[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Orientation in the Furan Nucleus. III. 5-Methyl-3-furoic Acid[1]

BY HENRY GILMAN, ROBERT R. BURTNER AND E. W. SMITH

Introduction

It is rather astonishing that despite the long history of furan compounds very little is known definitely concerning orientation in the furan nucleus. There are several reasons for this. First, furan compounds are reputedly highly sensitive to acidic reagents, and it is just such reagents which are most commonly involved in substitution reactions such as halogenation, nitration and sulfonation. Second, there is a pronounced tendency for substituents to occupy the alpha-positions when these are available. This makes the determination of the position of substituents in furan more difficult than in benzene, for absolute methods of orientation (like those used with signal success in the classical studies by Körner with benzene) are of limited application because not all of the theoretically possible isomers are formed in a given substitution reaction starting with furan or a mono-substituted furan or a di-substituted furan. Furthermore, if all possible isomers were formed and could be isolated, the absolute method for orientation would be of restricted applicability as can be readily ascertained by a comparison of isomeric furan and benzene types. Third, it is, at present, difficult to obtain beta-substituted furans, even by indirect methods, and only very recently have the simple beta-substituted furans like 3-furaldehyde, 3-furansulfonic acid, 3-chloromercurifuran, etc., become accessible. Fourth, analogies cannot be made confidently with related heterocycles like thiophene. Not only are there essential differences between thiophene and furan, but (and this is of greater importance) the positions of elements and groups in many nuclear substituted thiophenes have not been determined unequivocally. Furthermore, it appears that the structures now assigned to some nuclear substituted thiophenes are incorrect, and it would not be very surprising to find that analogies, if any are to be drawn, will be with furan and not with thiophene as a type. Fifth, physico-chemical methods have a particularly circumscribed utility, at this time, for such methods in general turn on comparisons with compounds of known constitution as standards, and relatively few such compounds are available.

The particular need is for reference or standard compounds having two nuclear substituents. Theoretically, there are four isomeric di-substituted furans, in which the nuclear substituents are alike. The paucity of reference compounds becomes obvious when we learn that there is no single, complete series of di-substituted furans having two like substituents.

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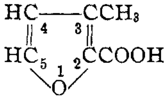
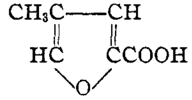
(1) For preceding papers in this series see: Gilman and Wright, *Iowa State Coll. J. Sci.*, **5**, 85 (1931); Gilman, Burtner and Smith, *Rec. trav. chim.*, **51**, 407 (1932).

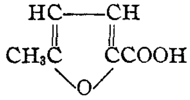
Theoretically, there are six isomeric di-substituted furans, in which the nuclear substituents are unlike. The present synthesis of 5-methyl-3-furoic acid (Formula VI) completes such a series, and makes available for the first time a group of reference compounds for the determination of the position of substituents in poly-substituted furans having both like and unlike substituents.



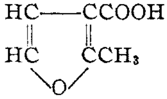
m. p. 134°
(I)[2]



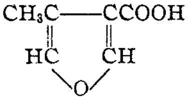
m. p. 129°
(II)[3]



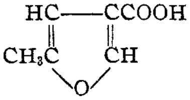
m. p. 109°
(III)[4]



m. p. 101°
(IV)[5]



m. p. 138–139°
(V)[6]



m. p. 119°
(VI)

The 5-methyl-3-furoic acid (VI) was synthesized by the following sequence of reactions

$$3,5\text{-}C_4H_2O(COOH)_2 \longrightarrow 3,5\text{-}C_4H_2O(COOCH_3)_2 \longrightarrow 3,5\text{-}C_4H_2O(COOCH_3)(COOH) \longrightarrow 3,5\text{-}C_4H_2O(COOCH_3)(COCl) \longrightarrow 3,5\text{-}C_4H_2O(COOCH_3)(CHO) \longrightarrow 3,5\text{-}C_4H_2O(COOH)(CHO) \longrightarrow 3,5\text{-}C_4H_2O(COOH)(CH{=}NNH_2) \longrightarrow 3,5\text{-}C_4H_2O(COOH)(CH_3).$$

The constitution of 5-methyl-3-furoic acid was confirmed by other reactions. First, it is known that one of the carboxyl groups in the initial dibasic acid occupies a β-position, because preferential pyrolytic decarboxylation gives 3-furoic acid. Second, the methyl group in the ultimate product (α-methyl-3-furoic acid) is in an α-position because decarboxylation yields 2-methylfuran (or sylvan). Only two α-methyl-β-furoic acids are possible: namely, IV and VI, and the new methylfuroic acid is certainly quite unlike the well-known 2-methyl-3-furoic acid (IV).

