TETRAHYDROFURANS

II. SPIRO COMPOUNDS CONTAINING THE TETRAHYDROFURAN RING

B. K. Wasson, J. A. Kernan, and J. M. Parker
Research Laboratories, Charles E. Frosst and Co., Montreal, Que.

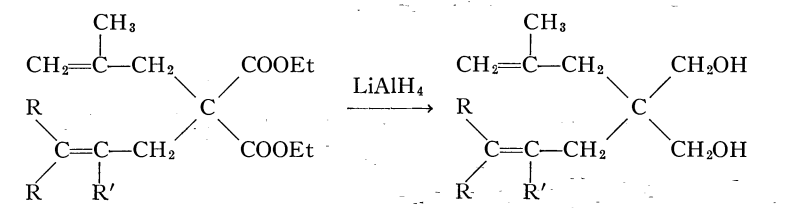
Received June 26, 1963

ABSTRACT

2-Allyl-2-methallyl-1,3-propanediol (IV) and 2,2-dimethallyl-1,3-propanediol (V) were cyclized in the presence of mineral acid to give 3,3,8-trimethyl-2,7-dioxaspiro(4.4)nonane (VIII) and 3,3,8,8-tetramethyl-2,7-dioxaspiro(4.4)nonane (IX), respectively. Similarly, 2-methallyl-2-(3-methyl-2-butenyl)-1,3-propanediol (VI) afforded 3,3,8,8-tetramethyl-2,7-dioxaspiro(4.5)decane (X). The diol VI was derived from diethyl methallylmalonate by condensation with 3-methyl-2-butenyl bromide, followed by reduction of diethyl methallyl(3-methyl-2-butenyl)malonate (III) with lithium aluminum hydride. The assigned structures of the spiro compounds were supported by infrared and nuclear magnetic resonance spectral analyses.

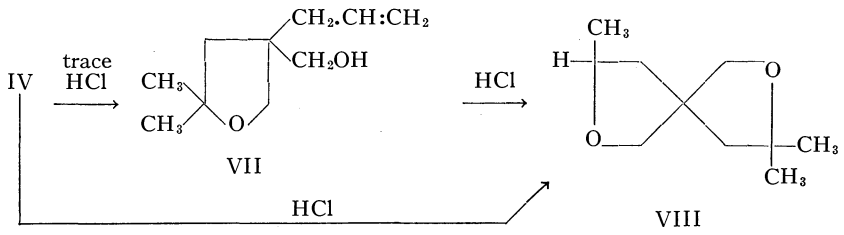
DISCUSSION

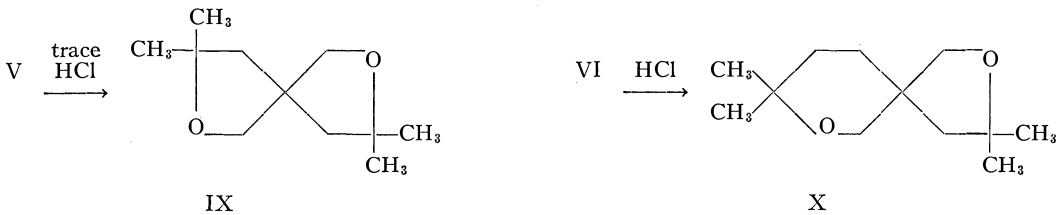
In a previous paper (1), the synthesis of 2,2-dimethyl-4-allyl-4-hydroxymethyltetrahydrofuran (VII) from 2-allyl-2-methallyl-1,3-propanediol (IV) was described. It was noted that during the distillation of VII a forerun contained material which exhibited no infrared absorption for the primary hydroxyl groups or the terminal double bonds present in IV and VII. It would appear that further cyclization occurred between the allyl and



I. R,R′ = H
II. R = H; R′ = CH_3
III. R = CH_3; R′ = H

IV. R,R′ = H
V. R = H; R′ = CH_3
VI. R = CH_3; R′ = H





the hydroxymethyl group of VII affording the bicyclo compound 3,3,8-trimethyl-2,7-dioxaspiro(4.4)nonane (VIII). This has now been confirmed. A sample of VII was heated 20 hours on the steam bath with concentrated hydrochloric acid to afford an excellent yield of VIII. Furthermore, VIII was obtained directly in high yield when IV was treated with 0.6 molar equivalents of concentrated hydrochloric acid.

