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## SHORT COMMUNICATIONS

*Dedicated to Full Member of the Russian Academy of Sciences B.A. Trofimov on his 70th anniversary*

# Synthesis of 2,5-Bis(butylsulfanyl)-2,3-dihydro-4*H*-pyran-2-carbaldehyde Acetals and Their Unexpected Isomerization

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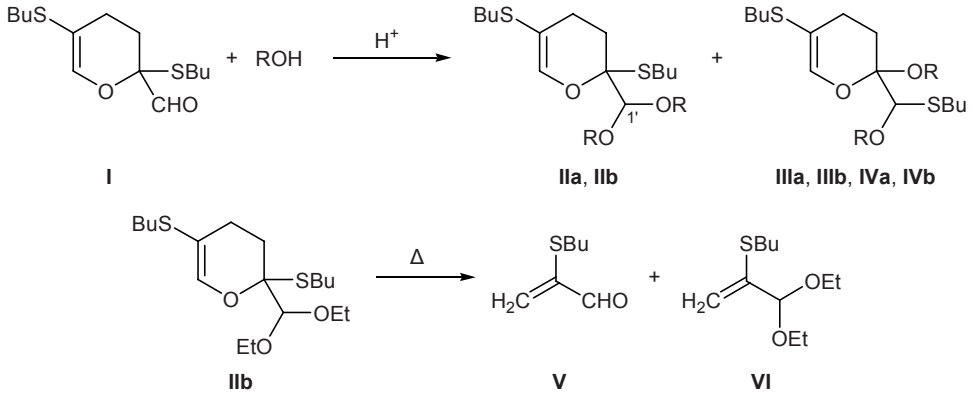
2,5-Bis(alkylsulfanyl)-2,3-dihydro-4*H*-pyran-2-carbaldehydes exhibit bacteriostatic effect [1]. 2,5-Bis(butylsulfanyl)-2,3-dihydro-4*H*-pyran-2-carbaldehyde is known as a strong and safe antiseptic [2]. We examined its reactions with alcohols in order to obtain new potential biologically active derivatives. Unlike 2,5-dialkoxy-2,3-dihydro-4*H*-pyran-2-carbaldehydes [3] which take up alcohols at the endocyclic double bond, the reaction of sulfur-containing analog **I** with alcohols in acid medium at room temperature (i.e., under comparable conditions) occurred at the carbonyl group. However, apart from the expected symmetric dialkyl acetal **II**, diastereoisomeric mixed acetals **III** and **IV** were always formed, regardless of the acid taken as catalyst (*p*-TsOH, $HClO_4$, $CF_3COOH$) or alcohol (MeOH, EtOH); the products are readily detected by gas chromatography–mass spectrometry.

To determine the product structure, isomer mixture obtained in the reaction of aldehyde **I** with methanol were separated by high-performance liquid chromatography (HPLC). The reaction with methanol was selected as model process, taking into account more facile identification of methyl derivatives by NMR spectroscopy. Judging by the intensities of signals from the acetal CH protons at δ 4.27 (**IIa**), 4.53 (**IIIa**), and 4.47 ppm (**IVa**) in the $^1$H NMR spectra, the product ratio changed from 2:1:1 to 1:1:(1–2) in 7–10 days, the conversion of the initial aldehyde being 80–100%. Analysis of the $^1$H and $^{13}$C NMR spectra of the first isomer allowed us to identify it as symmetric dimethyl acetal **IIa**. Formalistically, two other isomers **IIIa** and **IVa** result from exchange of OMe and SBu groups in the vicinal acetal and hemithioketal moieties (at the $C^{1'}$ and $C^2$ atoms).




R = Me (**a**), Et (**b**).

Compound **IIIa** was isolated as individual substance, and its structure was determined by $^1$H and $^{13}$C NMR spectroscopy using two-dimensional heteronuclear correlation techniques (HMBC and HSQC). The HMBC spectrum displayed a cross peak between the methoxy protons and C$^{1'}$, as well as a cross peak between protons in the second methoxy group and C$^2$. In addition, correlations between C$^2$ and 1′-H and between 6-H and C$^2$ and C$^5$ were observed. The $^1$H and $^{13}$C chemical shifts of compounds **IIIa** and **IVa** were very similar, indicating that these compounds are diastereoisomers.

