Notes

A Sigmatropic Rearrangement Involving Dimethyl Sulfoxide during an Oxidation of a Carbohydrate Derivative

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Dimethyl sulfoxide activated with dicyclohexylcarbodiimide, an acid anhydride, or another electrophilic reagent is a useful, mild oxidizing agent widely used in carbohydrate chemistry.[1] The activated dimethyl sulfoxide also reacts with phenols, aromatic amines, and thiophenols to give sulfonium salts, which through the corresponding ylides undergo sigmatropic rearrangements giving (methylthio)methyl substituted compounds.[2,3] However, we have found no report of this sigmatropic reaction in aliphatic systems. We report here a sigmatropic rearrangement involving dimethyl sulfoxide during the oxidation of a carbohydrate derivative.

As part of a synthetic effort related to the acyltetramic acid antibiotics streptolydigin[4] and tirandamycin,[5] we required, as an intermediate, methyl 4,6-*O*-benzylidene-2-methyl-2-deoxy-α-D-*threo*-hex-3-ulopyranoside (**5**), which has been obtained[6,7] by the oxidation of **4** with dimethyl sulfoxide and acetic anhydride. In our experiments, maximum yields of **5** were obtained at room temperature in 4.25 h. However, when the reaction was allowed to proceed for a much longer time, a different product was isolated. The compound was characterized to be methyl (2*R*)-4,6-*O*-benzylidene-2-methyl-2-((methylthio)-methyl)-2-deoxy-α-D-*threo*-hex-3-ulopyranoside (**6**, Scheme I) on the basis of ^{1}H NMR, ^{13}C NMR, IR, and mass spectra (cf. Experimental Section). The stereochemistry was established and the gross structure confirmed by X-ray crystallography (Figure 1).

The formation of **6** can be explained by the sigmatropic rearrangement sequence in Scheme II. Following the oxidation of the alcohol to the ketone **5**, the enolate of the latter, a, reacts with the acylated dimethyl sulfoxide to give the sulfonium salt b. Proton abstraction then gives the ylide c, which undergoes a sigmatropic migration. Formation of a single diastereomer could be explained by the steric effect of the anomeric methoxyl group, which hinders approach of the (methylthio)methyl group from the underside of the ring. According to this mechanism, the

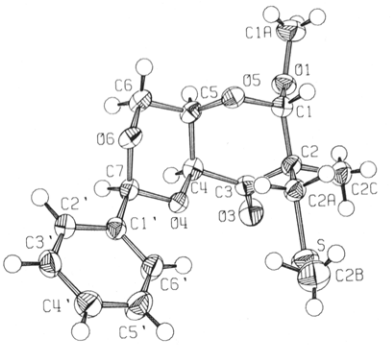
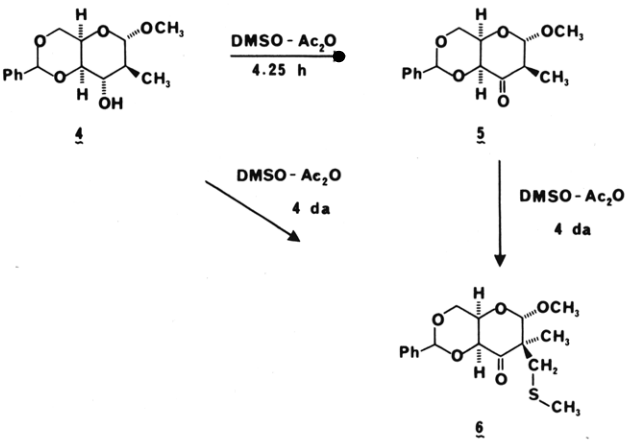
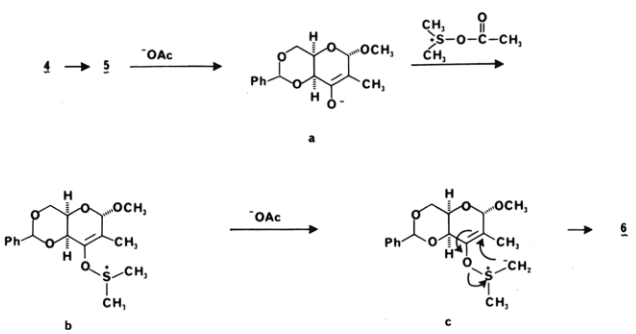


Figure 1. ORTEP drawing of methyl (2*R*)-4,6-*O*-benzylidene-2-methyl-2-((methylthio)methyl)-2-deoxy-α-D-hex-3-ulopyranoside, **6**, showing 35% electron-density probability ellipsoids.

