Pentadecylamino)-2-propanol *p*-aminobenzoate glycolate was recrystallized from a mixture of acetone, ether and pentane as an anhydrous salt, m. p. 101–103°.

Anal. Calcd. for $C_{27}H_{48}O_5N_2$: N, 5.83. Found: N, 5.79.

An attempt to prepare 1-[4-(2,6-dimethylheptyl)-amino]-2-propanol *p*-aminobenzoate borate was unsuccessful. The free base (described above) and boric acid were isolated from the attempted preparation, and evidently the base is not sufficiently basic to form a stable salt with boric acid. The free base could not be dissolved in a dilute water solution containing four or eight equivalents of boric acid.

1-Cyclohexylamino-2-propanol Phenylurethan Hydrochloride.—1-Cyclohexylamino-2-propanol (7.9 g.) was converted to the hydrochloride and heated with an equivalent quantity of phenyl isocyanate in chloroform solution for ninety hours at 50 to 55°. The product was isolated in the manner employed in the aminoethanol series[3]; yield 11.5 g. (73%), m. p. 192–193°.

Anal. Calcd. for $C_{16}H_{25}O_2N_2Cl$: Cl, 11.33. Found: Cl, 11.34.

Pharmacological data: Topical anesthetic activity, 1 × cocaine; infiltration anesthetic activity, 2 × procaine; LD_{50}, 200 mg./kg.

The 1-alkylamino-2-propanol *p*-aminobenzoate hydrochlorides in Table I and the additional salts described above were soluble in water at room temperature to the extent of 2% or more except for the hydrochlorides in which the alkyl group was 5-(2,8-dimethylnonyl) (1%); 6-hendecyl (0.55%) (all ±0.1%); 8-pentadecyl (and its glycolate) (less than 0.05%).

Pharmacological.—The pharmacological data included in Table II were obtained at the Merck Institute for Therapeutic Research, and will be published elsewhere in detail by Albert O. Seeler and Samuel Kuna. The method of testing is outlined in ref. 3.

Summary

A number of 1-alkylamino-2-propanols have been prepared by the hydrogenation of ketone-isopropanolamine mixtures in the presence of Adams platinum catalyst. The synthesis is convenient, and gives excellent yields.

The hydrochlorides of the 1-alkylamino-2-propanols have been esterified by reaction with *p*-nitrobenzoyl chloride in chloroform solution. The *p*-nitrobenzoate hydrochlorides were converted by catalytic hydrogenation into *p*-aminobenzoate hydrochlorides, and the local anesthetic activity of these esters has been studied.

NEW YORK, N. Y. RECEIVED FEBRUARY 23, 1944

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

Some 3,4-Disubstituted Pyridines[1]

BY JAMES L. WEBB[2] AND ALSOPH H. CORWIN

The researches of Rabe during the past twenty-five years have strongly suggested possible methods for the synthesis of the quinine alkaloids. Among possible intermediates are several 3,4-disubstituted pyridines. Some of the most important methods for the synthesis of these compounds[3] are due to Rabe,[4] McElvain and Goese,[5] Stevens, Beutel and Chamberlin[3] and Koelsch.[6] In consideration of its availability, 4-methylpyridine (γ-picoline) was utilized as the starting product for the preparations reported in this paper.

After all the work described here had been completed the paper by McElvain and Goese[5] appeared in which they describe the sulfonation of the 2-, 3-, and 4-methylpyridines and of pyridine itself using mercuric sulfate as catalyst. Their yields of 4-methylpyridine-3-sulfonic acid varied between 0–35%. Using basic mercuric sulfate catalyst our average yield of the very crude sodium 4-methylpyridine-3-sulfonate was 57%.

