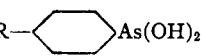


TABLE II
ARSENOUS ACIDS,^a R—As(OH)₂

R	Yield, %	Empirical formula	Arsenic, % ^b	
			Calcd.	Found
—NCN	46	C ₇ H ₇ AsN ₂ O ₂	33.13	32.81
—NHNH ₂	32	C ₆ H ₆ AsN ₂ O ₂	34.60	34.52
—NHCH ₂ SO ₃ Na	86	C ₇ H ₆ AsNNaO ₅ S	23.60	23.20
—NHCH ₂ CONHCH ₂ CH ₂ OH	64	C ₁₀ H ₁₅ AsN ₂ O ₄	24.77	24.67
—NHCH ₂ CON(CH ₂ CH ₂ OH) ₂	72	C ₁₂ H ₁₉ AsN ₂ O ₅	21.62	21.38
—OCH ₂ CONHCH ₂ CH ₂ OH	73 ^c	C ₁₀ H ₁₄ AsNO ₅	24.71	24.78
—OCH ₂ CON(CH ₂ CH ₂ OH) ₂	62	C ₁₂ H ₁₈ AsNO ₅	21.54	21.37
—OCH ₂ CONHC(CH ₂ OH) ₂	55	C ₁₂ H ₁₈ AsNO ₇	20.63	20.55

^a All compounds are colorless. ^b Determined by the method of Banks and Sultzberger, *THIS JOURNAL*, **69**, 1 (1947).
^c The same compound was also obtained from methyl 4-arsonosphenoxycetate and ethanolamine, yield 92%.

methylol group was formed on the amide nitrogen and one on the arylamino nitrogen in the last two instances. The position of the methylol group on nitrogen rather than on the benzene ring was proved by hydrolysis to 4-arsonophenoxyacetic acid and N-4-arsonophenylglycine.

4-Aminobenzearsonous acid reacted with sodium formaldehyde bisulfite to yield a sulfomethyl derivative. 4-Cyano- and 4-hydrazinobenzearsonous acid^{9,10} were obtained by reduction of the corresponding arsonic acids.

Experimental

Acetamides.—The methyl ester of 4-arsonophenoxyacetic acid or 4-arsonophenylglycine (0.1 mole) was dissolved in an excess of the amine (100 ml.) and heated to 80° for two hours. On adding the reaction mixture to an excess of alcohol (2 l.), the amine salt of the hydroxyalkylacetamide crystallized. It was filtered off and dried *in vacuo*. The free arsonic acids were liberated when the amine salts were dissolved in a small amount of water and made strongly acid to congo red paper with hydrochloric acid. The arsonic acids were recrystallized from water.

Arsonous Acids.—The arsonous acids were prepared from the corresponding arsonic acids by previously published methods.¹¹

(9) Banks, Controulis and Holcomb, *THIS JOURNAL*, **68**, 2102 (1946).

(10) U. S. Patent 2,390,529 (1945).

(11) Banks, Gruhzt, Tillitson, Controulis, Walker and Sultzberger, *THIS JOURNAL*, **66**, 1771 (1944); **69**, 5 (1947).

Methylol Amides.—The arsono-substituted acetamide (0.1 mole) or urea was dissolved in water (25 ml.) by the addition of sodium hydroxide to pH 7, or the sodium salt was dissolved in water, and 37% aqueous formaldehyde (1 ml. per gram) added. The mixture was heated to 80° for two hours, then concentrated *in vacuo* to a solid. The residue was dissolved in a minimum of water, filtered and the sodium salt crystallized upon the addition of alcohol and ether. The free arsonic acids could be obtained by carefully acidifying cold aqueous solutions of the salts.

Acetone 4-Arsonophenylhydrazone.—4-Hydrazinobenzearsonic acid¹⁰ (5.8 g.) was warmed with 25 ml. of acetone and 5 ml. of water until solution occurred. On chilling, a mass of pale red crystals was obtained. After two recrystallizations from water-acetone (1:2), a nearly white crystalline product was obtained. Unlike the initial material, the product did not give a silver mirror test with ammoniacal silver nitrate.