Scheme I



Scheme II



ketone **5** is an intermediate and, when preformed **5** was allowed to react with dimethyl sulfoxide–acetic anhydride, **6** was indeed obtained. As expected, a pentadeuterio **6** (M_r = 343) was obtained when **4** was allowed to react with [$^2H_6$]dimethyl sulfoxide–acetic anhydride. The deuterium atoms were located in the methylene and methyl groups attached to sulfur by ^{1}H NMR spectroscopy, which indicated the appropriate protons were missing (cf. Experimental Section). This rearrangement is similar to that reported for phenol with dicyclohexylcarbodiimide and dimethyl sulfoxide.[2]

Desulfurization of **6** with Raney nickel gave the *gem*-dimethyl compound **7**, providing one of the few reported examples of a *gem*-dialkyl carbohydrate.[8] Desulfurization

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(2) (a) Burdon, M. G.; Moffatt, J. G. *J. Am. Chem. Soc.* **1966**, *88*, 5855–5864. (b) Burdon, M. G.; Moffatt, J. G. *Ibid.* **1967**, *89*, 4725–4735. (c) Hayashi, Y.; Oda, R. *J. Org. Chem.* **1967**, *32*, 457–460.
(3) Hiraki, Y.; Kamiya, M.; Tanikaga, R.; Ono, N.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 447–452 and references cited therein.
(4) Rinehart, K. L., Jr.; Beck, J. R.; Borders, D. B.; Kinstle, T. H.; Krauss, D. *J. Am. Chem. Soc.* **1963**, *85*, 4038–4039.
(5) Duchamp, D. J.; Branfman, A. R.; Button, A. C.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 4077–4078.
(6) Costa, S. S.; Lagrange, A.; Olesker, A.; Lukacs, G.; Thang, T. T. *J. Chem. Soc., Chem. Commun.* **1980**, 721–723.
(7) Lukacs, G., communication.

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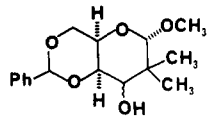
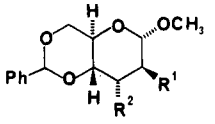
of pentadeuterio **6** gave dideuterio **7**. One of the methyl singlets in the ^1H NMR spectrum of **7** (at 1.28 ppm) was replaced by a broad one-proton peak in dideuterio **7**, from which the chemical shifts for the *gem*-dimethyl group were assigned (cf. Experimental Section).

Reactions employing other sulfoxides such as diethyl sulfoxide, tetramethylene sulfoxide, dibenzyl sulfoxide, and methyl phenyl sulfoxide under the same conditions did not produce similar rearrangement products. The same reaction carried out with the sugar derivatives **8** and **9**,[9] the former differing only in stereochemistry from **4**, stopped at the ketone stage and did not proceed further.



7



8 : $R^1 = CH_3$, $R^2 = OH$

9 : $R^1 = OH$, $R^2 = CH_3$

Experimental Section

General Data. Melting points, determined on a Kofler hot stage, are uncorrected. Infrared spectra were recorded on a Nicolet FT-IR spectrometer, Model 7199C, ^1H NMR spectra on a Varian HR 220 spectrometer by L. Johnson, and ^{13}C NMR spectra on a Varian XL-100 spectrometer by D. Warrenfeltz. Chemical shifts are reported in parts per million from internal tetramethylsilane standard. Low-resolution mass spectra were obtained by Dr. R. M. Milberg, M. E. Hemling, and M. K. Cochran on a Finnigan MAT CH5 mass spectrometer and high resolution data on a Finnigan MAT 731 mass spectrometer by J. C. Cook. Microanalyses were obtained by J. Nemeth and associates.

