The Chemical and Electrochemical Oxidation of 2,5-Dimethylfuran to 2,5-Dimethl-2,5-dimethoxydihydrofuran

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2,5-Dimethylfuran has been oxidized to 2,5-dimethyl-2,5-dimethoxydihydrofuran both chemically, with bromine in methanol in the presence of excess sodium carbonate, and electrochemically at a platinum anode. The product is a mixture of geometric isomers which was separated by preparative vpc to the point where each isomer was better than 90% pure. Nmr spectroscopy was used to assign structures to these isomers. Both the chemical and electrochemical oxidations result in a 50:50 mixture of the *cis* and *trans* isomers, within experimental error. An additional product of the electrochemical oxidation is 2,5-bis(methoxymethyl)furan, formed in very low yield with sodium methoxide as the electrolyte and in appreciably higher yield with ammonium nitrate as the electrolyte.

The formation of the *cis*- and *trans*-bicyclo[4.2.0]octa-2,4-diene-7,8-diol diacetates in the electrochemical oxidation of cyclooctatetraene has been shown to proceed nonstereospecifically.[1] The two products appear to be formed under conditions of kinetic rather than thermodynamic control, since the thermodynamically less stable *cis* isomer predominates slightly. This result is in marked contrast to the mercuric acetate oxidation of cyclooctatetraene which proceeds with complete stereospecificity to give only the *trans* isomer.

The stereospecificity of the chemical oxidation can be rationalized[2] as the result of neighboring-group participation at appropriate stages along the reaction path. The different course of the electrochemical oxidation has been attributed[1] to the intervention of different intermediates, the cyclooctatetraene radical cation and/or the dication, which alter or obviate the neighboring-group participation controlling the course of the chemical reaction.

2,5-Dimethylfuran can be oxidized either electrochemically[3] or chemically,[4] with bromine in methanol, to give 2,5-dimethyl-2,5-dimethoxydihydrofuran. In both reactions the product is a mixture of the *cis* and *trans* isomers, which have been neither separated nor determined quantitatively.

The electrochemical oxidation is of special interest, since 2,5-dimethylfuran is oxidized at an even lower potential (1.20 V *vs.* sce)[5] than cyclooctatetraene. It is, therefore, highly probable that the furan is oxidized in the primary electrode process and that the radical cation and/or the dication of 2,5-dimethylfuran are intermediates in the anodic oxidation.

The possible influence of the foregoing on the stereochemical course of the electrochemical reaction is the subject of the present investigation. 2,5-Dimethylfuran has been converted into 2,5-dimethyl-2,5-dimethoxydihydrofuran both chemically and electrochemically. The two geometric isomers have been separated to the point where each isomer was more than 90% pure, with the only contaminant being the other isomer. Structures have been assigned to these isomers, and the stereochemical course of the two reactions has been determined.

Results and Discussion

The chemical conversion of 2,5-dimethylfuran into 2,5-dimethyl-2,5-dimethoxydihydrofuran was effected by the reaction with bromine and methanol in the presence of a large excess of sodium carbonate following the procedure of Levisalles.[4] The product was a mixture of the *cis* isomer, I, and the *trans* isomer, II. These isomers were largely but not completely separated by preparative vpc using a Model A-700 Aerograph Autoprep, and the degree of separation achieved was determined both by nmr spectroscopy and analytical vpc using a Golay column. The nmr method indicated that the sample of the *cis* isomer contained 91% I and 9% II and that the sample of the *trans* isomer contained 94% II and 6% I. The analytical results by vpc were in excellent agreement, indicating that the former sample contained 91.4% I and 8.6% II and that the latter sample contained 95.3% II and 4.7% I.

The structural assignments for the two isomers are based on their nmr spectra, with the isomer having the shorter retention time on vpc being assigned the *cis* structure, I, and the isomer having the longer retention time on vpc being assigned the *trans* structure, II. The spectra were determined at 60 Mc in carbon tetrachloride with tetramethylsilane as an internal standard on a Varian A-60 spectrometer. Both isomers showed simple nmr spectra—three peaks, all of which were singlets. The compound assigned the *cis* structure gave peaks at τ 8.60 (CH_3), 6.78 (OCH_3), and 4.08 (vinyl H), with relative areas 3:3:1. The compound assigned the *trans* structure gave peaks at τ 8.52 (CH_3), 6.88 (OCH_3), and 4.08 (vinyl H), with relative areas 3:3:1.