Likewise, aldehyde **I** reacted with ethanol. The conversion of **I** in the presence of 10 mol % of *p*-toluenesulfonic acid was 24% in 14 days, while in the presence of 10 mol % of $HClO_4$ it was 50% in 24 h (according to the $^1$H NMR data). The ratio of stereoisomeric mixed acetals **IIIb**/**IVb** and acetal **IIb** was 2:5. Insofar as isomeric ethyl acetal mixture **IIb**–**IVb** boiled at a higher temperature, as compared to methyl analogs, we failed to isolate individual isomers by vacuum (1 mm) or molecular distillation ($10^{-3}$ mm). Heating to 175–200°C resulted in retro-Diels–Alder decomposition of **IIb** into 2-butylsulfanylprop-2-enal (**V**) and the corresponding acetal **VI**. Partial decomposition was also observed during GC–MS analysis (injector temperature 250°C; oven temperature 280°C). Therefore, the chromatograms contained a sharp peak of acetal **IIa** or **IIb** and two broadened peaks due to compounds **V** and **VI** which left the column as they gradually formed. Analogous facile retro-Diels–Alder reaction was observed previously for initial aldehyde **I** [4]. Unlike acetals **II**, isomeric products **III** and **IV** turned out to be thermally stable.

Acetal mixtures **IIb**–**IVb** isolated by column chromatography did not change their composition on prolonged storage (20°C, 3.5 weeks) or slight heating in chloroform (55°C, 2 h). The ratio of isomers **IIa**–**IVb** (1:1:1.3) in the three fractions isolated by high-vacuum distillation also did not change in the absence of acid even when the still temperature was raised from 127 to 140°C (over a period of 6 h). However, when isomer mixture **IIb**–**IVb** was kept in $CDCl_3$ in the presence of 10 mol % of *p*-toluenesulfonic acid for a month, their ratio changed toward increased fraction of mixed acetals **IIIb** and **IVb** (according to the $^1$H NMR data). These findings suggest that the isomerization of acetals **II** is not an intramolecular process (cf. spontaneous isomerization of 2-alkoxy-2-R-sulfanylpropanals into 1-alkoxy-1-R-sulfanylpropanones [5]), but it requires the presence of a catalyst.

**2,5-Bis(butylsulfanyl)-2-dimethoxymethyl-2,3-dihydro-4*H*-pyran (IIa).** A mixture of 5.6 g (19 mmol) of 2,5-bis(butylsulfanyl)-2,3-dihydro-4*H*-pyran-2-carbaldehyde, 65 ml of anhydrous methanol, 0.336 g (10 mol%) of *p*-toluenesulfonic acid, and 5 g of preliminarily calcined 3-Å molecular sieves was kept for 14 days at room temperature. The mixture was then passed through a column charged with potassium carbonate, and the solvent was removed under reduced pressure. Molecular distillation at a residual pressure of $10^{-3}$ mm (bath temperature 127–140°C) gave 4.5 g (69%) of acetal mixture **IIa**–**IVa**. Individual isomers were isolated by HPLC.

Compound **IIa**. $^1$H NMR spectrum, δ, ppm: 0.91 t and 0.92 t (6H, C**H**$_3$CH$_2$, $^3J$ = 6.9 Hz), 1.38 m (4H, CH$_3$C**H**$_2$), 1.51 m (4H, CH$_3$CH$_2$C**H**$_2$), 1.83 m and 2.66 m (2H, 3-H), 2.08 m and 2.46 m (4H, SCH$_2$), 2.55 m (2H, 4-H), 3.52 s (6H, OCH$_3$), 4.27 s (1H, 1′-H), 6.54 s (1H, 6-H). $^{13}$C NMR spectrum, $\delta_C$, ppm: 13.83 (CH$_3$); 21.73, 22.26, 23.53 (CH$_3$**C**H$_2$**C**H$_2$); 25.84 (C$^4$); 27.86 (C$^3$); 31.60, 31.87, 32.28 (SCH$_2$CH$_2$CH$_2$); 57.22 (OCH$_3$); 57.80 (OCH$_3$); 96.25 (C$^2$); 107.69 (C$^5$, C$^6$); 108.63 (C$^{1'}$). Mass spectrum, *m*/*z* ($I_{rel}$, %): 334 (3.8) [*M*]$^+$, 302 (69.0) [*M* – MeOH], 259 (6.7) [*M* – CH(OMe)$_2$], 213 (57.1) [*M* – MeOH – BuS], 185 (13.6), 160 (21.7), 123 (33.3), 101 (18.0) 75 (100) [CH(OMe)$_2$], 41(9.5), 29 (7.4) [Et].