The conditions necessary for the cyanide fusion of pyridine sulfonic acid salts are, at best, drastic since the reaction mixture contains the very basic cyanide ion and the temperature necessary for reaction is approximately 300–400°. We have found that the yield is inversely proportional to the time required for the fusion. Procedures which overcome some of the disadvantages inherent in this reaction are described in the Experimental Section. McElvain and Goese report a yield of 12% of the 3-cyano-4-methylpyridine. Our yield varied from 25–33% based on the crude sodium 4-methylpyridine-3-sulfonate.

While 2-, 3- and 4-cyanopyridine are hydrolyzed readily and in good yields by alkali to the corresponding pyridine carboxylic acids, the sterically hindered 3-cyano-2,4-dimethylpyridine on heating in a sealed tube in alkaline medium is converted only to the amide.[7] However, McElvain and Goese[5] successfully hydrolyzed 3-cyano-4-methylpyridine to 4-methylpyridine-3-carboxylic acid in 80% yield. Upon attempting to hydrolyze

(1) This paper is from the doctoral dissertation of James L. Webb, The Johns Hopkins University, 1943.

(2) Du Pont Fellow in Chemistry, 1942–43; American Can Company Fellow, 1943.

(3) Stevens, Beutel and Chamberlin, THIS JOURNAL, **64**, 1093 (1942).

(4) Rabe, *et al.*, *Ber.*, **64**, 2487 (1931).

(5) McElvain and Goese, THIS JOURNAL, **65**, 2233 (1943), and earlier papers.

(6) Koelsch, *ibid.*, **65**, 2458, 2459, 2460 (1943).

(7) Meyer, *J. prakt. Chem.*, [2] **78**, 519 (1908).

3-cyano-4-methylpyridine under similar conditions we obtained an anomalous product which has not been characterized.

3-Cyano-4-methylpyridine on acid hydrolysis gave 4-methylpyridine-3-carboxylic acid in yields of 78%.

In an attempt to prepare 4-methylpyridine-3-carboxamide from the acid by reaction with thionyl chloride followed by ammonia an anomalous crystalline product was obtained. This compound has been analyzed and found to contain sulfur and chlorine in addition to the expected carbon, nitrogen and hydrogen. No structure has been assigned to this material. This failure to secure the expected acid chloride is surprising since Baumgarten and Dornow[8] experienced no difficulty in the preparation of the acid chloride of 2-methylpyridine-3-carboxylic acid using thionyl chloride. This appears to be an exception to the rule that the reactions of a 2-methyl and of a 4-methyl substituted pyridine are the same.

The alcoholysis of 3-cyano-4-methylpyridine was not successful. However, 4-methylpyridine-3-carboxylic acid was esterified directly with a methanol–sulfuric acid mixture to give the desired ester in 85% yield. Methyl 4-methylpyridine-3-carboxylate was converted into the corresponding amide in yields of 78% by shaking with concentrated ammonia. This compound should be interesting physiologically as a result of its close structural similarity to pyridine-3-carboxamide (nicotinamide).[9]

We attempted unsuccessfully to prepare 3-acetyl-4-methylpyridine catalytically in a hot tube.[10] Several attempts in this Laboratory[11] to acylate 4-methylpyridine using boron trifluoride and acetyl chloride also have been unsuccessful. We were successful in introducing the acetyl group indirectly by ester condensation. This conversion of the ester group into an acetyl group has been carried out previously on both ethyl pyridine-3-carboxylate and ethyl 4-methylpyridine-3-carboxylate.[12a,12b] The methyl ester was used here.

Using a platinum catalyst in neutral solution 3-acetylpyridine,[12b] 3-acetyl-2-methylpyridine[13] and 3-acetyl-2,6-dimethylpyridine[13] have been reduced to the corresponding hydroxyethyl compounds. The yield of the alcohol was good in each case. We have reduced 3-acetyl-4-methylpyridine in neutral solution using Adams catalyst to racemic 1-(4′-methyl-3′-pyridyl)-ethanol in 85% yield. For dehydration to the vinyl compound several methods are available.[3,12a,14]

On two previous occasions chloral and 4-methylpyridine have been condensed in the presence of anhydrous zinc chloride.[15] The yields of 1,1,1-tri-chloro-3-(4′-pyridyl)-2-propanol were 8–9% and 16–18%. We have obtained yields of 40–43% (after one recrystallization). This increase in yield over those previously reported probably is accounted for by the purity of the 4-methylpyridine used in this work.

