[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

ATTEMPTS TO REARRANGE 3,4-SUBSTITUTED-2-ACETYLFURANS TO PYRIDOXINE

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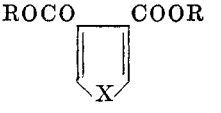
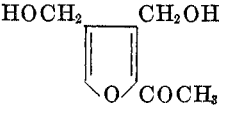
A recent report from this Laboratory described a new and general method for the synthesis of furan, thiophene, and pyrrole-3,4-dicarboxylic esters (I, X = O, S, and NH) (1) based on a four step sequence starting with esters of succinic acid. One of the reasons for the development of this method was to



I

investigate the use of furan-3,4-dicarboxylic acid ester (I, X = O) for a possible new synthesis of pyridoxine (Vitamin B_6). The conversion of 2-acylfurans to 3-hydroxypyridines by means of ammonia and ammonium salts is a rather general reaction.[1] Therefore, the plan was to convert the diester (I, X = O) to II or a closely related derivative and study its possible conversion to pyridoxine.



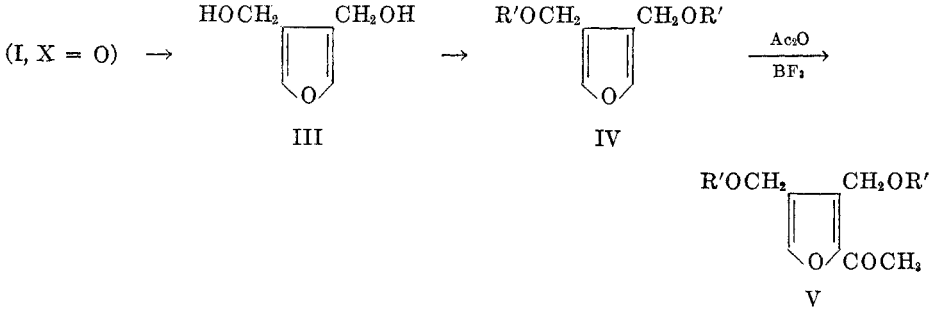
II

The present report describes the preparation of the diacetate of II and the failure of attempts to convert this furan derivative to Vitamin B_6. Since completion of this work, Elming and Clauson-Kaas (3) have developed an elegant six-step conversion of the diacetate of II to pyridoxine in good yield, so it appears that although direct conversion of II to Vitamin B_6 is unfeasible, the basic postulate of employing a furan precursor is a sound one.

Either dimethyl 3,4-furandicarboxylate (I, X = O, R = Me) or the corresponding diethyl ester (I, X = O, R = Et) were reduced by means of lithium aluminum hydride to 3,4-di[hydroxymethyl]furan (III) in good yield. Acylation of the glycol (III) afforded either the diacetate (IV, R′ = $COCH_3$) or the dibenzoate (IV, R′ = COC_6H_5). Friedel-Crafts acetylation of the esters IV proceeded very smoothly with acetic anhydride and boron trifluoride etherate to

[1] Publication of the present work, which was completed in 1949, is prompted by our learning of a parallel and independent investigation reported by Mosher, *et al.* in the accompanying paper (2). We are indebted to Prof. Mosher for communicating to us the results of his work. A survey of the literature on the conversion of 2-acylfurans to 3-hydroxypyridines will not be repeated here, since it is already adequately covered in the companion publication (2).

yield the 2-acetyl-3,4-di[acyloxymethyl]furans (V, R′ = $COCH_3$ or COC_6H_5). The yield of V from I (X = O) was in the range of 30–50%, and the over-all yield in converting ethyl succinate to V in seven steps was 15%.



Attempts then were made to convert the readily available V to pyridoxine. Application of the usual reagents and conditions for the transformation of 2-acetylfurans to 3-hydroxypyridines gave no significant conversion to the desired Vitamin B_6. The crude reaction mixtures were subjected to a sensitive microbiological assay procedure for pyridoxine (3), but no more than trace quantities of Vitamin B_6 activity ever were detected.