Reagents used were of reagent grade. Dimethyl sulfoxide was stored over calcium hydride, filtered, and mixed with an equal volume of dry benzene. Benzene was then distilled off under normal pressure, and dimethyl sulfoxide was distilled in vacuo. Acetic anhydride was distilled. Methyl α-D-galactopyranoside was purchased from Sigma Chemical Co.

Methyl 4,6-*O*-benzylidene-α-D-galactopyranoside (1)[10] [yield 75%, mp 175–177 °C (lit.[10] 177–178 °C)], **methyl 4,6-*O*-benzylidene-2,3-di-*O*-tosyl-α-D-galactopyranoside (2)**[10] [yield 96%, mp 179–181 °C (lit.[10] 182–183 °C)], **methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-gulopyranoside (3)**[10] [yield 49%, mp 178–179 °C (lit.[10] 178–179 °C)], and **methyl 4,6-*O*-benzylidene-2-deoxy-2-methyl-α-D-idopyranoside (4)**[11] [yield 80%, mp 118–119 °C (lit.[11] 117–118 °C)] were prepared according to published procedures.

Methyl (2*R*)-4,6-*O*-Benzylidene-2-methyl-2-deoxy-α-D-*threo*-hex-3-ulopyranoside (5).[7] A mixture of **4** (1 g), dimethyl sulfoxide (20 mL), and acetic anhydride (20 mL) was stirred at room temperature for 4.25 h, then poured into ice-cold water, and stirred for a few minutes. The precipitate was filtered and washed with cold water to give **5**; yield 0.82 g (83%). A small portion was recrystallized from hexane–chloroform: mp 156–157 °C (lit.[6] 140 °C); ^1H NMR ($CDCl_3$) 1.39 (d, 3 H, 2-CH_3, J = 7 Hz), 2.65 (dq, 1 H, H-2, J = 7.3, 2.7 Hz), 3.41 (s, 3 H, OCH_3), 4.05–4.45 (m, 4 H, H-4, H-5, and H-6), 4.81 (d, 1 H, H-1, J = 2.5 Hz), 5.54 (s, 1 H, H-7), 7.26–7.52 ppm (m, 5 H, ArH). Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.75; H, 6.48. Found: C, 64.47; H, 6.30.

Methyl (2*R*)-4,6-*O*-Benzylidene-2-methyl-2-((methylthio)methyl)-2-deoxy-α-D-*threo*-hex-3-ulopyranoside (6). A. From 4. A mixture of **4** (0.979 g), dimethyl sulfoxide[12] (20 mL), and acetic anhydride[12] (20 mL) was stirred for 4 days at room temperature, poured into water, and neutralized with sodium bicarbonate. The aqueous solution was extracted with chloroform, dried, and concentrated to give a dimethyl sulfoxide containing residue which was lyophilized to give a yellow solid. Chromatography of the solid over silica gel (petroleum ether–ethyl acetate, 1:1) gave **6** as a colorless crystalline solid: yield 0.70 g (59%); mp 146–148 °C; IR (KBr) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) 1.16 (s, 3 H, 2-CH_3), 1.98 (s, 3 H, SCH_3), 3.21 (AB quartet, 2 H, CH_2S, J = 12.8 Hz), 3.38 (s, 3 H, OCH_3), 3.9 (d, 1 H, H-5, J = 0.9 Hz), 4.18 (dd, 1 H, H_a-6), 4.40 (d, 1 H, H_e-6), 4.32 (d, 1 H, H-4, J = 1.4 Hz), 4.89 (s, 1 H, H-1), 5.54 (s, 1 H, H-7), 7.34–7.54 ppm (m, 5 H, ArH); ^{13}C NMR ($CDCl_3$) 16.3 (off-resonance, q, CCH_3) 17.5 (q, SCH_3), 41.3 (t, CH_2S), 54.8 (s, C-2), 55.7 (q, OCH_3), 63.4 (d, C-5), 69.1 (d, C-6), 79.4 (d, C-4), 100.9 (d, C-1), 105.9 (d, C-7), 126.2 and 128.2 (d, C-2′,3′,5′,6′), 129.2 (d, C-4′), 137.4 (s, C-1′), 202 ppm (s, C-3). Anal. Calcd for $C_{17}H_{22}O_5S$: C, 60.35; H, 6.50; mol wt, 338.1188. Found: C, 60.23; H, 6.52; mol wt, 338.1192 [HR electron ionization (EI)MS]. The X-ray crystallographic determination and data are found in the supplementary material.

