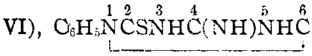
of ammonia and ethyl alcohol. From the reaction mass were isolated carbanilide and the triazine, which was very insoluble in boiling alcohol but dissolved in cold sodium hydroxide (10%).

α-Methyl-α,γ-dicarbethoxyguanidine (XXIV), $HNC(N(CH_3)COOC_2H_5)NHCOOC_2H_5$, was obtained from the potassium salt of dicarbethoxyguanidine and dimethyl sulfate in dry acetone on five hours of refluxing. Its structure was proved by the fact that it is different from the isomeric methylimino compound (IV).

Hydrolysis of Dicarbethoxyguanidine.—A boiling saturated alcoholic solution of potassium hydroxide was treated with an equivalent weight of dicarbethoxyguanidine and boiled for a few minutes. The solution was evaporated on the steam-bath, the residue made up to the original volume with water and evaporated twice, and finally dissolved in an equal volume of water and cooled. An almost quantitative yield of monocarbethoxyguanidine hydrate[15] was obtained. The hydrochloride melted at 128–130° and the picrate at 227°.

Phenyl Isocyanate and Carbethoxyguanidine. Carbethoxydicarboxanilidoguanidine (XXV), $(C_6H_5NHCONH)_2C(NCOOC_2H_5)$.—Carbethoxyguanidine was treated with an excess of phenyl isocyanate and the reaction completed on the steam-bath. A little carbanilide was formed but the main product was the above diurea.[16]

Phenyl Isothiocyanate and Carbethoxyguanidine. Hexahydro-1-phenyl-2-thio-4-imino-6-oxy-*s*-triazine (XXVI),



$C_6H_5\overset{1}{N}\overset{2}{C}S\overset{3}{N}H\overset{4}{C}(NH)\overset{5}{N}H\overset{6}{C}O$.—The mustard oil and guanidine were warmed in alcohol solution for eight hours or, with better yield, heated without a solvent at 115° for two hours. The triazine was difficultly soluble except in acids and strong bases.

It gave a **methyl thio ether** (XXVII) with dimethyl sulfate in dry acetone solution.

Summary

1-Methyl and 1-ethyl biuret have been formed from allophanic ester and carbonyldiurethan by the action of methyl and ethyl amines. Amines have been found to easily hydrolyze thioallophanic ester to thiourea.

Thiocarbonyldiurethan and its methyl ether have been found to give with amines alkyl and aryl dicarbethoxyguanidines. With hydroxylamine, hydrazine, *o*-phenylenediamine, and anthranilic acid, heterocyclic compounds have been synthesized.

From dicarbethoxyguanidine, monocarbethoxyguanidine and α-methyl-α,γ-dicarbethoxyguanidine, were obtained, while with aniline and with phenyl isocyanate triazines were formed.

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[15] Pinck and Blair, THIS JOURNAL, **49**, 509 (1927); Basterfield and Paynter, *ibid.*, **48**, 2177 (1926); Nencki, *Ber.*, **7**, 1588 (1874); *J. prakt. Chem.*, [2] **17**, 237 (1878).

[16] Johnson, *Am. Chem. J.*, **29**, 482; **30**, 172 (1903); Ref. 5, p. 2224.

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

The Preparation and Reactions of Some Furyl Isocyanates

BY A. T. BLOMQUIST[1] AND H. B. STEVENSON

A survey of the literature of the furan series affords relatively meager information regarding amines and their derivatives in which the nitrogen atom is directly attached to the furan nucleus. Only in those instances in which the furan nucleus has been substituted with negative groups, such as nitro, carboxyl and carbethoxyl, has it been possible to isolate aminofurans. Typical examples of amines which have been obtained in the furan series are 5-amino-2-furoic acid,[2] 3,4-diamino-5-nitro-2-furoic acid,[3] ethyl 5-amino-4-nitro-2-furoate[4] and ethyl 4-amino-5-acetamino-2-furoate.[5]

All attempts to isolate a simple amino derivative of furan, or of one of its homologs, have been unsuccessful. Marquis[2] attempted the preparation of α-aminofuran by decarboxylation of 5-amino-2-furoic acid and by hydrolysis of α-acetaminofuran. Freundler[6] and Leimbach[7] were also unsuccessful in preparing α-aminofuran by hydrolysis of the urethan obtained when furoyl azide was heated with methyl alcohol.