One of us (J. L. W.) wishes to express his thanks for a grant-in-aid from the Hynson, Westcott and Dunning Fund and for Fellowships for graduate study sponsored by E. I. du Pont de Nemours and Company and the American Can Company.

Experimental

All melting points are corrected.

Sulfonation of 4-Methylpyridine.—This reaction was carried out with 20% fuming sulfuric acid at 225–235° in an all-glass reaction vessel. The following apparatus was found to be satisfactory: a 3-liter balloon flask was fitted with two necks, one for a 360° thermometer and one for a glass stirrer which had as a bearing a snugly fitting piece of glass tubing. The original neck of the flask was sealed off; filling and emptying were accomplished through the stirrer or thermometer neck.

To this reaction vessel were added 6 g. of basic mercuric sulfate catalyst[16] and 1560 g. of 20% fuming sulfuric acid (commercial grade). Two hundred ninety-four grams (3 moles) of 95% 4-methylpyridine was added dropwise through the thermometer neck. The temperature was then raised to 225–235° and maintained for five hours. Vigorous stirring was necessary to prevent settling of the catalyst.

The reaction vessel was removed from the sand-bath and allowed to cool to room temperature. The crude sodium 4-methylpyridine-3-sulfonate was isolated in the usual manner and dried at 100°; average yield 334 g. (57%).

Pyridine was sulfonated under conditions identical with those described above. The yield of the crude sodium pyridine-3-sulfonate was 55%.

3-Cyano-4-methylpyridine.—To obtain rapid heating, a direct flame was preferred to a bath. However, glass was found to be unsatisfactory under these conditions. A suitable reactor with side arm was constructed from iron pipe. To lower the temperature of fusion, anhydrous sodium or potassium acetate and a mixture of sodium and potassium cyanides were used. Ten grams of anhydrous sodium acetate was placed on the bottom of the vessel to form a layer. A thorough mixture of 50 g. of crude sodium 4-methylpyridine-3-sulfonate, 100 g. of finely divided sodium cyanide, 20 g. of finely divided potassium cyanide and 10 g. of anhydrous sodium acetate was added, leaving the layer of sodium acetate intact. While cooling the receiver (a 125-cc. filter flask) with ice the vessel was heated as evenly as possible with the full force of two bunsen burners. Fusion of the mixture was accompanied by the distillation of 3-cyano-4-methylpyridine and a small amount of 4-methylpyridine and water.

The distillate was extracted immediately with ether and the solution was gently boiled with Norit A and filtered. After removal of the ether the remaining 3-cyano-4-methylpyridine was distilled under reduced pressure. This colorless crystalline nitrile had a characteristic odor. It was kept satisfactorily in an ice-box. The yield varied

(8) Baumgarten and Dornow, *Ber.*, **73**, 44 (1940).

(9) Dornow, *ibid.*, **73**, 78–80 (1940).

(10) Herbst and Manske, "Organic Syntheses," Vol. XVI, 47 (1936).

(11) These experiments were carried out by Mr. Marcus A. Naylor.

(12) (a) Strong and McElvain, THIS JOURNAL, **55**, 817 (1933); ref. 12; Iddles, Lang and Gregg, *ibid.*, **59**, 1945 (1937); Hurd and Webb, *ibid.*, **49**, 551 (1927). (b) Rabe and Jantzen, *Ber.*, **54**, 925 (1921).

(13) Baumgarten and Dornow, *ibid.*, **73**, 353 (1940); Dornow and Machens, *ibid.*, **73**, 355 (1940).

