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The Acid-catalyzed Reaction of Alicyclic Ketones with Formaldehyde. II.[1] The Reaction of Cycloheptanone and Cyclooctanone with Formaldehyde

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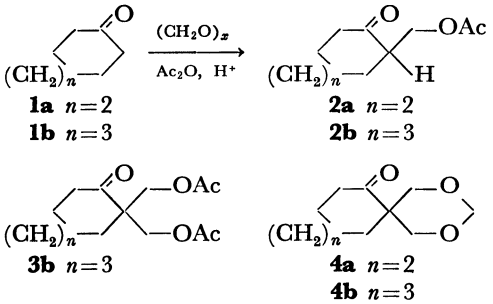
Synopsis. The acid-catalyzed reaction of cycloheptanone and cyclooctanone with formaldehyde gave predominantly 2,4-dioxaspiro[5.6]dodecan-7-one and 2,4-dioxaspiro[5.7]tridecan-7-one respectively.

In the previous paper,[1] we reported the reactions of cyclopentanone, cyclohexanone, and the alkyl-substituted cycloalkanones with formaldehyde in the presence of acid catalysts. The reactions produced hydroxymethyl derivatives, spiromono- and bis(1,3-dioxanes). The distribution of these products was markedly affected by both the skeletal structure and the substituent of the cycloalkanones. In this paper, we wish to report on the reactions of cycloheptanone (**1a**) and cyclooctanone (**1b**), together with the ring-size effect of cycloalkanones on the acid-catalyzed reaction.

The reaction of **1a** or **1b** with formaldehyde was carried out in a mixture of acetic acid and acetic anhydride in the presence of phosphoric acid at 60 °C. After the distillation of the resulting mixture, the products were isolated by preparative GLPC and were characterized on the basis of their chemical behavior and by spectroscopic methods.

The reaction of **1a** gave 2-acetoxymethylcycloheptanone (**2a**) and 2,4-dioxaspiro[5.6]dodecan-7-one (**4a**) in 21.4 and 43.8% yields respectively on the basis of the **1a** used. Similarly, the reaction of **1b** gave 2-acetoxymethylcyclooctanone (**2b**), 2,2-diacetoxymethylcyclooctanone (**3b**), and 2,4-dioxaspiro[5.7]tridecan-7-one (**4b**) in 8.7, 13.5, and 36.5% yields respectively.



Scheme 1.

The PMR spectra of **4a** and **4b** showed a methylenedioxy proton at δ 4.53 (a characteristic quartet in the AB-type) in both compounds, and their IR spectra showed an absorption due to a methylenedioxy group at 2775 cm^{-1} in **4a** and at 2745 cm^{-1} in **4b** respectively. From these results, the structure of **4a** and **4b** was assigned to spiromono(1,3-dioxane) derivatives. The structure of **3b** was confirmed by the fact that the identical diacetate was obtained by the acetolysis of **4b** in the presence of phosphoric acid.

The acid-catalyzed reaction of **1a** and **1b** was compared with that of cyclopentanone and cyclohexanone. The reactivity might decrease in the order of C_6->C_5->C_7->C_8-cycloalkanones, judging from the experiments undertaken. The product distribution was quite sensitive to the ring-size of the cyclic ketones. The reaction of C_7- and C_8-cycloalkanones afforded mainly spiromono(1,3-dioxanes), but not bis(1,3-dioxanes), which were yielded largely in the reaction of cyclohexanone. These facts seem to be explained by the increased transannular repulsions arising from the formation of bis(1,3-dioxanes) in C_7- and C_8-cycloalkanones.

Experimental

All the boiling and melting points are uncorrected. The IR spectra were measured using a JASCO model IR-A spectrophotometer. The PMR spectra were obtained on a JEOL MH-60 II spectrometer (60 MHz), using tetramethylsilane as the internal standard. The mass spectra were taken with a Hitachi Model RMU-6GC mass spectrometer at 70 eV.

Materials. The cycloheptanone (**1a**) and cyclooctanone (**1b**) were prepared by the reported method;[2] **1a**: bp 65—67 °C/2 mmHg; **1b**: mp 32—33 °C.