The more precise information now available concerning the behavior of furan compounds has made it seem possible that suitable conditions might be developed for the isolation of simple aminofurans. Indeed, several types of furan compounds (*e. g.*, α-furfuryl chloride[8] and 2-iodofuran[9]), which could not be obtained by earlier workers, have recently been isolated in the pure state. From a consideration of the behavior of

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[1] National Research Fellow in Chemistry.

[2] Marquis, *Ann. chim.*, [8] **4**, 196 (1905).

[3] Traube and Lazar, *Ber.*, **46**, 3438 (1913).

[4] Rinkes, *Rec. trav. chim.*, **51**, 353 (1932).

[5] Gilman and Burtner, THIS JOURNAL, **55**, 2903 (1933).

[6] Freundler, *Bull. soc. chim.*, **17**, 424 (1897).

[7] Leimbach, *J. prakt. Chem.*, [2] **65**, 35 (1902).

[8] Kirner, THIS JOURNAL, **50**, 1955 (1928).

[9] Gilman, Mallory and Wright, *ibid.*, **54**, 733 (1932).

other furan derivatives, particularly of those aminofurans which are known,[4,5] the β-aminofurans would be expected to be considerably more stable than the alpha derivatives, and their stability should be increased further by proper substitution of the furan nucleus with alkyl groups.

It was desired to obtain a number of substituted furyl isocyanates as intermediates in the synthesis of some furyl amines. The present paper describes the preparation and reactions of these isocyanates, which constitute a new class of compounds in the furan series. These isocyanates were prepared by means of the Curtius degradation or by Schroeter's[10] modification of the Curtius reaction[11] as shown below.

$$\begin{tikzcd}
RCOOH \arrow[r] \arrow[dr] & RCOOC_2H_5 \arrow[r] & RCONHNH_2 \arrow[r] & RCON_3 \arrow[r] & RNCO \\
 & RCOCl \arrow[urr] & & &
\end{tikzcd}$$

The modified method, in which a solution of the acid chloride in an inert solvent was heated with sodium azide, was not as satisfactory as the original method for producing the isocyanates in appreciable quantity.

The appropriate furoic ester was the starting point for the synthesis in every instance in which the usual Curtius method was used. Treatment of the various furoic esters with hydrazine hydrate produced the furoyl hydrazides in good yields. The hydrazides were converted to the furoyl azides by treatment with nitrous acid. Decomposition of the acid azides by heating in an inert solvent such as ligroin (b. p. 90–100°), followed by a careful fractional distillation of the reaction mixture under a reduced pressure of dry nitrogen gave the furyl isocyanates in good yields. The following substituted furyl isocyanates were prepared by the method outlined above; 5-methyl-2-furyl isocyanate, 5-bromo-2-furyl isocyanate, 2-methyl-3-furyl isocyanate, 2,5-dimethyl-3-furyl isocyanate and 2,4-dimethyl-3-furyl isocyanate. α-Furyl isocyanate could only be obtained in solution since it could not be separated from the solvent used in decomposing the azide. All attempts to decompose α-furoyl azide without a solvent resulted in violent explosions.