(14) Merchant and Marvel, THIS JOURNAL, **50**, 1197 (1928); Prelog, *et al.*, *Ber.*, **74**, 647 (1941).

(15) Rabe and Kindler, *ibid.*, **52**, 1847 (1919); Alberts and Bachmann, THIS JOURNAL, **57**, 1284 (1935).

(16) Varet, *Ann. chim. phys.*, [7] **8**, 111 (1896).

between 8 and 10 g. (26–33%, based on the crude sodium 4-methylpyridine-3-sulfonate), b. p. 64° (1–2 mm.). M. p. of the picrate (from an alcoholic solution) was 184.5–185.5°. The hydrochloride (from ether–alcohol mixture) sublimes unchanged at 208–209°.

Anal. Calcd. for $C_{13}H_9N_5O_7$: C, 44.96; H, 2.61. Found: C, 45.03; H, 2.53.

The use of vacuum, nitrogen or steam to remove the nitrile or of copper powder in the reaction mixture did not alter the yield.

4-Methylpyridine-3-carboxylic Acid (Homonicotinic Acid).—Alkaline hydrolysis: Five grams of 3-cyano-4-methylpyridine was refluxed with 50 cc. of 70% ethyl alcohol and 4 g. of sodium hydroxide. The colorless nitrile turned dark almost immediately and refluxing was continued until ammonia was no longer evolved. The reaction mixture was cooled in an ice-bath and neutralized with hydrochloric acid to congo red paper. A floc appeared which was filtered and dried in a desiccator; yield 4.5 g. The substance did not melt and was not satisfactorily recrystallized. **Acid alcoholysis:** To 10 g. of 3-cyano-4-methylpyridine in 10 cc. of absolute ethyl alcohol was added a mixture of 15 cc. of absolute ethyl alcohol and 20 g. of concentrated sulfuric acid. The mixture was then refluxed for seven hours and worked up in the usual manner. The yield of unreacted 3-cyano-4-methylpyridine was 7 g. (70%). None of the desired ester was obtained.

Acid hydrolysis: To 250 cc. of 75% sulfuric acid 24.4 g. of 3-cyano-4-methylpyridine was added with cooling. The solution was stirred and heated to 140° for six and one-half hours. After cooling the mixture was worked up in the usual manner using calcium hydroxide for the neutralization. The 4-methylpyridine-3-carboxylic acid was recrystallized from ethyl alcohol or ethyl acetate; yield 22 g. (77.7%), m. p. 215–216°.[5]

Reaction of 4-Methylpyridine-3-carboxylic Acid with Thionyl Chloride.—A mixture of 1.0 g. of 4-methylpyridine-3-carboxylic acid and 5.0 g. of thionyl chloride was refluxed for twenty minutes and the excess thionyl chloride was then removed under reduced pressure and the residue, protected under absolute ether, was reacted with ice-cold concentrated ammonia solution. A greenish crystalline material (0.6 g.) was obtained which after recrystallization from benzene was colorless and melted at 163–164°. In addition to carbon, hydrogen and nitrogen, chlorine and sulfur were found to be present. The compound was soluble in acid but insoluble in base. No structure has been assigned to the compound.

Anal. Found: C, 38.28, 38.11, 38.04, 38.81, 38.40; H, 1.25, 1.56, 1.39, 1.28, 1.49.

Esterification of 4-Methylpyridine-3-carboxylic Acid.—This reaction was carried out in the usual manner employing the following quantities: 13.7 g. of 4-methylpyridine-3-carboxylic acid, 25 cc. of absolute methyl alcohol and 13 cc. of concentrated sulfuric acid. The yield of the water-white methyl 4-methylpyridine-3-carboxylate was 12.8 g. (85%), b. p. 57–58° (1–2 mm.). The m. p. of the picrate (from an alcoholic solution) was 148–149°. The hydrochloride (from methyl alcohol–ether mixture) melted at 145–145.5°.

