(0.025 mole) of XIII in 40 ml. of absolute alcohol and 117 ml. of dry benzene were added 76.5 ml. of 0.324 molar absolute alcoholic potassium ethoxide solution and 9.9 ml. of 100% hydrazine hydrate. The flask was then fitted with a Soxhlet extractor containing a thimble nearly filled with 35 g. of Drierite, and the reflux condenser was capped by a calcium chloride tube. After the solution had been refluxed vigorously for sixteen hours on the steam-bath, solvent and excess hydrazine were distilled below 55° under reduced pressure. The residue was dissolved in 75 ml. of warm water, cooled in an ice-bath, covered with 200 ml. of ether, treated with 4 ml. of 6 *N* hydrochloric acid and then acidified with 10% acetic acid solution until no more precipitate formed. Cooling and stirring soon caused the oil to crystallize. The white product was collected by suction, washed with ether followed by ice water and desiccated to yield 8.12 g. (91%) of the hydrazide, m. p. 140–141°. Recrystallization of a sample from water (Darco) failed to alter the m. p. of the fine needles.

Anal. Calcd. for $C_{17}H_{19}O_4N_3S$: C, 56.49; H, 5.30. Found: C, 56.40; H, 5.57.

Owing to partial hydrolysis of the alkali salt caused by the water liberated when the hydrazine hydrate reacted with the ester, the yields of the hydrazide were below 55% before the expedient of introducing the desiccant was adopted for the vapor-phase removal of the water.

3-Benzoylamino-2-δ-carboxybutyl-4-thiophenecarboxylic Acid Azide (XV).—After 10.68 g. (0.029 mole) of XIV had been dissolved in 85 ml. of glacial acetic acid by the application of heat, the well-stirred solution was cooled in an ice-bath and treated with 3.42 ml. of concentrated hydrochloric acid. To the suspension of the hydrochloride thus formed was added dropwise during 0.8 hour a cold solution of 2.23 g. (0.032 mole) of sodium nitrite in 55 ml. of water. Throughout the reaction the internal temperature was maintained at 0°. When addition was completed the mixture was stirred for a further 0.7 hour and then 250 ml. of ice water was added via dropping funnel during 0.5 hour. The cold, white solid was collected on a filter, washed thoroughly with ice water and desiccated *in vacuo*. The chalk-like azide, which decomposed at 99–100°, weighed 10.2 g. (93% yield). A small sample exploded when heated over a flame. It slowly developed a pink color on standing.

Anal. Calcd. for $C_{17}H_{15}O_4N_4S$: C, 54.83; H, 4.33. Found: C, 55.11; H, 4.53.

3-Benzoylamino-4-carbethoxyamino-2-thiophene-δ-valeric Acid (XVI).—A solution of 10.2 g. (0.027 mole) of XV in 750 ml. of absolute alcohol was protected by a calcium chloride tube and heated gradually to boiling during 1.7 hours. This yellow solution was then refluxed on the steam-bath for seventeen hours. Alcohol was distilled until crystals had begun to form. Dilution with hot water followed by stirring and cooling caused the product to crystallize as a very pale-pink solid. After desiccation the urethan, m. p. 155.5–157°, weighed 10.2 g. (95% yield). Recrystallization of a sample from dilute alcohol (Darco) produced colorless micro-needles, m. p. 158–159°. Recrystallization did not raise the melting point.

Anal. Calcd. for $C_{19}H_{22}O_5N_2S$: C, 58.44; H, 5.68; N, 7.18. Found: C, 58.80; H, 5.92; N, 7.07.