These substituted furyl isocyanates, when freshly distilled under a reduced pressure of dry nitrogen, are colorless liquids possessing an extremely sharp odor and are very potent lachrymators. In general they are unstable when exposed to air and strong light, becoming colored and depositing tarry products. The substituted α-furyl isocyanates exhibited this sensitivity to a greater degree than did the substituted β-furyl isocyanates. Treatment of the isocyanates with water, methyl alcohol and phenylmagnesium bromide gave the corresponding disubstituted ureas, urethans and benzamides. The derivatives obtained from the α-furyl isocyanates were much less stable than those obtained in the beta series. Thus, the derivatives of 5-methyl-2-furyl isocyanate were isolated in analytical purity only with the greatest difficulty while it was not possible to obtain any derivatives from 5-bromo-2-furyl isocyanate or from a ligroin solution of α-furyl isocyanate. Of all the compounds prepared, 2,4-dimethyl-3-furyl isocyanate and its derivatives showed the greatest stability. This increase in stability was apparently due to the substitution of a methyl group for each of the hydrogen atoms on the carbons alpha to the carbon attached to the -NCO group.

On the basis of the above results it is expected that a simple furyl amine would be isolated most readily from 2,4-dimethyl-3-furyl isocyanate. This phase of the work is being continued in this Laboratory.

Experimental Part

I. Substituted Furoic Esters

(a) **Ethyl 5-Methyl-2-furoate.**—The method described by Rinkes[12] was used for the preparation of 5-methyl-2-furoic acid. The acid was converted to the acid chloride in the usual manner with thionyl chloride. Treatment of the acid chloride with excess of absolute ethyl alcohol produced the ethyl ester in practically quantitative yields; b. p. 88–89° at 10 mm.

(b) **Ethyl 5-Bromo-2-furoate.**—5-Bromo-2-furoic acid, which had been prepared by the usual method,[13] was converted to the ethyl ester by the method given in part I (a) above; b. p. 113° at 13 mm.

(c) **Ethyl 2,4-Dimethyl-3-furoate.**—This ester was prepared by decarboxylation, according to the method of Shepard, Winslow and Johnson,[13] of 4-methyl-3-carbethoxy-2-furylacetic acid, which was obtained readily by the partial saponification of the diethyl ester of 4-methyl-3-carboxy-2-furylacetic acid. The latter was obtained in excellent yields from ethyl acetonedicarboxylate,[14] chloroacetone, and ammonia according to the method of Rinkes.[15]

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(10) Schroeter, *Ber.*, **42**, 3356 (1909).

(11) Naegeli, Grüntuch and Lendorff, *Helv. Chim. Acta*, **12**, 227 (1929).

(12) Rinkes, *Rec. trav. chim.*, **49**, 1118 (1930); **52**, 337 (1933).

(13) Shepard, Winslow and Johnson, THIS JOURNAL, **52**, 2083 (1930).

(14) "Organic Syntheses," John Wiley and Sons, Inc., N. Y., 1932, Coll. Vol. I, p. 232.

(15) Rinkes, *Rec. trav. chim.*, **50**, 1127 (1931).

Alcoholic saponification of 48 g. of this diester gave 33 g. of crude 4-methyl-3-carbethoxy-2-furylacetic acid[16] from which there was obtained, after decarboxylation with copper-bronze, 22 g. of pure ethyl 2,4-dimethyl-3-furoate; b. p. 100–101° at 20 mm.[16]

(d) **Ethyl 2-Methyl-3-furoate.**—This ester was prepared by means of Benary's[17] modification of the Feist synthesis from α,β-dichloroethyl ether and acetoacetic ester using pyridine[18] as a condensing agent; b. p. 85–89° at 25 mm.

(e) **Ethyl 2,5-Dimethyl-3-furoate.**—This ester was prepared by decarboxylation, according to the method of Scott and Johnson,[18] of the monoethyl ester of methronic acid (5-methyl-4-carbethoxy-2-furylacetic acid) which was obtained by a modification of the method of Fittig.[19] Potassium succinate was used in place of sodium succinate together with acetoacetic ester and acetic anhydride. By this modification the time of the reaction was reduced to two hours and better yields of the monoethyl methronate were obtained (20%).

II. Substituted Furoyl Hydrazides

(a) The substituted α-furoyl hydrazides were prepared according to the method of Marquis[2] by heating, under a reflux condenser, the appropriate ester with an excess of absolute hydrazine hydrate at 125–130° for six to eight hours. The hydrazides were purified by crystallization from toluene, dilute alcohol or water.