Anal. Calcd. for $C_{14}H_{12}N_4O_9$: C, 44.22; H, 3.18. Found: C, 44.31; H, 3.15.

4-Methylpyridine-3-carboxamide.—This compound was prepared in the usual manner from methyl 4-methylpyridine-3-carboxylate by treatment with ammonia. Three grams of the ester yielded 21 g. (78%) of the 4-methylpyridine-3-carboxamide, m. p. 146.5–147°.

Anal. Calcd. for $C_7H_8ON_2$: C, 61.75; H, 5.92. Found: C, 61.56; H, 5.82.

Ester Condensation.—The condensation of methyl 4-methylpyridine-3-carboxylate with ethyl acetate was carried out under conditions similar to those described by Rabe and Jantzen[12b] using the following quantities: 12.4 g. of methyl 4-methylpyridine-3-carboxylate, 13.6 g. of absolute ethyl acetate and 40 cc. of concentrated hydrochloric acid. The yield of the 3-acetyl-4-methylpyridine varied between 40–50%, b. p. 57–58° (1–2 mm.). The picrate, prepared from an alcoholic solution, melted at 146–147°. The yield of unreacted methyl 4-methylpyridine-3-carboxylate was 3.1 g. (25%), b. p. 57–58° (1–2 mm.).

Hot Tube Reaction of 4-Methylpyridine-3-carboxylic Acid.—In an apparatus similar to that described for the preparation of methyl benzyl ketone[10] the following reaction was run: Thirteen and one-half grams (0.1 mole) of 4-methylpyridine-3-carboxylic acid kept in solution in 60 g. (1.0 mole) of acetic acid and 5 cc. of water by means of an infra-red lamp was dripped into the catalyst tube containing ThO_2 (on pumice) at 550° at the rate of 20 drops/min. A stream of purified nitrogen was swept through the tube at the rate of 3 bubbles/sec. Much tar was formed, but a small amount of distillate was collected. Finally, 4-methylpyridine-3-carboxylic acid which had sublimed back out of the tube along with the tar formed plugged the catalyst chamber, thus stopping the reaction.

The reaction products were neutralized and extracted with ether. The extract was dried over anhydrous potassium carbonate and distilled. Two fractions were obtained: Fraction I, 1.0 g., b. p. 38–40° (1–2 mm.); Fraction II, 1.7 g., b. p. 73–75° (1–2 mm.). By mixed melting points of the picrates, fraction I was shown to be 4-methylpyridine resulting from decarboxylation of the carboxylic acid. Fraction II gave an unmistakable ketone test with 2,4-dinitrophenylhydrazine and formed a picrate which melted at 162.5–163.5° but depressed the melting point of the picrate of a known sample of 3-acetyl-4-methylpyridine. Fraction II was not further identified.

Reduction of 3-Acetyl-4-methylpyridine.—In a Parr hydrogenator 11.3 g. of 3-acetyl-4-methylpyridine in 75 cc. of distilled water was reduced at 40 lb./sq. in. hydrogen pressure using 0.4 g. of Adams catalyst. The yield of racemic 1-(4′-methyl-3′-pyridyl)-ethanol was 10 g. (85.5%), b. p. 108–110° (1–2 mm.); m. p. of the picrate (from ethyl alcohol) was 133–134°; the hydrochloride (from ethyl alcohol–ether mixture) melted at 148–149°.

Anal. Calcd. for $C_8H_{12}ONCl$: C, 55.33; H, 6.97. Found: C, 55.22; H, 7.13.

Condensation of 4-Methylpyridine with Chloral.—This reaction was carried out in a manner very similar to that employed by Rabe[4] and Alberts and Bachmann[15] with only slight modification and using the following quantities: 175 g. (1.88 moles) of 4-methylpyridine, 276.7 g. (1.88 moles) of freshly prepared chloral and 12 g. of fused zinc chloride. The yield of 1,1,1-trichloro-3-(4′-pyridyl)-2-propanol after recrystallization from ethyl alcohol was 111 g. (42%), m. p. 162–163.5°. By recrystallization from ethyl acetate the m. p. could be raised to 168°.