2'-Keto-3,4-imidazolido-2-thiophenevaleric Acid (2,3,4,5-Tetradehydrobiotin) (XVIII).—A mixture of 1.92 g. (0.0049 mole) of XVI, 24 g. of C. P. potassium hydroxide and 84 ml. of reagent methanol was refluxed on the steam-bath for twelve hours in purified nitrogen. The heating was continued for another hour while steam was passed through the jacket of the condenser for the complete removal of the methanol under reduced pressure. The flask, with the white residue, was then cooled in an ice-salt-bath and 175 ml. of freshly boiled water cooled to 5° was added through the condenser. The atmosphere of nitrogen was maintained throughout this and the subsequent operation. Phosgene was bubbled through the solution with shaking for 0.9 hour, until the brown solution had become colorless and acid to congo red. The resulting gummy precipitate was dissolved in 5% potassium hydroxide solution, boiled with Darco and reprecipitated. The light-brown solid was dried, pulverized and extracted twice with ether; yield, 0.682 g. (58%); m. p. 248–250°. Recrystallizations, with decolorization, first from dilute alcohol and then from a large volume of water, produced colorless needles, m. p. 254–255° (dec.).

Anal. Calcd. for $C_{10}H_{12}O_3N_2S$: C, 49.98; H, 5.03. Found: C, 50.33; H, 5.25.

"Aromatic biotin" is practically insoluble in water, ether, chloroform, benzene, ethyl acetate, acetone and ligroin; it is soluble in alcohol, methanol, acetic acid and sodium bicarbonate solution. Although stable toward dilute alkali, the compound is transformed into an amorphous red-brown powder by strong mineral acids.

Acknowledgments.—The authors wish to thank Mr. A. W. Spang for the microanalyses, Dr. J. M. Vandenbelt for the determination and preparation of the ultraviolet absorption curves, and Dr. O. D. Bird for the microbiological assays.

Summary

The total synthesis of 2,3,4,5-tetradehydrobiotin is described.

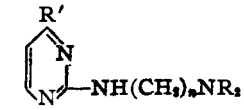
DETROIT, MICHIGAN RECEIVED JANUARY 8, 1945

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Heterocyclic Basic Compounds. IV. 2-Aminoalkylamino-pyrimidines[1]

BY ROBERT R. ADAMS[2,3] AND FRANK C. WHITMORE

In previous publications[4] a number of basically-substituted pyridine, triazine and quinoline derivatives was described and as an extension of this work it seemed desirable to prepare some of the corresponding pyrimidine compounds. The compounds studied in this paper may be represented by the following general formula, where R is an alkyl group or is fused in an heterocyclic nucleus and R' is an hydrogen atom or a methoxy, morpholino or piperidino radical.



These compounds were prepared by the alkylation

(1) Presented before the Division of Organic Chemistry of The American Chemical Society, Pittsburgh, Pennsylvania, September 6, 1943.

(2) This paper is taken in part from the doctoral dissertation of Robert R. Adams, The Pennsylvania State College, February, 1944.

(3) Present address: Parke, Davis and Co., Detroit, Mich.

(4) (a) Whitmore, Mosher, Goldsmith and Rytina, THIS JOURNAL, 67, 393 (1945); (b) Mosher and Whitmore, *ibid.*, 67, 662 (1945); (c) Yanko, Mosher and Whitmore, *ibid.*, 67, 664 (1945).