**5-Butylsulfanyl-2-[(butylsulfanyl)(methoxy)-methyl]-2-methoxy-2,3-dihydro-4*H*-pyran (IIIa).** $^1$H NMR spectrum, δ, ppm: 0.91 t and 0.92 t (6H, C**H**$_3$CH$_2$, $^3J$ = 7.4 Hz), 1.42 m (4H, CH$_3$C**H**$_2$), 1.50 m and 1.59 m (2H each, CH$_3$CH$_2$C**H**$_2$), 2.00 m (3H) and 2.32 m (1H) (3-H, 4-H), 2.49 t (2H, SCH$_2$, $^3J$ = 6.9 Hz), 2.62 m (2H, SCH$_2$), 3.30 s (3H, 2-OCH$_3$), 3.48 s (3H, 1′-OCH$_3$), 4.53 s (1H, 1′-H), 6.56 s (1H, 6-H). $^{13}$C NMR spectrum, $\delta_C$, ppm: 13.96 (CH$_3$); 21.85, 22.20, 22.8 (CH$_2$); 25.90 (C$^4$); 30.52–32.40 (CH$_2$, C$^3$); 50.01 (2-OCH$_3$); 58.43 (1′-OCH$_3$); 89.94 (C$^{1'}$); 100.35 (C$^5$); 143.4 (C$^6$). Mass spectrum, *m*/*z* ($I_{rel}$, %): 334 (4.3) [*M*]$^+$, 302 (16.0) [*M* – MeOH], 244 (21.7) [*M* – BuSH], 213 (34.8) [*M* – MeOH – BuS], 201 (70.2) [*M* – CH(OMe)SBu], 185 (29.4), 155 (32.6), 128 (20.6), 101 (100) [*M* – CH(OMe)SBu – MeOH], 75 (13.9), 57 (10.6) [Bu], 29 (10.9).

**Isomer IVa.** $^1$H NMR spectrum, δ, ppm: 0.91 t and 0.92 t (6H, C**H**$_3$CH$_2$), 1.42 m (4H, CH$_3$C**H**$_2$), 1.49 m and 1.60 m (2H each, CH$_3$CH$_2$C**H**$_2$), 2.05 m (4H, 3-H,

4-H), 2.50 t (2H, $CH_2S$, $^3J$ = 6.5 Hz ), 2.62 m (2H, $CH_2S$), 3.28 s (3H, 2-$OCH_3$), 3.50 s (3H, 1′-$OCH_3$), 4.47 s (1H, 1′-H), 6.53 s (1H, 6-H). $^{13}$C NMR spectrum, $\delta_C$, ppm: 13.68, 13.72 ($CH_3$); 21.59, 21.93, 22.30 ($CH_2$); 25.96 ($C^4$); 31.36, 31.65, 32.02, 32.14 ($CH_2$, $C^3$); 49.38 (2-$OCH_3$); 57.06 (1′-$OCH_3$); 89.81 ($C^{1'}$); 99.72 ($C^2$); 108.19 ($C^5$); 142.54 ($C^6$). Mass spectrum, *m*/*z* ($I_{rel}$, %): 334 (5.8) $[M]^+$, 302 (15.6) [*M* – MeOH], 244 (22.7) [*M* – BuSH], 213 (37.5) [*M* – MeOH – BuS], 201 (71.8) [*M* – BuSCH(OMe)], 185 (33.5), 155 (34.6), 128 (20.4), 113 (6.8), 101 (100), 85 (6.8), 75 (13.4), 57 (10.2) [Bu], 41 (17.3), 29 (10.2). Found (isomer mixture), %: C 57.37; H 8.87; S 19.18. $C_{16}H_{30}S_2O_3$. Calculated, %: C 57.49; H 8.97; S 19.18.

**2,5-Bis(butylsulfanyl)-2-diethoxymethyl-2,3-dihydro-4*H*-pyran (IIb).** A mixture of 4.9 g (17 mmol) of aldehyde **I**, 45 ml of anhydrous ethanol, 0.29 g (10 mol %) of $HClO_4$, and 5 g of preliminarily calcined 3-Å molecular sieves was kept for 24 h at room temperature. The mixture was then passed through a column charged with potassium carbonate, and the solvent was distilled off to obtain 5.34 g of a product mixture, a 1.2-g portion of which was subjected to column chromatography on aluminum oxide using hexane–ethyl acetate (5:3) as eluent. We isolated 0.60 g (43%) of a mixture of acetals **IIb**–**IVb** at a ratio of 5:1:1 (according to the $^1$H NMR data). This mixture was dissolved in $CDCl_3$ containing 0.002 g of *p*-toluenesulfonic acid (10 mol %), and the solution was kept for a month at 20°C; the isomer ratio changed to 1:1.3:1.2.