Summary

1. Four new N-hydroxyalkyl derivatives of 4-arsonoanilinoacetic acid and five corresponding derivatives of 4-arsonophenoxyacetic acid are reported. Representative salts are described.

2. The arsonic acids were reduced to the corresponding arsonous acids.

3. Several miscellaneous related arsenicals are also reported.

DETROIT 32, MICH.

RECEIVED AUGUST 27, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

C-Alkylation and O-Alkylation in the Synthesis of Substituted Furoic Acids

BY CHARLES D. HURD AND KENNETH WILKINSON

In the alkylation of ethyl sodio-oxaloacetate with ethyl bromopyruvate Sutter¹ claimed to have prepared 2,3,5-furantricarboxylic acid. That is to say, he assumed that C-alkylation had occurred followed by ring closure and the elimination of water. However, Reichstein² prepared the same tricarboxylic acid by partially decarboxylating furantetracarboxylic acid, and since pyrolysis of such acids causes preferential decarboxylation in the *alpha* position he contended that Sutter had

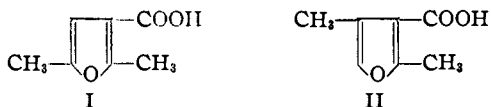
experienced O-alkylation and had obtained 2,3,4-furantricarboxylic acid. Archer and Pratt³ demonstrated that O-alkylation was the course followed in the analogous condensation between ethyl bromopyruvate and ethyl sodio- β -ketosuberate, since subsequent ring closure yielded 5-(3,4-dicarboxyfuryl)-valeric acid.

Similar interaction of acetoacetic ester and chloroacetone should produce 2,5-dimethyl-3-furoic acid (I) by C-alkylation, and 2,4-dimethyl-3-furoic acid (II) by O-alkylation. On the basis of

(1) Sutter, *Ann.*, **499**, 56 (1932).

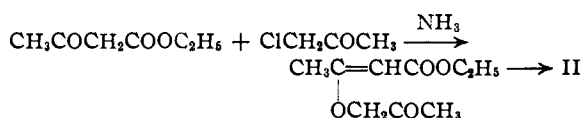
(2) Reichstein, *Helv. Chim. Acta*, **16**, 276 (1933).

(3) Archer and Pratt, *THIS JOURNAL*, **66**, 1656 (1944).

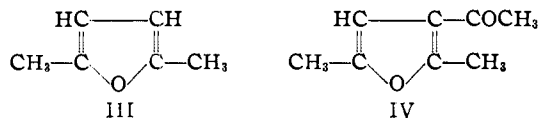


Archer and Pratt's work one might guess that chloroacetone and ethyl sodio-acetoacetate, followed by ring-closure, would yield II. Actually, this experiment was performed by Paal.⁴ His acid, m. p. 136°, has been assigned structure I rather than II, but it must be said that the evidence regarding structure may be questioned.

A few years later, Feist⁵ carried out a similar reaction between chloroacetone and acetoacetic ester, the base being ammonia instead of sodium ethoxide. His product melted at 122°. He suggested structure II, again without adequate proof. These steps would apply if O-alkylation occurred



We have repeated and confirmed both Paal's and Feist's observations. To establish conclusively the structures of the acids formed, we have synthesized I by an unequivocal method. For this work, 2,5-dimethylfuran (III) was chosen as a source material of unquestioned structure. It was converted into 3-acetyl-2,5-dimethylfuran (IV) by means of acetic anhydride and stannic



chloride. Since the only previous synthesis⁶ of IV involved autoclaving a mixture of succinic acid, acetic anhydride, sodium acetate and zinc chloride at 200°, the present synthesis of IV places the structure on a secure basis. Oxidation of this ketone by sodium hypiodite yielded an acid melting at 135° and obviously of structure I.