B. From 5. A mixture of the ketone **5** (0.15 g, 0.54 mmol), dimethyl sulfoxide (5 mL), and acetic anhydride (5 mL) was stirred for 4 days and worked up as in A to give 0.110 g of solid. Silica gel chromatography gave 0.07 g (38%) of **6**: mp 146–148 °C; ^1H NMR, spectrum identical with that for **6** obtained in A.

Reaction of 4 with [$^2H_6$]Dimethyl Sulfoxide and Acetic Anhydride. A solution of **4** (0.15 g, 0.54 mmol), [$^2H_6$]dimethyl sulfoxide (4 mL), and acetic anhydride (4 mL) was stirred at room temperature for 4 days and worked up as for the unlabeled compound. Chromatographic purification of the residue gave pure pentadeuterio **6**: yield 0.098 g (53%); mp 142–145 °C; ^1H NMR ($CDCl_3$) 1.16 (s, 3 H, 2-CH_3), 3.38 (s, 3 H, OCH_3), 3.90 (b s, 1 H, H-5), 4.31 (d, 1 H, H-4, J = 1.6 Hz), 4.18 (dd, 1 H, H_a-6, J = 13, 2 Hz), 4.41 (d, 1 H, H_e-6, J = 13 Hz), 4.89 (s, 1 H, H-1), 5.54 (s, 1 H, H-7), 7.34–7.52 ppm (m, 5 H, ArH). Anal. Calcd for $C_{17}H_{17}D_5O_5S$: mol wt, 343.1502. Found: mol wt, 343.1504 (HREIMS).

Desulfurization of 6 with Raney Nickel. Raney nickel (ca. 5 g) was added to a solution of **6** (0.25 g) in ethanol (25 mL), and the mixture was stirred overnight at room temperature. Nickel was filtered off, and the ethanol solution was concentrated. Chromatographic separation (silica gel, ethyl acetate–hexane, 1:1) gave two fractions. The first fraction, which contained small amounts of starting material as impurity, was further purified on HPLC (silica gel, hexane–ethyl acetate, 85:15) to give pure **7**: yield 0.036 g (22%, based on recovered starting material); ^1H NMR ($CDCl_3$) 1.11 (s, 3 H, α-2-CH_3), 1.28 (s, 3 H, β-2-CH_3), 3.40 (s, 3 H, OCH_3), 3.45 (s, 1 H, OH), 3.48 (b s, H-3), 3.81 (d, 1 H, H-5, J = 0.8 Hz), 4.06 (d, 1 H, H-4, J = 1.4 Hz), 4.14 (dd, 1 H, H_a-6, J = 12.5, 2 Hz), 4.34 (d, 1 H, H_e-6, J = 12.5 Hz), 4.43 (s, 1 H, H-1), 5.48 (s, 1 H, H-7), 7.33–7.51 ppm (m, 5 H, ArH). Anal. Calcd for $C_{16}H_{22}O_5$: mol wt, 294.1469. Found: mol wt, 294.1468 (HREIMS).

Desulfurization of Pentadeuterio 6 with Raney Nickel. Raney nickel (ca. 2 g) was added to a solution of pentadeuterio **6** (0.058 g) in ethanol (20 mL), and the mixture was stirred overnight. Nickel was filtered off, and the ethanol solution was concentrated. Chromatographic purification (preparative TLC, ethyl acetate–hexane, 1:1) gave an oil which was further purified on HPLC (silica gel, hexane–ethyl acetate, 85:15) to give pure dideuterio **7**: yield 0.01 g (20%); ^1H NMR ($CDCl_3$) 1.11 (s, 3 H, 2-CH_3), 1.24 (b s, 1 H, 2-CD_2H), 3.41 (s, 3 H, OCH_3), 3.47 (s, 1 H, H-3), 3.82 (s, 1 H, H-5), 4.07 (d, 1 H, H-4, J = 1.8 Hz), 4.15 (dd, 1 H, H_a-6, J = 12.5, 2 Hz), 4.35 (d, 1 H, H_e-6, J = 12.5 Hz), 4.44 (s, 1 H, H-1), 5.49 (s, 1 H, H-7), 7.34–7.52 ppm (m, 5 H, ArH). Anal. Calcd for $C_{16}H_{20}D_2O_5$: mol wt, 296.1593. Found: mol wt, 296.1594 (HREIMS).