Reaction of Cycloheptanone (1a) with Formaldehyde. To a stirred solution of paraformaldehyde (9.0 g, 0.3 mol), acetic anhydride (10.2 g, 0.1 mol), and 85% phosphoric acid (5.7 g, 0.05 mol) in glacial acetic acid (30 ml), **1a** (11.2 g, 0.1 mol) in glacial acetic acid (20 ml) was added over a 3-h period at 60 °C, after which the mixture was stirred at the same temperature for 7 h. The usual work-up gave 15.9 g of an oily product. The oil was then distilled under reduced pressure to give an unreacted **1a** (4.2 g, 37.1% yield, based on the **1a** used) and a colorless liquid (9.5 g, bp 67—113 °C/2 mmHg; GLPC analysis showed **2a**, **4a**, and the self-condensates of formaldehyde with peak area ratios of 31, 56, and 13% respectively). The latter distillate was separated by preparative GLPC (Apparatus: Yanaco G-80. Column, 30% Diethylene Glycol Succinate Polyester on Chamelite CK, 14 mm × 3 m. Temp, 170 °C. Carrier gas, H_2 at 280 ml/min) to afford **2a** (2.4 g, 21.4%) and **4a** (4.9 g, 43.8%), each as a colorless liquid; *2-acetoxymethylcycloheptanone (2a)*: d_4^{25} 1.0682, n_D^{25} 1.4640. PMR (CCl_4): δ 1.12—2.19 (br, 8H), 1.96 (s, 3H), 2.40 (m, 2H), 2.82 (m, 1H), and 3.98 (ABX, J_{AB}=11 Hz, J_{AX}=J_{BX}=6.0 Hz, $\Delta\nu_{AB}$=19.5 Hz, 2H). IR (neat): 1732 (vs), 1692 (vs), 1236 (vs), 1040 (s), and 1024 (s) cm^{-1}. Found: C, 65.42; H, 8.73%. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75%. *2,4-Dioxaspiro[5.6]dodecan-7-one (4a)*: Bp 112—113 °C/2 mmHg, d_4^{25} 1.1217, n_D^{25} 1.4880. MS: *m/e* 184 (M^+). PMR (CCl_4): δ 1.60 (br s, 6H), 1.94 (m, 2H), 2.36 (m, 2H), 3.63 (AB-q, J=12 Hz, 4H), and 4.53 (AB-q, J=5.7 Hz, 2H). IR (neat): 2775 (w), 1684 (vs), 1160 (vs), 1152 (vs), 1028 (s), 1004 (s), and 920 (s) cm^{-1}. Found: C, 65.37; H, 8.68%. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75%.

*Reaction of Cyclooctanone (**1b**) with Formaldehyde.* In a way similar to that in the reaction of **1a**, the reaction of **1b** (12.6 g, 0.1 mol) with paraformaldehyde (9.0 g, 0.3 mol) and acetic anhydride (10.2 g, 0.1 mol) gave 17.5 g of an oily product. The oil was distilled under reduced pressure to give an unreacted **1b** (5.2 g, 41.3%) and two colorless fractions (A: 8.2 g, bp 59—132 °C/0.1 mmHg; B: 1.8 g, bp 132—134 °C/0.1 mmHg). The A fraction (GLPC analysis indicated **2b**, **4b**, and the self-condensates of formaldehyde with peak area ratios of 15, 73, and 12% respectively) was then separated by preparative GLPC to afford **2b** (1.1 g, 8.7%) and **4b** (4.6 g, 36.5%), each as a colorless liquid; *2-Acetoxymethylcyclooctanone (**2b**)*: d_4^{25} 1.0565, n_D^{25} 1.4689. PMR (CCl_4): δ 0.82—2.10 (br, 10H), 1.95 (s, 3H), 2.23 (m, 2H), 2.87 (m, 1H), and 3.93 (ABX, $J_{AB}=11$ Hz, $J_{AX}=6.0$ Hz, $J_{BX}=8.7$ Hz, $\Delta\nu_{AB}=15$ Hz, 2H). IR (neat): 1732 (vs), 1696 (vs), 1232 (vs), 1044 (s), and 1028 (s) cm^{-1}. Found: C, 66.90; H, 9.13%. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15%. *2,4-Doixaspiro[5.7]tridecan-7-one (**4b**)*: bp 104—105 °C/0.1 mmHg. d_4^{25} 1.1076, n_D^{25} 1.4927. MS: *m/e* 198 (M^+). PMR (CCl_4): δ 1.48 (m, 8H), 2.17 (m, 4H), 3.72 (s, 4H), and 4.53 (AB-q, $J=6.0$ Hz, 2H). IR (neat): 2745 (w), 1682 (vs), 1170 (vs), 1154 (vs), 1134 (vs), 1064 (vs), 1040 (s), 1028 (vs), 921 (s) cm^{-1}. Found: C, 66.91; H, 9.13%. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15%.

On the other hand, the B fraction crystallized directly on standing and was recrystallized from cyclohexane to yield *2,2-diacetoxymethylcyclooctanone (**3b**)* (1.7 g, 13.5%) as white crystals; mp 65—66 °C; PMR (CCl_4): δ 1.16—2.10 (br, 10H), 1.98 (s, 6H), 2.42 (m, 2H), and 4.05 (AB-q, $J=12$ Hz, 4H). IR (CCl_4): 1740 (vs), 1693 (s), 1233 (s). 1219 (s), 1040 (s), and 1021 (s) cm^{-1}. Found: C, 62.28; H, 8.23%. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20%.

*Acetolysis of Spiromono(1,3-dioxane) (**4b**).* A solution of **4b** (198 mg, 1 mmol), acetic anhydride (204 mg, 2 mmol), and 85% phosphoric acid (57 mg, 0.5 mmol) in glacial acetic acid (1 ml) was stirred at 60 °C for 10 h. After a subsequent work-up, 190 mg of an oily mixture were obtained. The PMR analysis revealed that the reaction mixture consisted of an acetolysis product (12%) and unreacted **4b** (88%), which were isolated by preparative GLPC to give 22 mg (11.1% yield, based on the **4b** used) of the acetolysis product and 158 mg (79.8%) of **4b**. The IR spectrum of the acetolysis product was completely identical with that of **3b** obtained from **1b**.

References

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2) E. P. Kohler, M. Tishler, H. Potter, and H. T. Thompson, *J. Am. Chem. Soc.*, **61**, 1059 (1939); R. Adams, *Org. Synth.*, **34**, 24 (1954).