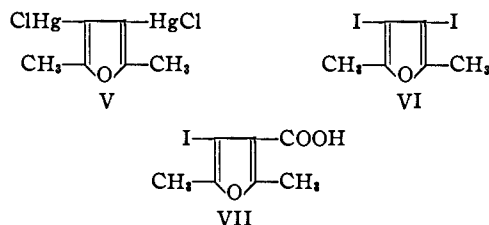
This proof of structure I fixes structure II as well, and establishes the fact that C-alkylation is involved in the reaction of chloroacetone with acetoacetic ester and sodium ethoxide, whereas O-alkylation occurs if ammonia is used as the base. That the initial products of C- and O-alkylation were different was evident also in the reactions of cyclization. The former, $\text{CH}_3\text{COCH}(\text{CH}_2\text{COCH}_3)\text{COOC}_2\text{H}_5$, which is a 1,4-diketone, undergoes ring closure promptly on treatment with concentrated sulfuric acid. The latter, $\text{CH}_3\text{C}(\text{OCH}_2\text{COCH}_3)=\text{CHCOOC}_2\text{H}_5$, undergoes practically no cyclization under these conditions. The method of cyclizing this material is to saponify, then acidify, a method not applicable to the C-alkylated compound since it promotes decarboxylation instead.

(4) Paal, *Ber.*, **17**, 2765 (1884).

(5) Feist, *ibid.*, **35**, 1540, 1551 (1902).

(6) Magnanini and Bentivoglio, *Gazz. chim. ital.*, **24**, I, 435 (1894).

Other reactions of dimethylfuran were developed during this work. Both mono- and dimer-curation (V) products were obtained by reaction with mercuric chloride. Both of these compounds reacted readily with iodine to yield 3-iodo-2,5-dimethylfuran and 3,4-diiodo-2,5-dimethylfuran (VI), respectively. Compound VI could not be



brought into reaction with magnesium even by using butyl ether and temperatures⁷ up to 140° or by employing a special magnesium alloy.⁸ It was inert also toward potassium cyanide when an attempt was made to form the nitrile. A small amount of Grignard exchange was observed between methylmagnesium iodide and VI, since the product yielded 2,5-dimethyl-4-iodo-3-furoic acid (VII) on carbonation. On the other hand, methylmagnesium iodide did not cause substitution of magnesium into the nucleus of 2,5-dimethylfuran. Instead, a coordination compound precipitated.

Experimental

3-Acetyl-2,5-dimethylfuran.—A mixture of 46 g. of 2,5-dimethylfuran, 64 g. of acetic anhydride, and 0.2 ml. of stannic chloride was refluxed for four hours and then distilled. The yield of product boiling at 196° was 53.3 g. or 77%. The oxime⁶ melted at 77°.

2,5-Dimethyl-3-furoic Acid.—A solution of iodine in aqueous potassium iodide was added to 1 g. of 3-acetyl-2,5-dimethylfuran and 4 ml. of 50% sodium hydroxide until there was an excess of iodine. The reaction was maintained at 60° for one-half hour, then the iodoform which formed in the reaction was extracted with ether. After warming off the ether, acidification and use of a small amount of bisulfite to remove the excess iodine yielded 2,5-dimethyl-3-furoic acid which was recrystallized from water, m. p. 135.4°. The neutral equivalent of this acid was found to be 139.8 (calcd., 140).

2,5-Dimethyl-3-furylmercuric Chloride.—A mixture of 10 g. of 2,5-dimethylfuran, 27 g. of mercuric chloride, 13 g. of sodium acetate trihydrate and 300 g. of water was warmed to 50° and shaken occasionally for three hours. The 14 g. of yellow cream solid which separated was dissolved in 50–60 ml. of hot acetone, filtered and precipitated by pouring into three volumes of water. This process was repeated before analysis.