Acknowledgment. This work was supported by NIH research Grant AI 01278 from the National Institute of Allergy and Infectious Diseases. Mass spectra were obtained on instruments supported in part by a grant from

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(11) Lagrange, A.; Olesker, A.; Costa, S. S.; Lukacs, G.; Thang, T. T. *Carbohydr. Res.* **1982**, *110*, 159–164.

(12) A mixture of 200 mL of dimethyl sulfoxide and 10 mL of acetic anhydride gave the same yield of **6**.

the National Institute of General Medical Sciences (GM 27029). We thank Dr. S. R. Wilson, University of Illinois, for X-ray structure determination.

Registry No. 4, 75879-82-2; 5, 75837-51-3; 6, 93403-85-1; 6-d_5, 93403-87-3; 7, 93403-86-2; 7-d_2, 93403-88-4; Me_2SO, 67-68-5; Me_2SO-d_6, 2206-27-1.

Supplementary Material Available: A description of X-ray crystal structure determination and listings of positional and thermal parameters and bond distances and angles for 6 (6 pages). Ordering information is given on any current masthead page.

Base-Induced Reaction of Acetylacetone with Substituted Benzoquinones[1]

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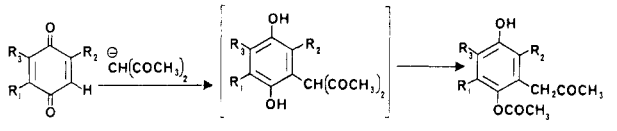
Received August 23, 1983

Among the prodigious efforts of Lee Irwin Smith and his co-workers in unraveling the rich chemistry enjoyed by quinone/enolate anion interactions[3] is the report of the reaction of the sodium salt of acetylacetone (2,4-pentanedione) with 2,3,5-trimethyl-1,4-benzoquinone (**1a**).[4] The product was identified as the (diacetylmethyl)-hydroquinone adduct **2a** apparently on the basis of analysis and conversion products. We desired the quinones deriving from such adducts[5] in connection with other work[6] and have studied the reaction of acetylacetone with a variety of substituted benzoquinones under basic conditions. The results described herein suggest a revised structure for Smith's adduct **2a** and reveal an additional reaction pathway for the base-induced reaction of quinones and acetylacetone.[7]

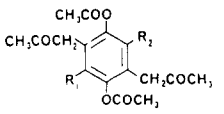


1 2 3

a $R_1=R_2=R_3=CH_3$
b $R_1=R_2=CH_3$, $R_3=H$
c $R_1=R_2=C_6H_5$, $R_3=H$
d $R_1=R_2=Cl$, $R_3=H$
e $R_1=H$, $R_2=R_3=Cl$

The reaction of trimethylbenzoquinone (**1a**) and acetylacetone in the presence of 1 equiv of sodium ethoxide in ethanol, as described by Smith,[4] gave varying yields of a white solid after acidification, melting as previously reported (129–130 °C). However, the spectral data obtained for this compound were consistent with the hydroquinone monoacetate **3a** resulting from **2a** via an acyl transfer. Particularly diagnostic were the two-proton singlet (benzylic hydrogens) at δ 3.52 in the ^1H NMR spectrum of **3a** and the ester and ketone carbonyl resonances in the ^{13}C NMR spectrum at 169.9 and 206.5 ppm, respectively. Treatment of **3a** with acetic anhydride gave the corresponding hydroquinone diacetate, while refluxing in acidic methanol converted **3a** to the benzofuran **5a**. Both of these transformations were described by Smith[4] for the supposed (diacetylmethyl)hydroquinone, **2a**, and are consistent with the actual structure **3a**. The formation of **5a** from **3a** results from initial hydrolysis, intramolecular hemiketal formation, and dehydration.