Study of the reaction of certain other 3,4-substituted-2-acylfurans with ammonia and ammonium salts is in progress.

EXPERIMENTAL[2]

3,4-Di[hydroxymethyl]furan. Lithium aluminum hydride (12 g.) was dissolved in 350 ml. of absolute ether. The mixture was stirred while a solution of 36.8 g. of dimethyl 3,4-furandicarboxylate (1) in 250 ml. of dry ether was added dropwise during 20 minutes. Stirring was continued for one-half hour, after which time the mixture was treated cautiously with 40 ml. of acetone and then with 25 ml. of water. The solution was stirred well, and the solid was filtered and extracted with two 300-ml. portions of hot ethanol. The alcoholic extracts were concentrated, and the resulting residue was extracted with ether to remove the product from inorganic material. The ether extract was combined with the original ether filtrate, the solvent was removed, and the glycol was distilled under reduced pressure; b.p. 146–148° (6 mm.); n_D^{25} 1.5021; yield, 70%.

Anal. Calc'd for $C_6H_8O_3$: C, 56.24; H, 6.29.
Found: C, 55.35; H, 6.64.

The product was rather hygroscopic and somewhat unstable in the presence of traces of acid. It crystallized on cooling in ice but remelted on warming to room temperature. Reduction of diethyl 3,4-furandicarboxylate with lithium aluminum hydride in a similar fashion gave the 3,4-di[hydroxymethyl]furan in 72% yield.

3,4-Di[acetoxymethyl]furan. 3,4-Di[hydroxymethyl]furan (15 g.) was mixed with 100 ml. of acetic anhydride and 50 ml. of dry pyridine, and the mixture was kept at room temperature for 20 hours. On fractionation *in vacuo* the diacetate was obtained in virtually quantitative yield, b.p. 134–137° (6 mm.); n_D^{25} 1.4666, m.p. 32–35°.

Anal. Calc'd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70.
Found: C, 56.50; H, 5.86.

The diacetate was also prepared very conveniently using the crude, undistilled dialcohol.

3,4-Di[benzoyloxymethyl]furan. 3,4-Di[hydroxymethyl]furan, 12.8 g., was dissolved in 100 ml. of dry pyridine, and to the ice-cooled solution was added, in portions during about

[2] Melting points and boiling points are uncorrected.

five minutes, 29 g. of benzoyl chloride. The solution was kept at room temperature for 16 hours, after which time it was warmed for 20 minutes on a steam-bath. Then it was concentrated *in vacuo* to remove pyridine, and the residue was diluted with 200 ml. of water. The mixture was neutralized with 11 g. of sodium carbonate, and the dibenzoate ester was filtered and washed with water; yield, 30 g. (89%). It was recrystallized from a mixture of benzene and petroleum ether, m.p. 100–102°.

Anal. Calc'd for $C_{20}H_{16}O_5$: C, 71.42; H, 4.80.

Found: C, 71.43; H, 4.57.

2-Acetyl-3,4-di[acetoxymethyl]furan. 3,4-Di[acetoxymethyl]furan (106 g.) was dissolved by heating in 60 ml. of acetic anhydride, and the mixture was cooled to 17°. Boron trifluoride etherate, 10 ml., then was added. An exothermic reaction took place, and the temperature was maintained at 40° by occasional cooling. After 50–60 minutes the exothermic reaction was complete, and the mixture then was kept at 45° for one-half hour. Acetic acid and acetic anhydride were removed by distillation under a vacuum with the bath temperature kept at 45°. The residue was taken up in about four volumes of ether, and the solution was washed several times with sodium bicarbonate solution and then was dried over magnesium sulfate. The ether was distilled, and the product was fractionated *in vacuo*, b.p. 170–180° (6 mm.); yield, 87 g. (68%). It crystallized on cooling and was recrystallized from benzene-petroleum ether, m.p. 55–57°.

Anal. Calc'd for $C_{12}H_{14}O_6$: C, 56.69; H. 5.55.

Found: C, 56.94; H, 5.83.