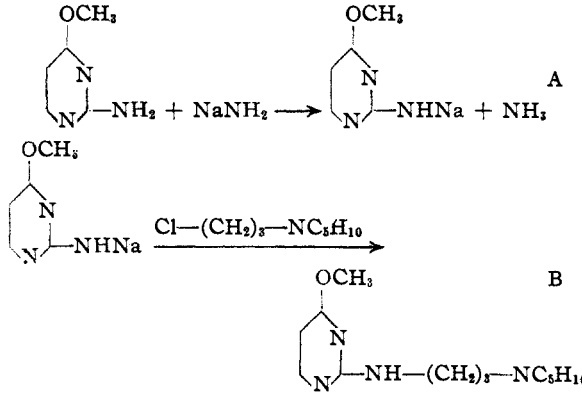
TABLE I

BASICALLY-SUBSTITUTED ALKYL CHLORIDES

Compound	B. p., °C. 25 mm.	Yield, %	Ref.	M. p., °C. Picrate	M. p., °C. Hydrochloride	Formula	Analyses, % Element	Calcd.	Found
$ClCH_2CH_2CH_2NEt_2$	70–75	52	10	171–172	85–86	$C_7H_{16}NCl\cdot HCl$	Cl	19.09	19.27
$ClCH_2CH_2CH_2N(n\text{-}Pr)_2$	97–105	75	..	119–120	84–87	$C_9H_{20}NCl\cdot HCl$	Cl	16.59	16.80
$ClCH_2CH_2CH_2N(n\text{-}Bu)_2$	118–130	68	10	108–110	.....	$C_{11}H_{24}NCl\cdot C_6H_3O_7N_3$	N	12.88	12.95[a]
$ClCH_2CH_2CH_2NC_5H_{10}$[b]	95–103	78	10	107–109	208–209	$C_8H_{16}NCl\cdot HCl$	Cl	17.96	17.91
$ClCH_2CH_2CH_2NC_4H_8O$[c]	110–115	87	..	130–132	168–170	$C_7H_{10}ONCl\cdot HCl$	Cl	17.84	17.75

[a] Analysis of picrate. [b] $-NC_5H_{10}$ represents the piperidino group (1-piperidyl radical). [c] $-NC_4H_8O$ represents the morpholino group (4-morpholinyl radical).

of the sodium salt of 2-amino-pyrimidine, or one of its derivatives, with a basically-substituted alkyl halide. The following is a typical example.



The starting materials for this work were 2-aminopyrimidine[5] and 2-amino-4-chloropyrimidine.[5] The 2-amino-4-chloropyrimidine was readily converted into 2-amino-4-methoxypyrimidine by sodium methoxide, into 2-amino-4-morpholinopyrimidine[6] by treatment with morpholine and into 2-amino-4-piperidinopyrimidine by treatment with piperidine. Although the preparation of 2-amino-4-methoxypyrimidine is mentioned in the literature,[7] no experimental details are given. We prepared this compound in 80 to 87% yields by the treatment of 2-amino-4-chloropyrimidine with commercial sodium methoxide in boiling methanol.

The basically-substituted alkyl halides used in these alkylations were prepared by two general methods: first, by conversion of the corresponding basically-substituted alcohol to the bromide by the action of hydrobromic acid according to the method of Amundsen and Kranz[8] or to the chloride by the action of thionyl chloride[9]; and secondly, by the reaction of two moles of a secondary amine with trimethylene chlorobromide using a modification of the method of Marxer[10] to give the desired basically-substituted alkyl chlorides. β-Dimethylaminoethyl chloride, β-diethylaminoethyl chloride and β-di-*n*-butylaminoethyl bromide were prepared by the first method while γ-diethylamino-, γ-di-*n*-propylamino-, γ-di-*n*-butylamino-, γ-piperidino- and γ-morpholino-propyl chlorides were prepared by the second method. Table I shows the physical properties of some of these compounds and their derivatives.

The reaction of example A was carried out by first refluxing equal molar quantities of 2-amino-4-methoxypyrimidine with sodamide in dry toluene and, after the evolution of ammonia had ceased, adding the basically-substituted alkyl halide and refluxing for twelve to twenty-four hours. In later work it was found that the sodium salts of 2-aminopyrimidine and 2-amino-4-methoxypyrimidine could be isolated, stored and used in subsequent experiments.

The sodium salt of 2-aminopyrimidine does not react satisfactorily with ethylene chlorohydrin, γ-chlorobutyronitrile, trimethylene chlorobromide, trimethylene bromide or trimethylene chlorohydrin.

We wish to thank Parke, Davis and Company for the grant which made this work possible and Dr. Harry S. Mosher for his interest and help in the work.