Anal. Calcd. for $\text{C}_8\text{H}_7\text{ClHgO}$: Hg, 60.60. Found: Hg, 60.64.

A product analyzing 64.0% mercury was obtained by using relatively more sodium acetate. From a mixture of 5 ml. of 2,5-dimethylfuran, 13.6 g. of mercuric chloride, 10 g. of anhydrous sodium acetate and 50 g. of water, kept at 40–50° for thirty minutes, was obtained 5.4 g. of a cream-colored product after filtration and rinsing with water till free of mercuric chloride. It still analyzed 64.0% after dissolving nine-tenths of it in 80 ml. of hot acetone, filtering, and precipitating with 150 ml. of water.

The mercury analysis is satisfactory for a compound

(7) Marvel, Blomquist and Vaughn, *THIS JOURNAL*, **50**, 2810 (1928).

(8) Sheppard, Winslow and Johnson, *ibid.*, **52**, 2086 (1930).

of the structure $C_8H_7O-Hg-C_8H_6O-HgCl$ (calcd. 64.1% Hg). At least, it appeared that both monomercurated and dimercurated furan nuclei were produced since iodination (I_2-KI reagent) yielded an oily mixture containing a substantial amount of solid 3,4-diiodo-2,5-dimethylfuran, m. p. 60.5°. Also, this mercurated product was much more soluble in hot acetone than compound (V), described below.

3-Iodo-2,5-dimethylfuran.—A mixture of 6.6 g. of 2,5-dimethyl-3-furylmercuric chloride (containing 60.6% Hg) and 50 g. of 2,5-dimethyl-3-furylmercuric chloride (containing 60.6% Hg) and 50 g. of water was shaken with an aqueous solution of iodine and potassium iodide until there was an excess of iodine. This was decolorized with sodium bisulfite. The mixture was treated with 0.5 g. of sodium bicarbonate and the oily product was steam distilled, ether extracted, dried over sodium sulfate and distilled; yield, 2.6 g. (62%) of b. p. 85.5–86° (20 mm.); n_D^{22} 1.5388; d_4^{20} 1.699. The compound decomposes in two weeks if exposed to light.

Anal. (by J. Anderson): Calcd. for C_8H_7IO : C, 32.45; H, 3.16. Found: C, 32.56; H, 3.20.

2,5-Dimethyl-3,4-furan-bis-(mercuric chloride) (V).—By heating 18.4 g. (0.19 mole) of 2,5-dimethylfuran and 108.4 g. (0.4 mole) of mercuric chloride in 150 ml. of water at 70° with intermittent shaking for one hour, 2,5-dimethyl-3,4-furan-bis-(mercuric chloride), a white solid, was formed. It was filtered and dried at 50° since temperatures above 80° caused extensive decomposition. This material is only slightly soluble in hot acetone.

Anal. Calcd. for $C_8H_6Cl_2Hg_2O$: Hg, 70.87. Found: Hg, 70.6.

3,4-Diiodo-2,5-dimethylfuran.—An aqueous solution of iodine and potassium iodide was added to 33.1 g. of 2,5-dimethyl-3,4-furan-bis-(mercuric chloride) suspended in 100 ml. of water until there was an excess of iodine which persisted after an hour of intermittent shaking. Thio-sulfate was then added to remove the excess of iodine. Any acids in the solution were neutralized by treatment with excess bicarbonate, after which the solution was steam distilled. The bicarbonate treatment removes traces of hydrodic acid which would promote resinification of the product. The oily distillate was extracted with ether, dried over anhydrous sodium sulfate, and the ether evaporated. The yield was 13 g. (41%) of white crystalline 3,4-diiodo-2,5-dimethylfuran, m. p. 60.8°. Its odor is similar to iodoform. It is stable in alcoholic solution, but in a crystalline state it completely decomposes in less than two months.