The basis for the structural assignments indicated above resides in the fact that the chemical shift of a group in the 2 position of the furan ring is affected both by the other group at the 2 position and the magnetic influence exerted by the group at the 5 position that is *cis* to it. Thus, if a 2-methyl is *cis* to a 5-methoxy it will absorb at lower field and lower τ value than if it is *cis* to another 5-methyl group. The same reasoning can be applied to the methoxyl peaks and permit the indicated structural assignments for the two isomers. The very

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[2] V. Georgian, L. Georgian, and A. V. Robertson, *Tetrahedron*, **19**, 1219 (1963).

[3] A. J. Baggaley and R. Brettle, *Chem. Commun.*, 107 (1966); *J. Chem. Soc., C*, 969 (1968).

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[5] L. Eberson and K. Nyberg, *J. Amer. Chem. Soc.*, **88**, 1686 (1966).

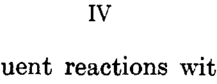
extensive and detailed studies by Gagnaire and Vottero[6] and by Hiraoka, Iwashige, and Iwai[7] on geometrical isomerism in 2,5-substituted furans assures a high degree of probability for the correctness of the present structural assignments in spite of the limited nature of the evidence.

The electrochemical oxidation of 2,5-dimethylfuran was carried out in methanol solution at a platinum anode using both ammonium nitrate and sodium methoxide as the electrolytes. Only the experiments using sodium methoxide are pertinent to the question of the stereochemical course of the reaction, since a trace of sulfuric acid in ether instantaneously converts either isomer, I or II, into a mixture of the two isomers, which on standing undergoes decomposition. The individual isomers were unchanged after standing overnight in the refrigerator, but after 1 month at room temperature there was significant interconversion (~30%) in a reaction accompanied by some decomposition. Fortunately, the two isomers were not interconverted on the Golay column used for the analytical determinations of the isomeric compositions. This is clearly attested to by the coincidence of the results obtained where both the nmr method and the vpc method were used to analyze the same samples.

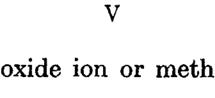
In a typical electrolysis using sodium methoxide, in which 1.94 equiv of charge/mol of the furan was passed through the solution, 5.2% of the 2,5-dimethylfuran was recovered, 20.5% was converted into I, 20.3% was converted into II, and 0.22% was transformed to 2,5-bis(methoxymethyl)furan, III. The two geometric isomers are thus formed in equivalent amounts within experimental error.

This isomeric composition is essentially the same as that observed in the chemical preparation. Analysis by analytical vpc of the 2,5-dimethyl-2,5-dimethoxydihydrofuran fraction from two different chemical preparations gave in one case 48% I and 52% II and in the other case 51% I and 49% II. This is not a surprising result even though the two reactions probably involve significantly different mechanisms. Unlike the cyclooctatetraene oxidation, the present reaction involves neither a valence-bond tautomerism nor potentialities for neighboring-group participation to exert stereochemical control.

The present experiments do not permit a detailed description of the reaction mechanism of the electrochemical oxidation. Since 2,5-dimethylfuran is oxidized at a low anodic potential,[5] it is reasonably probable that the furan is oxidized to the radical cation, IV, and/or the dication, V, at the electrode and that



IV



V

subsequent reactions with methoxide ion or methanol result in I or II.

The formation of even a small amount of 2,5-bis(methoxymethyl)furan, III, is of some interest, since oxidation of the side chain rather than the ring might be considered indicative of a radical mechanism. It is at least conceivable that methoxide ion competes to some extent with the furan in the primary anodic reaction, that some methoxyl radicals are formed, and that hydrogen abstraction from the methyl groups by these radicals leads eventually to III. This possibility receives further support from the fact that the decomposition of benzoyl peroxide in 2,5-dimethylfuran gave 2-methyl-5-benzoyloxymethylfuran and 2,5-bis(benzoyloxmethyl)furan as the only isolable products.

To test this radical reaction possibility the electrochemical oxidation was run with ammonium nitrate as the electrolyte, since nitrate ion is oxidized at a relatively low potential.[8] The result, though not conclusive, is suggestive. An electrochemical oxidation, in which 2.42 equiv of charge/mol of the furan was passed through the solution, resulted in 18.1% I and 17.8% II, and the yield of III increased by more than an order of magnitude to 2.9%.

Experimental Section

2,5-Dimethylfuran was obtained from Pfaltz and Bauer, Inc., and redistilled before use, a middle cut, bp 90.5–91°, being used.