(b) All of the substituted β-furoyl hydrazides were prepared by heating, under a reflux condenser, the corresponding ester with 100% excess of absolute hydrazine hydrate at 135–140° for forty-eight hours. These hydrazides were all purified by crystallization from water. Small portions were purified further for analysis by sublimation at 2 mm.

TABLE I

SUBSTITUTED FUROYL HYDRAZIDES

Furoyl hydrazides	Formula	M. p., °C.	Analysis,[20] % Calcd.	Found
5-Methyl-2-[a]	$C_6H_8O_2N_2$	61–62	20.00	19.80, 19.96
5-Bromo-2-[b]	$C_5H_5O_2N_2Br$	135.5–136	13.16	13.58
2,4-Dimethyl-3-	$C_7H_{10}O_2N_2$	144–145	18.18	18.04
2-Methyl-3-	$C_6H_8O_2N_2$	149.5–150	20.00	19.80
2,5-Dimethyl-3-	$C_7H_{10}O_2N_2$	136–136.3	18.18	18.12

[a] Recrystallized from toluene.

[b] Recrystallized from 25% alcohol.

III. Substituted Furoyl Azides

The substituted furoyl azides were prepared by a method similar to that described by Marquis[2] for α-furoyl azide. To a dilute aqueous solution[21] of the appropriate hydrazide cooled to 0–5° there was added a slight excess of sodium nitrite. A dilute solution of an excess of acetic acid was then added slowly with stirring. The reaction mixture was stirred and maintained between 5 and 10° for one hour after all of the acetic acid had been added.[22] The azide, which separated out during this period, was then separated from the aqueous solution by extraction with ice-cold ether. The ether soution was washed several times with ice water and dried over anhydrous magnesium sulfate. The solution was placed in a refrigerator while drying overnight. After allowing the ether solution to come to room temperature, it was filtered and the ether removed by drawing dry air through the solution. The residue obtained was practically pure azide. The solid azides were purified for analysis by subliming at room temperature and at a pressure of 1–2 mm.

IV. Substituted Furyl Isocyanates

(a) **Preparation by the Modified Curtius Method.**—The procedure outlined by Naegeli, Grüntuch and Lendorff[11] was used to convert 5-methyl-2-furoyl chloride and α-furoyl chloride into the corresponding isocyanates. In a 200-cc. round-bottomed flask attached to a reflux condenser there was placed 9.1 g. of Kahlbaum's sodium azide, which had been activated according to the method of Nelles,[23] and 20 cc. of dry ligroin (b. p. 90–100°). To this mixture was then added a solution of 13.5 g. of 5-methyl-2-furoyl chloride in 10 cc. of dry ligroin. The upper end of the reflux condenser was then attached to a gas washing bottle filled with a small amount of sulfuric acid. The reaction mixture was slowly heated by an oil-bath. At 70° evolution of nitrogen took place at an appreciable rate. The temperature was raised slowly to 100° and held there until evolution of nitrogen had ceased. The total time of heating was 1.5 hours. After cooling, the reaction mixture was filtered in the absence of air, and the filtered solution was quickly transferred to a vacuum distillation apparatus in which the distillation could be carried out under a reduced pressure of nitrogen. After removal of the low boiling ligroin at a pressure of 100 mm., the 5-methyl-2-furyl isocyanate was obtained as a colorless liquid boiling at 53–54° at 35 mm. About 4 g. of the isocyanate was obtained.

TABLE II

SUBSTITUTED FUROYL AZIDES

Furoyl azides	Formula	M. p., °C.	N analyses,[20] % Calcd.	Found
5-Methyl-2-	$C_6H_5O_2N_3$	35–36	27.81	27.77
5-Bromo-2-	$C_5H_2O_3N_3Br$	66–67	19.44	19.22
2,4-Dimethyl-3-	$C_7H_7O_2N_3$	Liq.	...	...
2-Methyl-3-	$C_6H_5O_2N_3$	22–23	18.54[a]	18.50
2,5-Dimethyl-3-	$C_7H_7O_2N_3$	24–25	16.97[a]	15.82

[a] Nitrometric determination of the azide.