Experimental Part

Dimethyl 2,4-furandicarboxylate was obtained in a 90% yield in accordance with the directions of Feist.[7]

4-Carbomethoxy-2-furoic Acid, $C_4H_2O(COOCH_3)(COOH)$.—One-tenth mole of potassium hydroxide in 50 cc. of absolute methyl alcohol was added to 0.1 mole of the dimethyl ester in 50 cc. of methyl alcohol, and after refluxing until no color test was observed with phenolphthalein, the ester salt was acidified in the cold with hydrochloric acid to yield 14.5 g. of the ester acid melting at 100–105°. Crystallization from water

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(2) Asahina, *Acta Phytochimica*, **2**, 1 (1924).

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

(4) Hill, *Ber.*, **22**, 607 (1889); Blanksma, *Chem. Weekblad*, **33**, 33 (1912).

(5) Plancher and Albini, *Atti. acad. Lincei*, [5] **13**, I, 39 (1904); Benary, *Ber.*, **44**, 493 (1911); Gilman, Burtner and Smith, *Rec. trav. chim.*, **51**, 407 (1932).

(6) Reichstein and Zschokke, *Helv. Chim. Acta*, **14**, 1270 (1931).

(7) Feist, *Ber.*, **34**, 1992 (1901).

yielded lustrous white plates melting at 132.5°; neutralization equivalent, calcd., 170; found, 172.8.

Anal. Calcd. for $C_7H_6O_5$: C, 49.41; H, 3.56. Found: C, 49.42; H, 3.85.

4-Carbomethoxy-2-furoyl Chloride, $C_4H_2O(COOCH_3)(COCl)$.—The ester acid chloride was prepared by heating (after the initial vigorous reaction) a benzene solution of the ester-acid with thionyl chloride; and, on recrystallization from carbon tetrachloride, it melted at 83–84°.

Anal. Calcd. for $C_7H_5O_4Cl$: Cl, 18.81. Found: Cl, 18.86 and 18.63.

4-Carbomethoxy-2-furaldehyde, $C_4H_2O(COOCH_3)(CHO)$.—Catalytic reduction was effected by the procedure of Rosenmund.[8] A few details will be given because the method has not been described for furan compounds and we have had consistent success in converting a miscellany of furoyl chlorides to the corresponding furaldehydes. Four and one-half grams (0.023 mole) of the ester acid chloride, 1.8 g. of the palladium–barium sulfate catalyst and 25 cc. of dry xylene were placed in a 200-cc. three-necked flask provided with a stirrer, condenser and delivery tube for admitting hydrogen. A small U-tube containing sulfuric acid was attached to the end of the condenser to prevent the entry of moisture and to serve as an indicator for the pressure of hydrogen. The mixture was gently refluxed (bath temp., 125°) with vigorous stirring, and a stream of dry hydrogen was bubbled through at a rate to maintain a slight positive pressure. Hydrogen chloride was evolved immediately, and reduction was continued until no further hydrogen chloride was evolved. The cooled mixture was filtered, and after removing the solvent there remained 3.5 g. of a pale yellow solid melting at 91–92°. After crystallization from methyl alcohol the ester aldehyde melted at 93.5°. The yield was 99%, and the compound gave positive Schiff and aniline acetate tests. The phenylhydrazone of 4-carbomethoxy-2-furaldehyde is a tan crystalline compound melting at 114–115°.

Anal. Calcd. for $C_7H_6O_4$: C, 54.54; H, 3.89. Found: C, 54.68; H, 3.62.

