[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

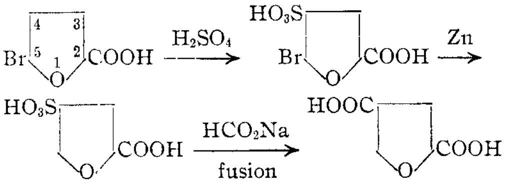
Orientation in the Furan Nucleus. VII. Di-α-substituted Furans

BY HENRY GILMAN, N. O. CALLOWAY AND E. W. SMITH

Introduction

There are here presented two pieces of evidence which permit the formulation of a rule of orientation for di-α-substituted furans, having one substituent which in benzene is an *o,p*-director and another substituent which in benzene is a *m*-director. The third substituent was introduced, in one case, by sulfonation of 5-bromo-2-furoic acid, and, in the other case, by a Friedel–Crafts acetylation of ethyl 5-methyl-2-furoate.

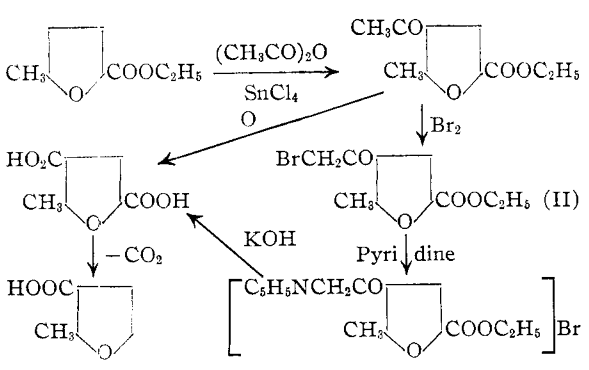
5-Bromo-2-furoic Acid.—The sulfonation of 5-bromo-2-furoic acid introduces one sulfonic acid group in a β-position, and the sulfonic group has been assigned to the 3-position.[1] In accordance with the following sequence of transformations,



(I)

the sulfonic acid group has assumed a 4- and not a 3-position. This proof of the position of the sulfonic group is based on the assumption that fusion of sulfonic acids or their salts with sodium formate is essentially reliable.[2]

Ethyl 5-Methyl-2-furoate.—The directing influences of the methyl and carboethoxy groups were established in the following manner.



The acetyl group was converted to a carboxyl group by (1) permanganate oxidation and by (2) the procedure elaborated by Fuson[3] which involves the cleavage of an acylpyridinium halide by alkali. There is no uncertainty concerning the constitution of the 2-methyl-3-furoic acid because all six possible isomeric methylfuroic acids have been prepared[4] by methods which leave no doubt of the correctness of the structures assigned them. Incidentally, this is the only entire series of isomeric di-substituted furans with unlike substituents and it was completed with the object of having available a series of reference compounds for the determination of orientation by a relative method.

A possible weakness of these transformations centers about the use of a modified Friedel–Crafts reaction. Admittedly, this condensation reaction is sometimes quite unreliable for the proof of structure, although it has been undeservedly maligned at times.[5] For our immediate purposes it is significant that we start with a methyl group in an α-position and end up with a methyl group in an α-position. If rearrangement occurred, it must therefore have involved essentially either or both the acetyl and carboethoxy groups. Other studies[6] of the Friedel–Crafts reaction with acyl-substituted furans have shown no evidence for the migration of an acyl group. Also, the fact that diethyl 2,5-furandicarboxylate is largely recovered after attempted Friedel–Crafts reactions is presumptive evidence against migration of a carboethoxy group. Apparently, therefore, none of the groups rearrange, and this is particularly so with the methyl group in the compound under consideration.

Rule of Orientation.—It is unfortunate that a rule of orientation should revolve on reactions which have more than a taint of suspicion, and it is doubtful if there is any other pair of reactions like fusion of a sulfonic salt and the Friedel–Crafts reaction which are in greater ill repute for orientation purposes. However, other than the replacement of carboxyl by nitro which now appears to be reliable, they supply the best present evidence for orientation of di-α-substituted furans. Disubstituted furans are governed by the same

---

[1] Hill and Palmer, *Proc. Am. Acad.*, **23**, 206 (1887).

[2] Steinkopf, *Ann.*, **501**, 179 (1933).

[3] Babcock, Nakamura and Fuson, THIS JOURNAL, **54**, 4407 (1932). See, also, Bamberger, *Ber.*, **20**, 3344 (1887).

[4] THIS JOURNAL, **55**, 403 (1933).

[5] Ruzicka, Pieth, Reichstein and Ehmann, *Helv. Chim. Acta*, **16**, 275 (1933).

[6] Gilman and Calloway, THIS JOURNAL, **55**, 4197 (1933). See also, Mosettig and van de Kamp, *ibid.*, **55**, 3444 (1933).

general rules of orientation that underlie substitution in benzene, with the notable difference that there is a pronounced tendency against the formation of isomers in furan substitution,[7] so that sulfonation of 5-bromo-2-furoic acid, for example, gives largely, if not exclusively, one bromo-sulfofuroic acid. If in a di-α-substituted furan one of the substituents is an *o,p*-director in benzene and the other a *m*-director in benzene, then the entering group assumes a β-position contiguous to the *o,p*-director. Isomers are to be expected, of course, with a compound like 5-methyl-2-ethylfuran.