When α-furoyl chloride was used in place of 5-methyl-2-furoyl chloride in the procedure described above, it was not possible to separate the α-furyl isocyanate from the ligroin by distillation.

(b) **Preparation by Heating the Azide in an Inert Solvent.**—In a 50-cc. round-bottomed flask equipped with a reflux condenser there was placed 5 g. of the appropriate furoyl azide and 10 cc. of dry ligroin (b. p. 90–

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(16) Feist, *Ber.*, **35**, 1550 (1902).

(17) Benary, *ibid.*, **44**, 493 (1911).

(18) Scott and Johnson, THIS JOURNAL, **54**, 2552 (1933).

(19) Fittig and v. Eynern, *Ann.*, **250**, 178 (1889).

(20) These analyses, micro-Dumas, were made by Mr. M. T. Bush.

(21) In the preparation of 5-bromo-2-furoyl azide a dilute solution of the corresponding hydrazide in 50% alcohol was treated with nitrous acid at +20°.

(22) In the preparation of the three substituted β-furoyl azides the aqueous solutions of the hydrazides were treated with one-half the theoretical amount of sodium nitrite and acetic acid at +20°. Following this addition, the reaction mixture was cooled to +10° and the remainder of the sodium nitrite and acetic acid was added.

(23) Nelles, *Ber.*, **65**, 1345 (1932).

100°). After attaching the upper end of the reflux condenser to a gas drying tower filled with a small amount of sulfuric acid, the reaction flask was slowly heated by an oil-bath to 70°. At this temperature evolution of nitrogen began to proceed slowly in most cases. The temperature was then gradually increased until it reached 100°; this generally required about one hour. The temperature was held at 100–110° until no more nitrogen was evolved. The reaction mixture was then cooled, a second portion of azide (5 g.) added, and the decomposition repeated as described above. After the second portion had been decomposed, the cooled reaction mixture was quickly transferred to a small vacuum distillation apparatus which had been thoroughly swept out with dry nitrogen. The distillation was carried out under reduced pressure with dry nitrogen entering through the ebulliator tube. After removal of the low boiling fraction, which consisted of ligroin, the isocyanate.was obtained as the main fraction.

TABLE III

SUBSTITUTED FURYL ISOCYANATES

Furyl isocyanates	Formula	B. p., °C.	N analyses,[20] % Calcd.	N analyses,[20] % Found
5-Methyl-2-[a]	$C_6H_5O_2N$	53–54 (35 mm.)	11.38	11.29 11.41
5-Bromo-2-[b]	$C_5H_2O_2NBr$	75 (35 mm.)	7.44	7.12 7.10
2,4-Dimethyl-3-	$C_7H_7O_2N$	74–75 (31 mm.)	10.21	10.22
2-Methyl-3-	$C_6H_5O_2N$	42 (15 mm.)	11.38	11.68
2,5-Dimethyl-3-	$C_7H_7O_2N$	68 (20 mm.)	10.21	10.29

[a] Became yellow on standing for a few hours and deposited a yellow tar. [b] Became very dark in color even when kept in sealed tubes in absence of light.