Catalytic Reduction of 3-(4′-Pyridyl)-acrylic Acid.—The 3-(4′-pyridyl)-acrylic acid prepared from 1,1,1-trichloro-3-(4′-pyridyl)-2-propanol according to Rabe[4,12b] was purified by taking up in ammonia and boiling with Norit A, filtering and reprecipitating with acetic acid. Using 9.3 g. of the acrylic acid dissolved in 75 cc. of distilled water as the ammonium salt, 5 g. of Raney nickel and 610 lb./sq. in. hydrogen pressure the reduction was carried out at 190° for four hours. The reduced material was isolated by evaporation of the solvent and esterified in 100 cc. of absolute ethyl alcohol with dry hydrogen chloride gas. The yield of the racemic ethyl 3-(4′-piperidyl)-propionate was 5.7 g. (49.6% based on the acrylic acid), b. p. 76–80° (1–2 mm.). The chloroplatinate melted sharply at 186° with decomposition. Rabe[4,12b] reported 190° (dec.).

Summary

1. Several new 3,4-disubstituted pyridines, with their derivatives, are reported.

2. The yield of 4-methylpyridine-3-sulfonic acid resulting from the sulfonation of 4-methylpyridine has been improved.

3. An anomalous reaction between 4-methylpyridine-3-carboxylic acid (homonico-

tinic acid) and thionyl chloride is described.

4. The yield of 1,1,1-trichloro-3-(4'-pyridyl)-2-propanol resulting from the condensation of 4-methylpyridine with chloral has been raised from 18 to 42%.

BALTIMORE, MARYLAND RECEIVED APRIL 18, 1944

[CONTRIBUTION FROM THE DIVISION OF MEDICINAL CHEMISTRY, THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

Homosulfanilamides[1]

BY FRANK H. BERGEIM AND WILLIAM BRAKER

In 1940 several homosulfanilamides were reported by Miller, Sprague, Kissinger and McBurney[2] as having no significant protective action against experimental streptococcal infections in mice. Similar results had been obtained with 4-homosulfanilamide in this Institute. Later Klarer[3] reported that 4-homosulfanilamide was effective in the treatment of experimental gas gangrene in mice. It appeared desirable to retest some of the homosulfanilamides which we had previously prepared and also to prepare some additional heterocyclic homosulfanilamides for such evaluation. The compounds which we prepared are listed in Table I. They were tested for activity in experimental gas gangrene by the Division of Microbiology and the Division of Pharmacology of this Institute.[4]

TABLE I

HOMOSULFANILAMIDES

Name	M. p., °C.	Empirical formula	Nitrogen, % Calcd.	Found
4-Homosulfanilamide hydrochloride	256[a]	$C_7H_{11}N_2O_2SCl$	12.58	12.28
N^1-Methyl-4-homosulfanilamide hydrochloride	245–247	$C_8H_{13}N_2O_2SCl$	11.83	11.88[b]
2-(4-Homosulfanilamido)-thiazole hydrochloride	276–277	$C_{10}H_{12}N_3O_2S_2Cl$	13.73	13.72[c]
2-(4-Homosulfanilamido)-4,6-dimethylpyrimidine	231–232	$C_{13}H_{16}N_4O_2S$	19.17	18.61[d]
2-(N^4-Acetyl-4-homosulfanilamido)-thiazole	169–170	$C_{12}H_{13}N_3O_3S_2$	13.50	13.28
2-(N^4-Phthaloyl-4-homosulfanilamido)-4,6-dimethylpyrimidine	233–235	$C_{21}H_{18}N_4O_4S$	13.26	13.07
2-(N^4-Phthaloyl-4-homosulfanilamido)-thiazole	207–208	$C_{18}H_{13}N_3O_4S_2$	10.52	10.32
N^4-Sulfanilamido-4-homosulfanilamide	199–201	$C_{18}H_{15}N_5O_4S_2$	12.28	12.37[e]
N^4-(N^4-Acetylsulfanilamido)-4-homosulfanilamide	199–201	$C_{16}H_{17}N_5O_5S_2$	10.96	10.75
N^4-Succinyl-4-homosulfanilamide	147–149	$C_{11}H_{14}N_2O_5S$	9.79	9.96[f]
1-Homosulfanilamide	170[g]	$C_7H_{10}N_2O_2S$		