On the basis of such a generalization, it appears that the positions assigned by Rinkes to his nitration products, as well as his formulations,[8] are correct; and that most of the positions assigned by Hill and co-workers[7] for their halogenation and sulfonation products probably warrant revision. This remains to be established.

Experimental Part

Sodium Formate Fusion of Di-sodium β-Sulfo-α-furoate (Reaction (I)).—A powdered intimate mixture of 9 g. of the disodium salt and 9 g. of sodium formate was slowly heated, in essential accordance with the general directions of Meyer.[9] The melt was dissolved in water, and the solution decolorized, filtered, acidified and extracted with ether. Evaporation of the ether yielded a small quantity of crystalline product which when sublimed melted at 258°. A mixture with 2,4-furandicarboxylic acid (m. p. 266°) melted at 264–265°. Several attempts to secure more of the dibasic acid by fusion were unsuccessful.

Acetylation of Ethyl 5-Methyl-2-furoate.—The 5-methyl-2-furoic acid was prepared by the directions of Scott and Johnson,[10] and its ethyl ester by the method of Hill and Jennings.[11]

The general directions for acylation were those described recently.[6] The compounds used were 26.2 g. (0.17 mole) of ethyl 5-methyl-2-furoate; 18.2 g. (0.17 mole) of acetic anhydride in 100 cc. of dry, thiophene free-benzene; and 88.4 g. (0.34 mole) of stannic chloride. The reaction flask, protected from atmospheric moisture, was heated at 60° for twenty-four hours, after which the mixture was poured into 300 cc. of iced water and the benzene layer separated. The aqueous layer was extracted with benzene, and the combined benzene solution was washed with water, then with sodium bicarbonate, and finally dried over sodium sulfate. The residue obtained after removing the benzene by distillation was crystallized from petroleum ether (b. p. 80°) and yielded 18 g. or a 54% yield of ethyl 4-acetyl-5-methyl-2-furoate which melts at 99°.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.19; H, 6.17. Found: C, 61.52; H, 6.40.

Two grams of the ester was hydrolyzed by 20% potassium hydroxide to yield 4-acetyl-5-methyl-2-furoic acid which, after sublimation *in vacuo*, melted with decomposition at 235°. *Neutral equivalent:* calcd., 168.1; found, 170.4.

Permanganate Oxidation of 4-Acetyl-5-methyl-2-furoic Acid.—Two grams (0.012 mole) of the acetyl acid was dissolved in 5.9 g. of calcium hydroxide suspended in 100 cc. of water, and 1 g. of potassium hydroxide was then added. To this mixture, cooled by iced water, was added dropwise and with vigorous stirring a solution of 2.53 g. of potassium permanganate in 200 cc. of water. On working up the product in a customary manner (the acidified solution being extracted several times with ether) there was obtained 0.05 g. of 5-methyl-2,4-furandicarboxylic acid which after sublimation *in vacuo* melted at 270–272°. *Neutral equiv.:* calcd., 85; found, 86.8. Inasmuch as a check experiment yielded the same small quantity of product, oxidation was then effected by alkali cleavage of the pyridinium salt.

Alkali Cleavage of Acylpyridinium Salt.—The ethyl 4-bromoacetyl-5-methyl-2-furoate, prepared by bromination of the acetyl ester in a mixture of acetic acid and acetic anhydride, melted at 67–68° after crystallization from alcohol.

The bromoacetyl ester and pyridine were refluxed in ether for two hours to give a 65% yield of the pyridinium bromide which melted at 210–212° with decomposition.

One and one-half grams of the 2-methyl-5-carboethoxy-3-furoylmethylpyridinium bromide [Reaction (II)] was heated for five minutes with 15 cc. of 15% potassium hydroxide, allowed to stand for ten minutes, decolorized, filtered, cooled, and acidified with hydrochloric acid. The ether extracts of the acid solution gave 0.4 g. of 5-methyl-2,4-furandicarboxylic acid, melting at 270–272° and showing no depression in a mixed melting point determination with the dibasic acid obtained by permanganate oxidation.

Decarboxylation of 5-Methyl-2,4-furandicarboxylic Acid.—Decarboxylation experiments were carried out separately with dibasic acid obtained by permanganate oxidation and *via* the pyridinium bromide. In each case 0.04 g. of dibasic acid was heated in a micro vacuum-sublimation apparatus, without a catalyst, for five minutes to 280–300°. The compound subliming up to 200° melted sharply at 100–101°, and a mixed melting point determination with authentic 2-methyl-3-furoic acid showed no depression.

Summary

In the sulfonation of 5-bromo-2-furoic acid and in the acetylation of ethyl 5-methyl-2-furoate the substituent assumes the 4-position, and no significant quantity of isomer appears to form. Accordingly, if in a di-α-substituted furan one of the substituents is an *o,p*-director in benzene and the other a *m*-director, the entering element or group is directed to that β-position contiguous to the *o,p*-director.

AMES, IOWA RECEIVED SEPTEMBER 25, 1933

---

(7) *Chem. Reviews*, **11**, 323 (1932).

(8) Rinkes, *Rec. trav. chim.*, **51**, 349 (1932).

(9) Meyer, *Ber.*, **3**, 112 (1870).

(10) Scott and Johnson, THIS JOURNAL, **54**, 2553 (1932).

(11) Hill and Jennings, *Am. Chem. J.*, **15**, 176 (1893).