4-Carboxy-2-furaldehyde, $C_4H_2O(COOH)(CHO)$.—Hydrolysis of the ester aldehyde, by refluxing 3.5 g. with 50 cc. of 6 *N* hydrochloric acid for fifteen minutes, gave a 94% yield of the acid aldehyde which, after crystallization from hot water, melted at 158–159°. This compound also gave the above-mentioned aldehyde tests; neutralization equivalent, calcd., 140; found, 143.1.

4-Carboxy-2-furaldehyde Hydrazone, $C_4H_2O(COOH)(CH{=}NNH_2)$.—A 90% yield of the hydrazone, melting at 145–146°, was obtained from 2.9 g. of the acid aldehyde and 2.1 g. of hydrazine hydrate in 10 cc. of absolute ethyl alcohol. The mixture, kept initially at about −15° for one and one-half hours, was warmed for a few minutes at about 75° and then worked up in a customary manner.

5-Methyl-3-furoic Acid, $C_4H_2O(COOH)(CH_3)$.—The hydrazone was converted by the usual Wolff–Kischner method to the methylfuroic acid by means of potassium hydroxide (pellets) and absolute ethyl alcohol. A slight evolution of gas was noticed during a two-hour period of heating at about 70°, and after standing overnight at room temperature, heating was continued for four hours, at the end of which time gas evolution had practically ceased. The yield of 5-methyl-3-furoic acid was 31%, and the compound melts at 119° after crystallization from hot water; neutralization equivalent, calcd., 126; found, 130.

Anal. Calcd. for $C_6H_6O_3$: C, 57.14; H, 4.76. Found: C, 56.91; H, 5.32.

Decarboxylation to 2-Methylfuran, $C_4H_3OCH_3$.—Decarboxylation of 0.9 g. of 5-methyl-3-furoic acid by the method of Johnson using quinoline and copper–bronze was effected at 215°. The evolution of carbon dioxide commenced at about 200°, and the

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(8) Rosenmund and Zetzsche, *Ber.*, **51**, 578 (1918).

reaction product when worked up in a customary manner gave about 0.5 cc. of a clear, pleasant smelling liquid. This was definitely identified as 2-methylfuran by converting it to 5-methyl-2-chloromercurifuran by means of mercuric chloride and sodium acetate. A mixed melting point determination with an authentic specimen melting at 132° showed no depression.

Summary

The first complete series of di-substituted furans, particularly useful as reference or standard compounds in studies on orientation of nuclear substituents of furan, has been made available by the synthesis of 5-methyl-3-furoic acid.

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Aliphatic Tertiary Alcohols and Chlorides Containing the Normal Amyl Group and the Related Olefins and their Ozonolysis

BY FRANK C. WHITMORE AND F. E. WILLIAMS[1]

The primary purpose of this research was to supply intermediates for the preparation of certain complex pinacolyl alcohols for use in rearrangement studies.[2] The series of tertiary alcohols chosen contained combinations of the five normal alkyls up to amyl with each alcohol containing at least one amyl group. The *n*-amyl group was chosen because of the present availability of that alcohol in large quantity.[3] Twelve of the fifteen possible alcohols of this type have been prepared in this study. Of these only four have been prepared elsewhere. These are dimethylamylcarbinol,[5] methylethylamylcarbinol,[3] diethylamylcarbinol[3,4] and triamylcarbinol.[6] The triamylcarbinol was kindly supplied by Dr. Marvel. The twelve carbinols were prepared by means of the Grignard reagent in yields of 40–75%. The chief difficulty was in the distillation of the carbinols. All traces of acid had to be removed before distillation and a suitably low pressure was necessary.

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[1] Presented in partial fulfilment of the requirements for the Ph.D. degree at the Pennsylvania State College. This study was finished in August 1930.

[2] (a) Whitmore, THIS JOURNAL, **54**, 3274, 3431 (1932); (b) Whitmore and Woodburn, *ibid.*, **55**, 361 (1933).

[3] The alcohol used in this work was generously supplied by the Sharples Solvents Corporation of Philadelphia.

[4] Masson, *Compt. rend.*, **132**, 483 (1901); V. Braun and Sobecki, *Ber.*, **44**, 1927 (1911).

[5] Davies, Dixon and Jones, *J. Chem. Soc.*, **131**, 468 (1930).

[6] Moyer and Marvel, "Organic Syntheses," Vol. XI, 1931, p. 100.