TABLE IV

DERIVATIVES OF SUBSTITUTED FURYL ISOCYANATES

Compound	Formula	M. p., °C	N analyses,[20] % Calcd	N analyses,[20] % Found
sym-Di-(5-methyl-2-furyl) urea[a]	$C_{11}H_{12}O_3N_2$	182[b]	12.72	12.65
sym-Di-(2,4-dimethyl-3-furyl) urea[c]	$C_{13}H_{16}O_3N_2$	285[b]	11.29	11.20
sym-Di-(2-methyl-3-furyl) urea[c]	$C_{11}H_{12}O_3N_2$	227[b]	12.72	12.90
sym-Di-(2,5-dimethyl-3-furyl) urea[c]	$C_{13}H_{16}O_3N_2$	247[b]	11.29	11.32
5-Methyl-2-furyl benzamide[d]	$C_{12}H_{11}O_2N$	75–80	6.97	7.10
2,4-Dimethyl-3-furyl benzamide[e]	$C_{13}H_{13}O_2N$	169–170	6.51	6.41
2-Methyl-3-furyl benzamide[f]	$C_{12}H_{11}O_2N$	137.8–138	6.97	6.75
Methyl 5-methyl-2-furylcarbamate	$C_7H_9O_3N$	64–66	9.03	9.11
Methyl 2,4-dimethyl-3-furylcarbamate	$C_8H_{11}O_3N$	95–96	8.28	8.13
Methyl 2-methyl-3-furylcarbamate	$C_7H_9O_3N$	liq.[g]	9.03	9.55
Methyl 2,5-dimethyl-3-furylcarbamate	$C_8H_{11}O_3N$	liq.[h]	8.28	8.43

[a] Recrystallized from 50% alcohol. [b] Determined on the electric block.[24] [c] Recrystallized from 95% alcohol. [d] Washed with hot pet. ether to remove diphenyl and sublimed. [e] Washed with ether to remove diphenyl and sublimed. [f] Washed with ether to remove diphenyl, recrystallized from 50% alcohol, and sublimed. [g] B. p. 128° at 14 mm. [h] B. p. 107° at 2.5 mm.

All the isocyanates listed in Table III were prepared by the method outlined above. It was possible to carry out the decomposition of 2-methyl-3-furoyl azide and 2,5-dimethyl-3-furoyl azide without using a solvent. Attempts to decompose α-furoyl azide by heating without a solvent always resulted in explosions. All the isocyanates were colorless liquids when freshly distilled. They had a characteristically sharp odor and were very strong lachrymators. They are best preserved by sealing in glass bulbs.

V. Derivatives of Substituted Furyl Isocyanates

(a) **Preparation of sym. Disubstituted Ureas.**—Two grams of the isocyanate was placed in a small flask with 10 cc. of freshly boiled distilled water. The reaction mixture was allowed to stand at room temperature for two days protected from the air by means of a water seal. The solid urea thus formed was purified either by crystallization from 95% alcohol or from dilute (50%) alcohol.

(b) **Preparation of Substituted Furyl Benzamides.**—A solution of 5 g. of the appropriate isocyanate in 50 cc. of dry ether was added slowly with stirring to an ether solution containing an excess of phenylmagnesium bromide. The temperature of the reaction mixture was held at −50° during this addition. The reaction mixture was then decomposed in the usual way with ice and ammonium chloride, the ethereal solution of the benzamide washed with water and dried over magnesium sulfate. After removal of the ether, the solid residue was recrystallized either from ether or petroleum ether. Analytical samples were obtained by subliming the benzamides at 2 mm.

(c) **Preparation of Methyl Substituted Furylcarbamates.**—Three of the urethans were prepared by refluxing the corresponding acid azide with an excess of absolute methyl alcohol. The excess alcohol was removed by distillation and the residue distilled under reduced pressure.

Methyl 2,4-dimethyl-3-furylcarbamate was obtained by treating a solution of absolute methyl alcohol in ether, cooled to −50°, with an ethereal solution of 2,4-dimethyl-3-furyl isocyanate. After removal of the ether and excess methyl alcohol, a white crystalline residue was obtained. The urethan was recrystallized twice from ligroin (b. p. 90–100°). A small portion was purified by sublimation.

Summary

1. A number of substituted furyl isocyanates and several of their derivatives have been prepared in a pure state.

2. The substituted β-furyl isocyanates are much more stable toward air, light and heat than are the substituted α-furyl isocyanates. This difference in stability is also found in the derivatives of the isocyanates.

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(24) Dennis and Shelton, THIS JOURNAL, **52**, 3128 (1930).