[a] Reported by Miller, *et al.*, prepared by a different procedure, to have melting point 248–249° (THIS JOURNAL, **62**, 2099 (1940)). [b] Calcd.: Cl, 15.00. Found: Cl, 15.27. [c] Calcd.: S, 20.98. Found: S, 20.43. [d] Calcd.: S, 10.97. Found: S, 10.52. [e] Calcd.: S, 18.76. Found: S, 18.71. [f] Calcd.: S, 11.18. Found: S, 11.15. [g] Prepared in 92% yield by the catalytic reduction procedure of Miller, *et al.*, THIS JOURNAL, **62**, 2099 (1940). Calcd.: S, 17.27. Found: S, 17.36.

Of the compounds tested 4-homosulfanilamide and N^1-methyl-4-homosulfanilamide were the most effective in local treatment of experimental gas gangrene in mice.

For the preparation of 4-homosulfanilamide we found it more convenient if, instead of catalytically reducing *p*-cyanobenzenesulfonamide (Miller, *et al.*[2]), we chlorosulfonated N-acetylbenzylamine, treated the resultant crystalline sulfonyl chloride with ammonia, and finally hydrolyzed the acetyl compound with aqueous alcoholic hydrochloric acid. The hydrochloride salt obtained melted at 256°. Miller, *et al.*, reported a melting point at 248–249°. They mention having chlorosulfonated N-acetylbenzylamine, but did not identify the sulfonyl chloride nor report the hydrolysis of N^4-acetyl-4-homosulfanilamide.

The N^1-heterocyclic homosulfanilamides are not as readily prepared as the corresponding heterocyclic sulfanilamides by the general procedure of treating the required acetamidosulfonyl chloride with an amino heterocycle, followed by hydrolysis. In the preparation of 2-(4-homosulfanilamido) - 4,6 - dimethylpyrimidine, improved yields were obtained by chlorosulfonating α-phthalimidotoluene instead of α-acetamidotoluene.

Experimental Part[5]

N-Acetyl-4-homosulfanilyl Chloride.—Ten grams of acetylbenzylamine was added to 30 cc. of chlorosulfonic acid while maintaining the temperature below 15°. The temperature was then raised to 50–60° and held at this point

(1) The nomenclature used in this paper conforms in general to that accepted for sulfanilamides. Structure (I) $NH_2C_6H_4SO_2NH_2$ has been designated 4-homosulfanilamide and structure (II) $NH_2C_6H_4CH_2SO_2NH_2$ 1-homosulfanilamide. The nitrogen of the sulfonamido group is N^1 and that in the group para to the sulfonamido group is N^4.

(2) E. Miller, J. M. Sprague, L. W. Kissinger and L. F. McBurney, THIS JOURNAL, **62**, 2099 (1940).

(3) J. Klarer, *Klin. Wochschr.*, **20**, 1250 (1941); *cf.* Klarer, U. S. Patent 2,288,531 (1942).

(4) Dorothy M. Hamre, H. A. Walker, Wolcott B. Dunham, H. B. van Dyke and Geoffrey Rake, *Proc. Soc. Exp. Biol. Med.*, **55**, 170–173 (1944).

(5) All melting points are uncorrected.