***cis-* and *trans*-2,5-Dimethyl-2,5-dimethoxydihydrofuran.**—The procedure of Levisalles,[4] in which 2,5-dimethylfuran in methanol is treated with bromine in the presence of a large excess of sodium carbonate, was followed exactly. The yield of 2,5-dimethyl-2,5-dimethoxydihydrofuran was 41%, bp 45–50° (9 mm), $n^{28}\mathrm{D}$ 1.4290. The geometric isomers were separated on a Model A-700 Aerograph Autoprep, fitted with a column, 20 ft long × $\frac{3}{8}$ in. in diameter, and packed with 30% SE-30 on 45/60 Chromosorb W. The temperature was programmed from 85 to 200°.

The fraction rich in the isomer having the shorter retention time on vpc, later shown by nmr to be the *cis* isomer, I, had $n^{28}\mathrm{D}$ 1.4260. The fraction rich in the isomer with the longer retention time, the *trans* isomer, II, had $n^{28}\mathrm{D}$ 1.4280.

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found for the fraction rich in I: C, 60.82; H, 8.85. Found for the fraction rich in II: C, 60.55; H, 8.90.

As previously indicated, the purities of the two fractions were determined both by nmr and vpc. These vpc analyses and all others reported were carried out in a Perkin-Elmer Model 154 vapor fractometer, fitted with a Perkin-Elmer large-diameter Golay column of 0.06-in. i.d. and 300-ft length in which the stationary phase was Ucon polyglycol LB-550-X.

2,5-Bis(methoxymethyl)furan has been prepared previously from 2,5-bis(chloromethyl)furan.[9] A sample, sufficient for our purposes, was obtained by refluxing 2,5-dimethyfuran with 2 equiv of N-bromosuccinimide in carbon tetrachloride, removing the succinimide by filtration, and adding excess sodium methoxide in methanol to the filtrate. The mixture was refluxed 1 hr, filtered, concentrated, and distilled at water-pump pressure. The crude product was twice redistilled at 8 mm finally yielding the desired product, bp 79–80°, $n^{28}\mathrm{D}$ 1.4666. This index of refraction agrees with that reported,[9] and the product showed a single peak in vpc.

Electrochemical Preparations.—The electrolysis cell was a water-jacketed, 200-cc beaker fitted with a magnetic stirring bar, a thermometer, and a Teflon cover to which was attached the appropriate electrode assembly. The electrodes were two pieces of platinum, 0.025 cm thick and 2.5 cm wide immersed to a depth of 5 cm and at a separation of 2 cm. Current was provided by a variable-voltage power supply, and the current during the electrolyses was kept constant by manually adjusting the applied voltage as required.

In a typical experiment a solution of ammonium nitrate (12 g, 0.185 mol) and 2,5-dimethylfuran (20 ml, 17.8 g, 0.185 mol) in methanol (130 ml) was electrolyzed at 3 A until 43,200 coulombs of charge was passed through the solution. The

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solution was made strongly basic by adding a solution of sodium methoxide in methanol. Most of the methanol was removed by distillation, and the residue was taken up in ether (500 ml) and extracted with two 50-ml portions of water. The ether solution was dried over magnesium sulfate and then concentrated to 100 ml for vpc analysis.

In experiments with sodium methoxide as the electrolyte, sodium (2.3 g, 0.1 g-atom) was allowed to react with methanol (125 ml). 2,5-Dimethylfuran (25 ml, 22.2 g, 0.231 mol) was added to the solution which was then electrolyzed at 2 A until 43,200 coulombs of charge had passed through the solution. The solution was taken up in ether (500 ml) and extracted with two 100-ml portions of water. The ether solution was dried over magnesium sulfate and concentrated to 100 ml for vpc analysis.

Decomposition of Benzoyl Peroxide in 2,5-Dimethylfuran.—Benzoyl peroxide (4.84 g, 0.02 mol) in 2,5-dimethylfuran (175 ml) was maintained at 75–80° for 24 hr. The solution was taken up in ether (500 ml) and extracted with two 50-ml portions of a solution of sodium bicarbonate (8.2 g) in water (100 ml). Acidification of the bicarbonate extract yielded 1.4 g of benzoic acid, mp 120–122°.

The ether solution was dried over magnesium sulfate, and the ether was removed, yielding 6 g of an oil. This oil was distilled in three portions in a short-path still and yielded first a solid which adhered to the condenser and then a liquid. The total yield of solid, which proved to be the known 2,5-bis(benzoyloxymethyl)furan,[10] was 1.8 g, mp 77–78° after two crystallizations from hexane. The yield of liquid, almost certainly 2-methyl-5-benzoyloxymethylfuran, was 2.1 g. After redistillation it had $n^{24}\text{D}$ 1.5345.