A search of the literature failed to reveal a prior synthesis of methylsubstituted-2,7-dioxaspiro(4.4)nonanes. The Patterson, Capell, and Walker Ring Index (2) lists the parent 2,7-dioxaspiro(4.4)nonane but the actual reference (3) described the preparation of the dilactone 1,6-dioxo-2,8-dimethyl-2,7-dioxaspiro(4.4)nonane by treatment of diallylmalonic acid with hydrobromic acid.

3,3,8,8-Tetramethyl-2,7-dioxaspiro(4.4)nonane (IX), a second member of this series, has now been prepared in excellent yield by the acid-induced ring-closure of 2,2-dimethallyl-1,3-propanediol (V). The diol V was obtained by reduction (4) of diethyl dimethallylmalonate (II) with lithium aluminum hydride (5). The ring-closure was vigorously exothermic, even with only a trace of acid present, requiring a solvent to modify the reaction temperature. This confirms the greater activity of the methallyl double bond over that of the allyl double bond. It has already been shown (1) that a molecule containing a methallyl group and a hydroxymethyl group attached to the same carbon atom will condense, according to Markownikoff's rule, to form a tetrahydrofuran rather than a tetrahydropyran ring. Therefore, during the cyclization of 2,2-dimethallyl-1,3-propanediol (V) two tetrahydrofuran rings are formed yielding the 2,7-dioxaspiro(4.4)nonane ring system.

Investigation of the above cyclization was extended to include one member of the methylsubstituted-2,7-dioxaspiro(4.5)decanes. The preparation of 3,3,8,8-tetramethyl-2,7-dioxaspiro(4.5)decane (X) was accomplished by treating the sodio derivative of diethyl methallylmalonate with 3-methyl-2-butenyl bromide to give diethyl methallyl-(3-methyl-2-butenyl)malonate (III). Reduction of III with lithium aluminum hydride afforded 2-methallyl-2-(3-methylbutenyl)-1,3-propanediol (VI) and acid treatment of VI gave X. The crystalline dicarbamate was obtained from VI in high yield.

No information is available concerning the methyl derivatives of 2,7-dioxaspiro(4.5) decane. The literature of related compounds is very scanty, however, one reference (6) was discovered which described a ketolactone, 9,9-bis(hydroxymethyl)-2,7-dioxaspiro-(4.5)decane-3,10-dione. 3,3,8,8-Tetramethyl-2,7-dioxaspiro(4.5)decane (X) represents the first member of this series to be synthesized. The structure X was assigned rather than the isomeric 3,3-dimethyl-8-isopropyl-2,7-dioxaspiro(4.4)nonane or 3,9,9-trimethyl-2,8-dioxaspiro(5.5)undecane, since the ring-closure between the 3-methyl-2-butenyl- and hydroxymethyl groups would follow the normal Markownikoff rule of addition.

Assignment of structures to the cyclized products was supported by infrared absorption and nuclear magnetic resonance (n.m.r.) data. The cyclization of each of the three diols, IV, V, and VI, to the dioxaspiro compounds, VIII, IX, and X, required an increase in the number of methyl groups, the formation of cyclic ether, and the loss of terminal unsaturation and of hydroxyl groups. An inspection of the infrared spectra of IV, V, VI, VIII, IX, and X showed that these changes did occur. They were exhibited by the appearance of a doublet (*gem*-dimethyl) in the 7.25–7.35 μ region in place of the single band at 7.3 μ attributed to each starting diol, by the loss of the two bands at 3.25 and 6.1 μ (terminal unsaturation), the loss of the band at 11.2 μ (methallyl), the absence of the band at 10.95 μ (allyl) from the spectrum of VIII which was originally present in that of IV, the loss of the band at 3 μ (hydroxyl) and the shifting and narrowing of the

9.6–9.8 μ band (hydroxyl) to 9.5 μ (cyclic ether) (7). In addition, the spectra of VIII, IX, and X possessed a strong band at 12.9–13.0 μ (believed to be *gem*-dimethyl). The infrared spectrum of X showed a strong band at 9.25 μ. This was attributed to the C—O vibration in the tetrahydropyran ring, since the C—O vibration for the tetrahydrofuran ring occurred at 9.5 μ for VIII, IX, and X. It is believed that the above-described cyclizations have general application and will be discussed in future publications.