Experimental

γ-Morpholinopropyl Chloride.—A solution of 300 g. (3.53 moles) of morpholine (Carbide and Carbon Chemical Corp.) and 360 g. (2.29 moles) of trimethylene chlorobromide (Dow Chemical Company) in 900 ml. of dry benzene was allowed to stand at room temperature for one hour with occasional shaking. The temperature of the reaction mixture was raised until refluxing began and then the heat was removed, after which the mixture refluxed for about one-half hour. Heat was again applied and the mixture was refluxed for three hours, cooled, and the morpholine hydrobromide, 268 g., removed by filtration and washed with anhydrous ether. The filtrate was extracted with 3 *N* hydrochloric acid, the benzene layer was discarded and the combined aqueous extracts were made strongly alkaline with 10 *N* sodium hydroxide solution. The oil layer was separated and the aqueous solution extracted with ether. The combined ether extracts and oil layer were dried over potassium carbonate and the residue, after removal of the ether, was distilled from a modified Claisen flask to give 206.8 g. (73.7%), boiling at 113–115° at 25 mm. pressure.

2-Amino-4-methoxypyrimidine.—To a solution of 86 g. (1.59 moles) of commercial sodium methoxide in 900 ml. of methanol, 100 g. (0.775 mole) of 2-amino-4-chloropyrimidine was added in four portions over a period of one hour. After spontaneous refluxing had ceased, the mixture was refluxed an additional one and one-half hours. The solvent was distilled, the last traces being removed under

(5) Furnished by the Calco Chemical Division, American Cyanamid Co.

(6) Banks, THIS JOURNAL, **66**, 1131 (1944).

(7) Hilbert and Johnson, THIS JOURNAL, **52**, 1154 (1930).

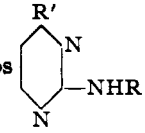
(8) Amundsen and Kranz, *ibid.*, **68**, 305 (1941).

(9) Slotta and Behnisch, *Ber.*, **68**, 758 (1935).

(10) Marxer, *Helv. Chim. Acta*, **24**, 209–225E (1941).

TABLE II

BASICALLY-SUBSTITUTED PYRIMIDINE COMPOUNDS



R	R′	B. p., °C., 3 mm.	M. p., °C.	Yield, %	M. p., °C. Picrate	Di·HCl salt	Formula	Analyses, % Element	Calcd.	Found
—$CH_2CH_2NMe_2$	H	90–95	..	29.4	195–197	220–221	$C_8H_{14}N_4 \cdot 2HCl$	Cl	29.71	29.58
—$CH_2CH_2NEt_2$	H	107–110	..	63.5	157	148–150	$C_{10}H_{18}N_4 \cdot 2HCl$	Cl	26.59	26.42
—$CH_2CH_2N(n\text{-}Bu)_2$	H	150–153[a]	..	61.0[b]	143–144	141–143	$C_{14}H_{26}N_4 \cdot 2HCl$	Cl	22.02	22.10
—$CH_2CH_2CH_2NEt_2$	H	115–116	..	62.0	167.5	150–151	$C_{11}H_{20}N_4 \cdot 2HCl$	Cl	25.23	25.20
—$CH_2CH_2CH_2N(n\text{-}Pr)_2$	H	125–126	..	57.0	144–148	110–112	$C_{13}H_{24}N_4 \cdot 2HCl$	Cl	22.98	22.88
—$CH_2CH_2CH_2N(n\text{-}Bu)_2$	H	135–136	..	75.6	149–150.5	99–100	$C_{16}H_{28}N_4 \cdot 2HCl$	Cl	21.10	21.08
—$CH_2CH_2CH_2NC_5H_{10}$[e]	H	130–134	57.9	51.6	180	175–177	$C_{12}H_{20}ON_4 \cdot 2HCl$	Cl	24.19	24.22
—$CH_2CH_2CH_2NC_4H_8O$[f]	H	133–138	..	27.4	181–182	205–207	$C_{11}H_{18}ON_4 \cdot 2HCl$	Cl	24.04	24.09
—$CH_2CH_2NEt_2$	—OCH_3	118–127	..	36.8[c]	189–192	129–131	$C_{11}H_{20}ON_4 \cdot 2HCl$	Cl	23.89	23.86
—$CH_2CH_2N(n\text{-}Bu)_2$	—OCH_3	156–160	..	27.7	165–167	61–64	$C_{15}H_{28}ON_4 \cdot 2HCl$	Cl	20.11	19.97
—$CH_2CH_2CH_2NEt_2$	—OCH_3	130–133	..	35.1	148–149.5	119–121	$C_{12}H_{22}ON_4 \cdot 2HCl$	Cl	22.83	22.83
—$CH_2CH_2CH_2NC_5H_{10}$[e]	—OCH_3	160–163	Oily solid	29.1[c]	200	.....	$C_{13}H_{22}ON_4$	N	22.37	22.31
—$CH_2CH_2CH_2NC_4H_8O$[f]	—OCH_3	161–162	60–62	38.5[c]	216–217	.....	$C_{12}H_{20}O_2N_4$	N	22.20	22.40
—$CH_2CH_2CH_2NC_4H_8O$[f]	—NC_4H_8O	275–280[d]	79–82	54.6	205.5–206.5	.....	$C_{15}H_{24}O_2N_8$	N	22.77	22.66
—$CH_2CH_2CH_2NC_4H_8O$[f]	—NC_5H_{10}	250–275[d]	93–94	46.7	176–178	.....	$C_{16}H_{27}ON_8$	N	22.95	23.31