Anal. (by P. Craig): Calcd. for $C_8H_6I_2O$: C, 20.70; H, 1.72. Found: C, 20.93; H, 1.62.

2,5-Dimethyl-4-iodo-3-furoic Acid.—To a solution of 0.1 mole of methylmagnesium iodide in 25 ml. of ether was added 2.2 g. of 3,4-diiodo-2,5-dimethylfuran in 10 ml. of ether. The mixture was refluxed for one hour and then carbonated by pouring over solid carbon dioxide. The mixture was acidified with 30% sulfuric acid and extracted with ether, then the ether was extracted with 5% potassium hydroxide. Evaporation of the ether yielded 1.9 g. or 87% of the starting material. Acidification of the alkaline solution and extraction with ether gave 0.2 g. of 2,5-dimethyl-3-iodo-4-furoic acid which was recrystallized from 50% methanol: m. p. 208.8°.

Anal. (by P. Craig): Calcd. for $C_7H_7IO_3$: C, 31.59;

H, 2.63; neut. equiv., 266. Found: C, 31.43; H, 2.48; neut. equiv., 265.

2,4-Dimethyl-3-furoic Acid via O-Alkylation.—A stream of ammonia gas was passed through a flask containing 100 ml. of ether, 28 g. of chloroacetone and 39 g. of ethyl acetoacetate. After thirty minutes the reaction was stopped, the ammonium chloride which had formed was filtered off, and the ether evaporated. The residual oil was fractionated under reduced pressure yielding 15 g. (27%) of a fraction boiling at 95–98° at 14 mm.; n_D^{20} 1.482. This alkylation product was saponified by warming with a slight excess of 5% sodium hydroxide for thirty minutes. Acidification of the hot solution yielded upon cooling pure 2,4-dimethyl-3-furoic acid, m. p. 123°; reported⁵ 122°.

2,5-Dimethyl-3-furoic Acid via C-Alkylation.—After dissolving 7 g. of sodium in 100 ml. of absolute alcohol, 40 g. of ethyl acetoacetate was added and the solution was brought to refluxing temperature. To it was added 28 g. of chloroacetone over a period of two hours. After refluxing for an additional hour, the mixture was cooled, the sodium chloride filtered off and washed with alcohol, and the alcohol distilled away from the high boiling product. Fractionation under reduced pressure yielded 29 g. (43%) of a liquid boiling at 126–128° at 14 mm.; n_D^{20} 1.4385. This boiling point is considerably higher and the refractive index significantly lower than the analogous constants from the ammonia reaction.

Three grams of this alkylation product was poured into 10 ml. of concentrated sulfuric acid. After five minutes it was poured over cracked ice. The mixture was extracted with ether, the ether evaporated, and the oil remaining saponified with 5% sodium hydroxide solution on a steam-bath for ten minutes. Acidification yielded 0.4 g. (18%) of 2,5-dimethyl-3-furoic acid, m. p. 135.4°. A mixed melting point with an authentic sample prepared from the acetylation of 2,5-dimethylfuran followed by a hypiodite oxidation showed no depression.

Summary

The synthesis of 2,5-dimethyl-3-furoic acid from 2,5-dimethylfuran is described by a method which proves its structure. The same acid is made starting with chloroacetone and ethyl sodio-acetoacetate, a process involving C-alkylation of the acetoacetic ester. A different acid, 2,4-dimethyl-3-furoic acid, results from reaction of chloroacetone and ethylacetoacetate in the presence of ammonia. This involves O-alkylation of the acetoacetic ester.

Mercuration studies on 2,5-dimethylfuran are reported.

3,4-Diiodo-2,5-dimethylfuran was inactive toward magnesium, but did undergo an exchange reaction with methylmagnesium iodide to yield upon carbonation, 2,5-dimethyl-4-iodo-3-furoic acid.

2,5-Dimethylfuran did not undergo a Grignard exchange with methylmagnesium iodide.

EVANSTON, ILLINOIS

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