Nuclear magnetic resonance data, given for 3,3,8-trimethyl-(VIII) and 3,3,8,8-tetramethyl-2,7-dioxaspiro(4.4)nonanes (IX) in the experimental section, has proved that only tetrahydrofuran rings were formed to provide spiro compounds containing methyl groups. Similarly the n.m.r. spectrum of X confirmed the presence of the 2,7-dioxaspiro-(4.5)decane skeletal system containing one tetrahydrofuran and one tetrahydropyran ring. Since this spectrum has shown that neither two tetrahydrofuran nor two tetrahydropyran rings were present, the two alternate isomeric structures 3,3-dimethyl-8-isopropyl-2,7-dioxaspiro(4.4)nonane and 3,9,9-trimethyl-2,8-dioxaspiro(5.5)undecane are eliminated.

3,3,8-Trimethyl-2,7-dioxaspiro(4.4)nonane (VIII) was effective as an anticonvulsant. The pharmacological activities of the 2,7-dioxaspiro(4.4)nonanes and the 2,7-dioxaspiro-(4.5)decanes will be reported elsewhere.

EXPERIMENTAL

Boiling points and melting points (Fisher–Johns apparatus) are uncorrected. Analytical samples of liquids were prepared by distillation through a 24-in., 8-mm diameter Nester and Faust spinning band column. Infrared absorption spectra were obtained with a Beckman IR-5 spectrophotometer equipped with a sodium chloride prism. Solids were examined as potassium bromide pellets, and liquids as thin films. The n.m.r. spectra were taken on a Varian 60 Mc high resolution spectrophotometer. In all cases integration of areas was carried out and the number of protons corresponding to each signal is indicated. Values are given in parts per million (p.p.m.) with tetramethylsilane used as the standard.

Preparation of Diethyl Mono- and Di-substituted Malonates

Diethyl methallylmalonate and diethyl allylmethallylmalonate (I) were prepared by standard methods from the literature (5). Methallyl chloride and diethyl methallylmalonate afforded diethyl dimethallylmalonate (II) in an 80% yield, b.p. 153–158° at 15–20 mm. 3-Methyl-2-butenyl bromide and diethyl methallylmalonate gave diethyl methallyl(3-methyl-2-butenyl)malonate (III) in an 84% yield. Redistillation afforded an analytical sample, b.p. 149–150° at 14 mm, n_D^{25} 1.4581. Anal. Calc. for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28. Found: C, 67.67; H, 9.14. Infrared: λ_{max} 3.25, 6.1 (terminal unsaturation), 5.75 (carbonyl), 7.25–7.32 (methyl), 8.3–8.5 (ester), 11.15 μ (methallyl).

Preparation of 3,3,8-Trimethyl-2,7-dioxaspiro(4.4)nonane (VIII)

Method A

From 2,2-Dimethyl-4-allyl-4-hydroxymethyltetrahydrofuran (VII).—Distilled VII (25 g) was treated dropwise with 6.5 ml of concentrated hydrochloric acid. The temperature of the reaction mixture rose from 25° to 35° and was accompanied by faint discoloration. The mixture was allowed to stand for 30 minutes and was warmed overnight on a steam bath. After it had been cooled, the reaction mixture was made alkaline with 6 *N* sodium hydroxide and extracted with ether. The ethereal extract was washed with water, dried, and evaporated to give 23 g of a liquid residue. Distillation of this residue afforded 20.8 g (83%) of VIII, b.p. 68–74° at 6–8 mm, n_D^{25} 1.4439. An analytical sample had a boiling point of 70.5–71.0° at 6 mm, n_D^{25} 1.4436. Anal. Calc. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.29; H, 10.64. The infrared spectrum of VIII showed the presence of two bands in the methyl region and the absence of bands associated with unsaturation and hydroxyl groups. N.m.r. signals: multiplet centered at 3.60 p.p.m. (—CH—O—CH_2—C—CH_2—O—, area = 5H), multiplet centered at 1.77 p.p.m. (—C—CH_2—C—CH_2C—, area = 4H), triplet at 1.20, 1.16, 1.10 p.p.m. (methyls, area = 9H).

Method B

From 2-Allyl-2-methallyl-1,3-propanediol (IV).—Distilled IV (25 g) was treated with 6.5 ml of concentrated hydrochloric acid. The temperature of the cooled solution rose rapidly to 80°. The reaction mixture was warmed 7 hours on the steam bath and was worked up as described in method A. Distillation afforded 20.2 g (81%) of VIII, b.p. 77–83° at 8–10 mm, n_D^{25} 1.4438. The infrared absorption of this product was identical with that from the product obtained by method A.