[a] B. p. at 5 mm. [b] Prepared from di·*n*-butylaminoethyl bromide. [c] Prepared from the sodium salt of 2-amino-4-methoxypyrimidine. [d] B. p. at 11 mm. [e] —NC_5H_{10} represents the piperidino group (1-piperidyl radical). [f] —NC_4H_8O represents the morpholino group (4-morpholinyl radical).

reduced pressure, and the residue was treated with 200 ml. of cold water. The crude product was removed by filtration, washed with two 50-ml. portions of cold water, dried and twice crystallized from toluene to yield 78.5 g., 81%, of the purified product, m. p. 119–120°.

2-Amino-4-piperidinopyrimidine and 2-Amino-4-morpholinopyrimidine.—A total of 10 g. (0.0775 mole) of 2-amino-4-chloropyrimidine was added to 19.8 g. (0.233 mole) of piperidine in the following manner. Approximately 4 g. was added, the mixture stirred for five minutes and then warmed carefully until the vigorous reaction started; the mixture was cooled slightly and the remaining 2-amino-4-chloropyrimidine added in small portions with stirring at such a rate that the mixture just remained liquid and boiling. After the addition was complete, the reaction mixture was stirred until it crystallized, the crystalline mass was crushed as fine as possible and treated with 25 ml. of cold water. After digestion for one-half hour, the crystalline product was removed by filtration, washed with two 15-ml. portions of water and dried in the air, yield 12.9 g., 93.5%. The product was purified by recrystallization from toluene, m. p. 146–147°. The picrate was prepared in ethanol and after recrystallization melted at 200–201°.

Anal. Calcd. for $C_8H_{14}N_4$: N, 31.42. Found: N, 31.05.

In a similar manner 2-amino-4-morpholinopyrimidine[6] was prepared in 84.2% yield, m. p. 160–161°, picrate (from ethanol) m. p. 219–221°.

Anal. Calcd. for $C_8H_{12}ON_4$: N, 31.08. Found: N, 31.17.

Sodium Salt of 2-Aminopyrimidine and 2-Amino-4-methoxypyrimidine.—A mixture of 28.5 g. (0.3 mole) of 2-aminopyrimidine and 11.7 g. (0 3 mole) of sodamide in 150 ml. of dry toluene was refluxed for three hours. At the end of approximately one-half hour the vigorous evolution of ammonia had practically ceased and the reaction mixture was a white semisolid. The product was removed by filtration from the hot solution and washed with two 150-ml. portions of anhydrous ether. The last traces of ether were removed under reduced pressure in a vacuum desiccator. The product was a white, finely divided powder which apparently was not hygroscopic; yield 32.6 g. (93%).

The sodium salt of 2-amino-4-methoxypyrimidine was prepared in an analogous manner; yield 70–74%. No attempt was made to purify either of these intermediates further.