2-Acetyl-3,4-di[acetoxymethyl]furan oxime. The acetyl compound, 30 g., was mixed with 24.6 g. of hydroxylamine hydrochloride, 19.35 g. of sodium acetate, 100 ml. of water, and 100 ml. of ethanol. The mixture was refluxed for 75 minutes, concentrated *in vacuo*, and the residue was extracted with benzene, ether, and chloroform. The extracts were dried over magnesium sulfate and concentrated to small volume. The product which crystallized was filtered and washed with an ether-petroleum ether mixture; yield, 25.3 g. (79%). A sample was recrystallized from a mixture of benzene and petroleum ether, m.p. 78–79°.

Anal. Calc'd for $C_{12}H_{15}NO_6$: C, 53.53; H, 5.62.

Found: C, 53.80; H, 5.60.

2-Acetyl-3,4-di[benzoyloxymethyl]furan. 3,4-Di[benzoyloxymethyl]furan, 16.8 g., was mixed with 7 ml. of acetic anhydride, and the mixture was warmed to 75° to dissolve the solid. Boron trifluoride etherate, 1 ml., was added, and the temperature was maintained at 60° by occasional cooling for 35 minutes. The reaction mixture was concentrated *in vacuo* to remove acetic acid and acetic anhydride, and the residue was taken up in ether. The resulting solution was washed well with water and then with aqueous sodium bicarbonate. It was dried over magnesium sulfate, and the ether was distilled. The residue was crystallized from a benzene-petroleum ether mixture; yield, 9.0 g. (48%), m.p. 94–96°.

Anal. Calc'd for $C_{22}H_{18}O_6$: C, 69.83; H, 4.79.

Found: C, 70.06; H, 4.96.

Attempts to rearrange 2-acetyl-3,4-di[acetoxymethyl]furan to pyridoxine. Many attempts to rearrange the furan derivative to Vitamin B_6 were made using a wide range of reagents and conditions. Liquid ammonia, aqueous ammonia, and alcoholic ammonia were used with or without added ammonium salts such as ammonium chloride, ammonium sulfate, and ammonium formate. Temperatures in the range of 100° to 160° were employed with heating periods of 1½–3 hours. Several experiments were also carried out using sodium amide in either liquid ammonia or xylene as solvents. In all cases complex and often dark colored reaction mixtures were obtained. In order to determine if pyridoxine had been formed during the reactions, no attempt was made to separate the constituents of the mixtures, but rather the reaction mixtures were submitted to a sensitive microbiological assay procedure for pyridoxine, and the level of the vitamin was determined quantitatively.[3] All assays showed at most only traces of Vitamin B_6 activity in the range of 0.05 mg. to

[3] We are indebted to Mr. Frank Streightoff who carried out these assays according to the method of Stokes, *et al.* (4) using the organism *Neurospora sitophila*; Pyridoxineless No. 9276 of the American Type Culture Collection.

1.70 mg. per gram of starting material. Thus it would appear that the conversion to pyridoxine or its acetyl derivatives was certainly less than one percent. Pure pyridoxine triacetate (5) under the conditions of the microbiological test assayed 44%, so it is obvious that pyridoxine esters, though they were possible products of the rearrangement, were likewise absent from the various reaction mixtures.

SUMMARY

1. Dialkyl 3,4-furandicarboxylates have been converted to 2-acetyl-3,4-di[acyloxymethyl]furans in a three step process.

2. The 2-acetyl-3,4-di[acyloxymethyl]furans on heating in ammoniacal solutions under various conditions have not been converted to pyridoxine to any significant extent.

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(2) WILLIAMS, KAUFMANN, AND MOSHER, *J. Org. Chem.*, **20**, 1139 (1955).
(3) ELMING AND CLAUSON-KAAS, *Acta Chem. Scand.*, **9**, 23 (1955).
(4) STOKES, LARSEN, WOODWARD, AND FOSTER, *J. Biol. Chem.*, **150**, 17 (1943).
(5) HARRIS AND STILLER, U.S. Patent 2,349,267, May 23, 1944.