Isomer **IIb**. $^1$H NMR spectrum, δ, ppm: 0.90 t and 0.91 t (3H each, C**H**$_3$CH$_2$CH$_2$, $^3J$ = 7.2 Hz), 1.23 t and 1.24 t (3H each, C**H**$_3$CH$_2$O, $^3J$ = 7.0 Hz), 1.39 m and 1.51 m (4H each, CH$_3$C**H**$_2$CH$_2$, 1.83 m and 2.66 m (1H each, 3-H, 4-H), 2.08 m and 2.47 m (2H each, $SCH_2$), 2.61 m (2H, 3-H, 4-H), 3.49 q and 3.52 q (1H each, 1′-$OCH_2$, $^3J$ = 7.0 Hz), 3.62 q and 3.65 q (1H each, 1′-$OCH_2$, $^3J$ = 7.0 Hz), 4.41 s (1H, 1′-H), 6.53 s (1H, 6-H). The chemical shifts of 1′-H in minor diastereoisomeric 5-butylsulfanyl-2-[(butylsulfanyl)-(ethoxy)methyl]-2-methoxy-2,3-dihydro-4*H*-pyrans (**IIIb**/**IVb**) were δ 4.52 and 4.63 ppm. The other signals were obscured by those of the major isomer. Mass spectrum of **IIb**, *m*/*z* ($I_{rel}$, %): 362 (1.7) $[M]^+$, 316 (56.4) [*M* – EtOH], 287 (2.3), 272 (2.2) [*M* – BuS], 259 (2.2) [*M* – $CH(OEt)_2$], 227 (42.0) [*M* – EtOH – BuS], 199 (13.4), 186 (2.2), 174 (20.6), 137 (38.4) [*M* – EtOH – BuS – BuSH], 115 (8.7), 103 (100) [$CH(OEt)_2$], 89 (4.35) [SBu], 75 (27.2) [SPr], 59 (2.0), 47 (18.3) [$CH_2$=$S^+$H], 29 (10.9) [Et]. Mass spectrum of **IIIb**, *m*/*z* ($I_{rel}$, %): 362 (1.7) $[M]^+$, 316 (18.3) [*M* – EtOH], 287 (1.6), 272 (29.9) [*M* – BuSH], 227 (46.5), 215 (100) [*M* – CH(OEt)SBu], 199 (57.7) [*M* – CH(OEt)SBu – O], 183 (36.6), 171 (18.5), 155 (11.6), 142 (33.0), 129 (68.9), 113 (26.0), 101 (52.7), 85 (23.4), 73 (61.4), 57 (39.0), 41 (40.0), 29 (51.4) [Et]. The retention times of **IIb**, **IIIb**, and **IVb** were 16.65, 16.74, and 16.80 min, respectively; weight ratio 5:1:1. The mass spectra of **IIIb** and **IVb** were identical in *m*/*z* values and relative intensities. The fragmentation patterns under electron impact of methyl and ethyl acetals were similar in couples **IIa**/**IIb** and **IIIa**/**IIIb**. Found (mixture of isomers **IIb**, **IIIb**, and **IVb**), %: C 59.90; H 9.51; S 17.91. $C_{18}H_{34}S_2O_3$. Calculated, %: C 59.66; H 9.64; S 17.69.

The isolation of acetal **IIb** by vacuum or molecular distillation was accompanied by retro-Diels–Alder decomposition with formation of compounds **V** and **VI** which were reported previously [6].

The $^1$H and $^{13}$C NMR spectra were recorded on a Bruker DPX-400 spectrometer at 400.13 MHz for $^1$H and 100.61 MHz for $^{13}$C using $CDCl_3$ as solvent and hexamethyldisiloxane as internal reference. Gas chromatographic–mass spectrometric analysis was performed on a Hewlett–Packard 5971A mass selective detector (electron impact, 70 eV) coupled with an HP-5890 gas chromatograph (Ultra-2 column, 5% of phenylmethylsilicone; injector temperature 250°C, oven temperature 70–280°C, temperature ramp 20 deg/min). HPLC analysis was performed on a Hewlett-Packard 1100 instrument equipped with a UV diode matrix detector (temperature 20°C; ODS HYpersil column, 250 × 4.6 mm, grain size 5 μm; eluent acetonitrile–water, 70:30).

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