Similar reactions of 2,5-dimethyl-1,4-benzoquinone (**1b**) and 2,5-diphenyl-1,4-benzoquinone (**1c**) with acetylacetone enolate gave the analogously rearranged adducts **3b** and **3c**, respectively, in 60–75% yields. We found benzyltrimethylammonium hydroxide (Triton B) to be a convenient base for promoting the reaction, although KOH and $NaOCH_3$ produced almost identical results. In the case of these disubstituted quinones a small (<10%) amount of a minor product was obtained that is formulated respectively as **4b** and **4c** on the basis of spectral data. The formation of such diadducts apparently arise via a second addition of the enolate to the quinone formed by oxidation of the hydroquinone resulting from initial conjugate addition. The corresponding benzofurans **5** and benzodifurans **6** were obtained after refluxing in acidic methanol, thus establishing a convenient two-step synthesis of these substituted heterocyclic systems.[8]



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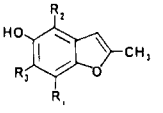

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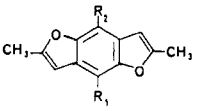

6

The reaction of 2,5-dichloro-1,4-benzoquinone (**1d**) under similar conditions produced the unrearranged hydroquinone **7** which precipitated from the methanolic reaction mixture. The rearranged adducts **3d** and **4d** were detected in the ^1H NMR spectrum of the crude product but were not isolated. The high oxidation potential of the starting quinone apparently causes oxidation of the initially formed hydroquinone **2d** prior to acyl transfer, and then a second addition of enolate occurs. The limited solubility of **7** precludes subsequent rearrangement. But when **7** was dissolved in THF and treated with Triton B, **4d** was isolated in nearly quantitative yield. Concomitant reduction of starting quinone during the reaction is evident from the isolation of the diacetate of 2,5-dichloro-1,4-benzohydroquinone after acetylation of the concentrated filtrate from the removal of **7**. The diacetate of **2d** was also isolated from the acetylation mixture by fractional crystallization.

The slow addition of the quinone to acetylacetone (2 equiv) in the presence of Triton B gave **7** in 68% yield (based on **1b**). A simple recycling procedure utilizing Ag_2O oxidation of the crude reaction mixture and addition of excess acetylacetone resulted in an aggregate 78% con-

(1) Portions of this work were presented at the 1977 Pacific Conference on Chemistry and Spectroscopy, Anaheim, CA, Oct 1977, abstr no. 44.

(2) Address correspondence to the University of Connecticut.

(3) For a fine review see: Finley, K. T. In "The Chemistry of the Quinonoid Compounds"; Patei, S., Ed.; Wiley: London, 1974; pp 877–1144, Chapter 17.

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(5) For previous reports of such quinones see: (a) Bernatek, E.; Ramstad, S. *Acta Chem. Scand.* **1953**, *7*, 1351–6. (b) Bernatek, E.; Johnsgard, M.; Stensrud, T. *Ibid.* **1967**, *21*, 575–5. (c) Kallmayer, H. J. *Arch. Pharm. (Weinheim, Ger.)* **1973**, *306*, 257–67. (d) Wikholm, R. J. Ph.D. Dissertation, University of California, Irvine, 1971; pp 105–6.

(6) Wikholm, R. J.; Moore, H. W. *J. Am. Chem. Soc.* **1972**, *94*, 6152–8.

(7) After this work was completed and disclosed,[1] the correct structure for Smith's adduct was reported in the Russian literature: Makovetskii, V. P.; Dzvinchuk, I. B.; Svishchuck, A. A. *Ukr. Khim. Zh. (Russ. Ed.)* **1978**, *44*, 996–8; *Chem. Abstr.* **1978**, *90*, 22500.

(8) These benzofurans and benzodifurans will be the subject of a future communication: Wikholm, R. J., to be submitted for publication.

0022-3263/85/1950-0382$01.50/0