2-(γ-Piperidinopropylamino)-pyrimidine.—A mixture of 7.86 g. (0.083 mole) of 2-aminopyrimidine and 3.23 g. (0.083 mole) of sodamide in 50 ml. of dry toluene was stirred and heated for twelve hours in an oil-bath at 125°. During this time the white sodium salt of 2-aminopyrimidine separated from the reaction mixture. The mixture was cooled, 20 g. (0.124 mole) of freshly distilled γ-piperidinopropyl chloride added, the mixture heated at 125° for eighteen hours, cooled and placed in the refrigerator overnight. The solid, 5.1 g., was removed by filtration and washed with two 10-ml. portions of dry toluene. The residue was discarded and the filtrate extracted with four 50-ml. portions of 3 *N* hydrochloric acid. The combined aqueous extracts were extracted with two 50-ml. portions of ether to remove traces of toluene, warmed on the steam cone to expell the dissolved ether, cooled and made strongly alkaline with 10 *N* sodium hydroxide solution. The oil layer was diluted with 50 ml. of ether, separated, and the aqueous solution extracted with four 50-ml. portions of ether. The combined ether extracts were dried over potassium carbonate, the ether removed on the steam-bath and the residue distilled from a modified Claisen flask. The fraction boiling at 130–134° at 3 mm. was collected; yield 9.4 g., 51.6%. The product solidified on standing and after recrystallization from petroleum ether melted at 57–59°. The hydrochloride was prepared by bubbling dry hydrogen chloride into an anhydrous ether solution of the product. The ether was removed by decantation and the hydrochloride recrystallized from *n*-butanol–ethyl acetate–ether mixture, m. p. 175–177°. The picrate was prepared in ethanol and after recrystallization melted at 180°.

2-(γ-Morpholinopropylamino)-4-methoxypyrimidine.—A mixture of 15 g. (0.102 mole) of the sodium salt of 2-amino-4-methoxypyrimidine and 22 g. (0.135 mole) of freshly distilled γ-morpholinopropyl chloride in 100 ml. of dry toluene was heated at 125° in an oil-bath for eighteen hours. The mixture was cooled and the product isolated in the manner previously described; yield 9.9 g., 38.5%.

Summary

2-Aminopyrimidine and its 4-substituted derivatives react with sodamide to give a sodium salt which may be alkylated with basically-substituted alkyl halides. Fifteen basically-substituted pyrimidines have been prepared in this manner.

The sodium salt of 2-aminopyrimidine does not react satisfactorily with ethylene chlorohydrin, γ-chlorobutyronitrile, trimethylene chlorobromide, trimethylene bromide or trimethylene chlorohydrin.

STATE COLLEGE, PENNA. RECEIVED FEBRUARY 10, 1945

[CONTRIBUTION NO. 557 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Furan and Tetrahydrofuran Derivatives. III. The Synthesis of Certain 3,4-Diaminofuran Derivatives[1]