Preparation of 2,2-Dimethallyl-(V) and 2-Methallyl-2-(3-methyl-2-butenyl)-1,3-propanediol (VI)

A solution of 214.5 g of diethyl dimethallylmalonate (II) in 500 ml of anhydrous ether was added dropwise to a vigorously stirred mixture of 45.6 g of lithium aluminum hydride in 1250 ml of anhydrous ether maintained at 5–20°. The reaction mixture was stirred for 2 hours, cooled, and decomposed by successive additions of methanol–ether, methanol–water, and water. The solids were triturated several times with ether. The combined ethereal extracts were washed with water and evaporated to give an oily residue. Distillation of this residue afforded 136.5 g (93%) of V, b.p. 162.5–172° at 15–20 mm. Infrared: λ_{max} 3.0 (hydroxyl), 3.25, 6.1 (terminal unsaturation), 9.6–9.8 (hydroxyl), 11.2 μ (methallyl).

A similar reduction of diethyl methallyl(3-methyl-2-butenyl)malonate (III) with lithium aluminum hydride gave a 94% yield of VI, b.p. 148–165° at 9 mm, which crystallized as white needles, m.p. 54.5–55.0°. Anal. Calc. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.74; H, 11.22. Infrared: λ_{max} 3.0 (hydroxyl), 3.22, 6.1 (terminal unsaturation), 6.9 (methylene), 7.25 (methyl), 9.5–9.8 (hydroxyl), 11.25 μ (methallyl). The dicarbamate of VI was prepared (1) in an 85% yield as white crystals, m.p. 140.5–146°. Recrystallization from aqueous methanol afforded an analytical sample having a melting point of 145–146°. Anal. Calc. for $C_{14}H_{24}N_2O_4$: C, 59.13; H, 8.51; N, 9.85. Found: C, 59.17; H, 8.24; N, 9.95. Main infrared bands: λ_{max} 2.93, 2.97, 5.9, 6.25, 7.1, 7.45, 9.4, 11.1, and 12.75 μ.

Preparation of 3,3,8,8-Tetramethyl-2,7-dioxaspiro(4.4)nonane (IX)

A solution of 83.9 g of the diol V in 59.5 ml of tetrahydrofuran was treated with 1.9 ml of concentrated hydrochloric acid. The temperature of the solution rose spontaneously to 60°. The solution was cooled, left 1 hour at room temperature, and refluxed for 2 hours. The solvent was evaporated and the residue dissolved in ether. The ethereal solution was washed with dilute alkali, then with water, and dried. The solvent was evaporated to give 73.7 g of a pale yellow residue. Distillation of this residue afforded 68.3 g (81%) of IX, b.p. 115–121° at 21 mm. An analytical sample of IX had a boiling point of 109–110° at 30–31 mm, n_D^{25} 1.4404. Another specimen had a boiling point of 207.5–208° at atmospheric pressure. Anal. Calc. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 72.05, 72.13; H, 11.43, 11.19. The infrared spectrum of IX showed the absence of unsaturation and of hydroxyl groups and the presence of two bands in the methyl region. N.m.r. signals: quartet centered at 3.73 p.p.m. (—O—CH_2—C—CH_2—O—, area = 4H), 1.81 p.p.m. (C—CH_2—C—CH_2—C—, area = 4H), doublet at 1.19 and 1.16 p.p.m. (methyls, area = 12H).

Preparation of 3,3,8,8-Tetramethyl-2,7-dioxaspiro(4.5)decane (X)

A solution of 30 g of the diol VI in 110 ml of tetrahydrofuran was treated dropwise during 15 minutes with 28 ml of 6 *N* hydrochloric acid. The temperature of the solution rose from 22° to 33°. The solution was refluxed for 3 hours and the solvents evaporated to give 31.9 g of crude X. An analytical sample had a boiling point of 94.0–94.5° at 6 mm, n_D^{25} 1.4505. Anal. Calc. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.66; H, 11.14. The infrared spectrum indicated the absence of unsaturation and hydroxyl groups and the presence of methyl groups (7.25, 7.35 μ). N.m.r. signals: quartet centered about 3.63 and 3.41 p.p.m. (—O—CH_2—C—CH_2—O—, area = 4H), multiplet centered at 1.50 p.p.m. (—C—CH_2—CH_2—C—CH_2—C—, area = 6H), doublet at 1.17 and 1.12 p.p.m. (methyls, area = 12H).

ACKNOWLEDGMENTS

The authors are indebted to Dr. A. Taurins and Dr. C. Stammer of McGill University for n.m.r. analyses, and E. Frank and M. Dillon of our laboratory for elemental analyses. We also wish to acknowledge the capable assistance of A. Franck and O. Kristiansen.

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