Anal. Calcd for $C_{13}H_{12}O_3$: C, 71.94; H, 5.95. Found: C, 71.02; H, 5.56.

Registry No.—2,5-Dimethylfuran, 3710-43-8; I, 18801-74-6; II, 18801-75-7; 2,5-bis(methoxymethyl)furan, 18801-76-8; 2-methyl-5-benzoyloxymethylfuran, 18801-77-9.

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Nucleosides. LV. Synthesis of a Sulfur-Bridged Thymine Anhydro Nucleoside and Derivatives[1,2]

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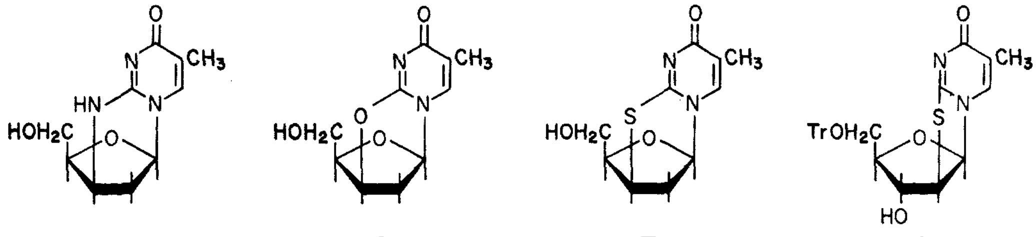
Treatment of 2-*O*-methyl-3′-*O*-mesylthymidine (**13**) in dimethylformamide with hydrogen sulfide afforded (*S*)-2,3′-anhydro-1-(2,3-dideoxy-β-D-*threo*-pentofuranosyl)-2-thiothymine (**3**). Compound **3** was cleaved in alkali to yield the relatively stable mercapto derivative, 1-(2,3-dideoxy-3-mercapto-β-D-*threo*-pentofuranosyl)-thymine (**14**). Acid-catalyzed treatment of **14** with acetone gave the oxathiolane derivative, 1-[2,3-dideoxy-3,5(*S*,*O*)-isopropylidene-β-D-*threo*-pentofuranosyl]thymine (**15**). Compound **14** was oxidized to the intermolecular disulfide, **17**. The sulfur-bridged anhydro nucleoside (**3**) was also obtained by treatment of 2,5′-anhydro-3′-*O*-mesylthymidine (**5**) in dimethylformamide with hydrogen sulfide. From the latter reaction a second product was obtained and identified as the internal disulfide of 1-(trideoxy-3,5-dimercapto-β-D-*threo*-pentofuranosyl)thymine (**8**). An alternate and preferred synthesis of **8** from di-*O*-mesylthymidine (**11**) is described. The ultraviolet absorption spectrum of the 3′-mercapto derivative (**14**) as a function of pH revealed the presence of *two* dissociations with apparent pK_a values of 10.2 and ~8.4. The higher of these is due to ionization of the N-3 proton. The ionization associated with pK_a ~ 8.4 is interpreted as a reflection of the rupture of a weak hydrogen bond between the 3′-mercapto group and the 2-carbonyl.

Previous studies[3] on the use of anhydropyrimidine nucleosides as intermediates for the alteration of the sugar moiety led to the synthesis of nitrogen-bridged isosteres (**1**) of the 2,3′-anhydro nucleoside (**2**) (Scheme I). An obvious corollary to this work would be the introduction of sulfur as the bridge atom, such as **3**. Such "(*S*)-2,3′-anhydro" or epithio structures could serve as precursors for the preparation of 2′,3′-dideoxy-3′-mercapto nucleosides of the *xylo* (*lyxo*) configuration and possibly could lead by reduction to nucleosides devoid of the 2-oxo substituent in the aglycon.

The first synthesis of a sulfur-bridged anhydro nucleoside was achieved by Shaw and Warrener[4] starting from preformed 2-thioribofuranosylthymine which gave, subsequently, the (*S*)-2,2′-anhydro nucleoside derivative **4**. Later, several studies[5] described the

SCHEME I



1 2 3 4

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[1] This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U.S. Public Health Service (Grant No. CA 08748).

[2] Presented in part at the 21st *Intern. Congr. Pure Appl. Chem., Prague, 1967*, in press.

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[4] G. Shaw and R. N. Warrener, *J. Chem. Soc.*, 50 (1959).

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