BY KLAUS HOFMANN AND ANNA BRIDGWATER

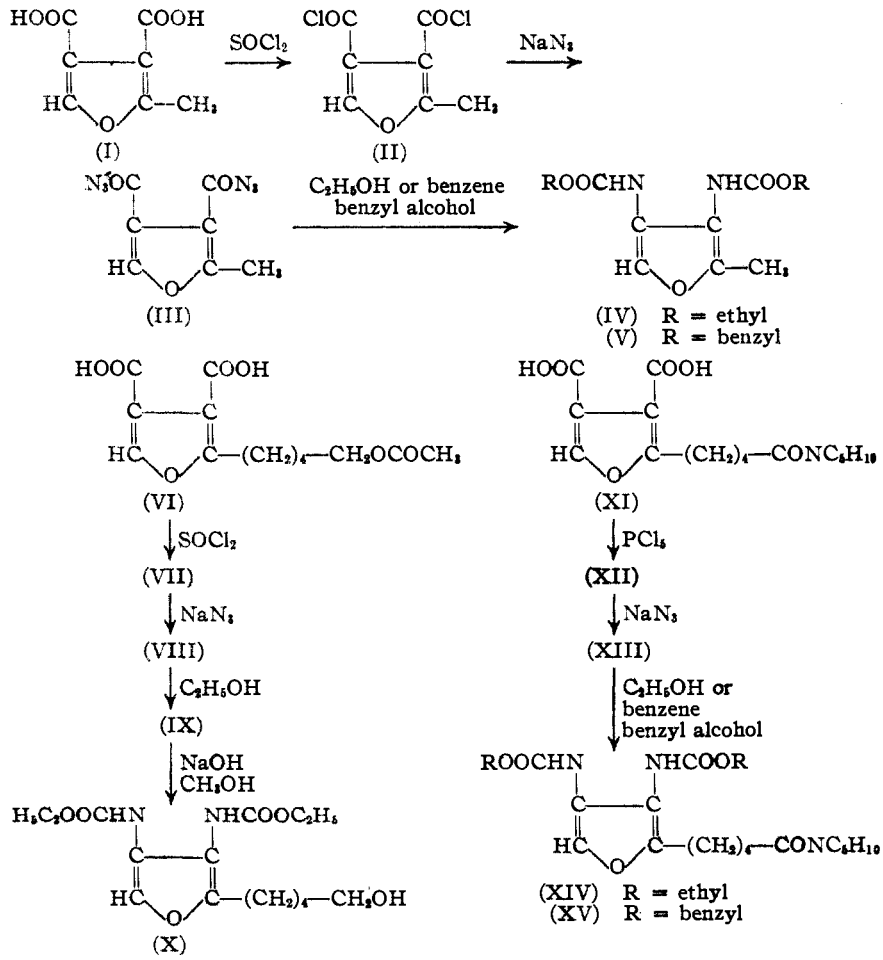
In recent communications[2,3] suitable procedures have been described for the preparation of a number of 3,4-dicarboxyfurans. These studies are being continued and the present report deals with the preparation of certain 3,4-diaminofuran derivatives which are needed for synthetic work on biotin analogs.

Aminofurans are very unstable unless they contain carboxy or nitro groups attached to the furan nucleus, and only two alkyl aminofurans have been described in the literature.[4]

For the present our attention has been focused on the preparation of urethans of 3,4-diaminofurans which should be stable, crystalline compounds. Blomquist and Stevenson[5] have synthesized a number of simple aminofuran derivatives by the Curtius degradation of the corresponding carboxylic acids, and this approach seemed applicable to the 3,4-dicarboxyfurans. The easily available 3,4-dicarboxy-2-methylfuran (I)[6] was chosen as a model compound for a study of the Curtius degradation of 3,4-dicarboxyfurans.

Many unsuccessful attempts were made to prepare the dihydrazide of 3,4-dicarboxy-2-methylfuran. Treatment of its dimethyl ester with hydrazine hydrate under a variety of experimental conditions did not afford the desired dihydrazide, and the standard Curtius method was therefore abandoned. A modification of the Curtius procedure, which involves treatment of acid chlorides with sodium azide and decomposition of the corresponding azides has been applied successfully to the preparation of a number of furyl isocyanates and urethans.[7]

This procedure seemed promising since 3,4-dicarboxyfurans are smoothly converted into their acid chlorides. Thus, 3,4-dicarboxy-2-methyl-



(1) The authors wish to express their appreciation to Ciba Pharmaceutical Products, Inc., and to The Buhl Foundation for their generous support of this work.

(2) Hofmann, THIS JOURNAL, **66**, 51 (1944).

(3) Hofmann, *ibid.*, **67**, 421 (1945).

(4) Stevenson and Johnson, *ibid.*, **59**, 2525 (1937).

(5) Blomquist and Stevenson, *ibid.*, **56**, 146 (1934).

(6) Alder and Rickert, *Ber.*, **70**, 1354 (1937).

(7) Singleton and Edwards, THIS JOURNAL, **60**, 540 (1938).