Notes

Acid-Catalyzed Rearrangements of Aldehydo Ozonides

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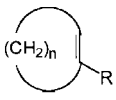
Mono- and polycyclic peroxides have been attracted considerable attention as models or analogues of an increasing number of peroxidic natural products, some of which possess attractive pharmacological properties.[1-3] [3+2] cycloaddition reactions between carbonyl oxides generated in situ by ozonolysis of olefins, and carbonyl components are well established.[4-6]

Ozonolyses of cycloolefins **1** in presence of carbonyl compounds **2a** and **2b**, however, revealed a partially anomalous behavior as compared to other carbonyl compounds **2c** and **2d**. A priori, one would have expected that the primary intermediates of type **3** are trapped by carbonyl compounds to give cross-ozonides of type **4**. But in addition to **4**, variable amounts of the isomeric product of type **5** were obtained in the case of carbonyl compounds **2a** and **2b**.[7-9]

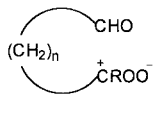


1

2

	a	b	c	d
R^1	H	CH_3	CH_3	Ph
R^2	H	H	CN	CN

Although direct reaction of carbonyl oxides **3** with carbonyl compound **2** in general produced the normal [3+2] adducts **4** rather than the isomeric 1,2,4,6-tetroxepanes **5**, it was considered possible that acid-catalyzed rearrangement of the former **4** under mild conditions might provide an alterative route to additional derivatives of the latter **5**.



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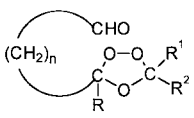

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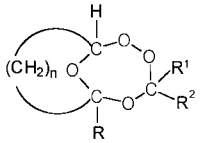
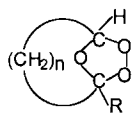


5

Thus, treatment of cross-ozonide **4Aa** with trifluoroacetic acid (TFA) led to formation of a mixture of compound **6A**, together with dialdehyde **7a**. The formation of monoozonide **6A** is in line with the known fact that 5-membered cycloolefins give high yields of monoozonides.[10-12]



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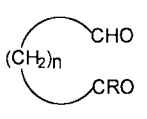


7

	a	b	c	d	e	f	g
n	3	4	5	6	10	3	4
R	H	H	H	H	H	CH_3	CH_3

The results for the acid-catalyzed rearrangement reactions are summarized in Table 1. Treatment of cross-ozonide **4Ba** with TFA gave the isomeric tetroxepane **5Ba** and hexananedial **7b**. Under similar reaction conditions cross-ozonides **4Ea**, **4Eb**, and **4Ga** gave variable results: **4e** was recovered unchanged and **4Eb** and **4Ga** afforded a complex mixture of unidentified products and dialdehydes **7**. The lack of formation of monoozonides **6B-6E** is in line with the experience that the tendency for intramolecular [3+2] cycloaddition of intermediates of type **3** decreases with increasing ring size of the parent cycloolefin.

Following acid catalysed opening of the trioxolane ring in the system above, a variety of processes may take place, including intramolecular recombination to give the desired tetroxepane **5Ba**, elimination of a carbonyl compound such as formaldehyde followed by recombination to give an monoozonide **6A**, and elimination of a carbonyl oxide fragment to generate the dicarbonyl compound **7**.

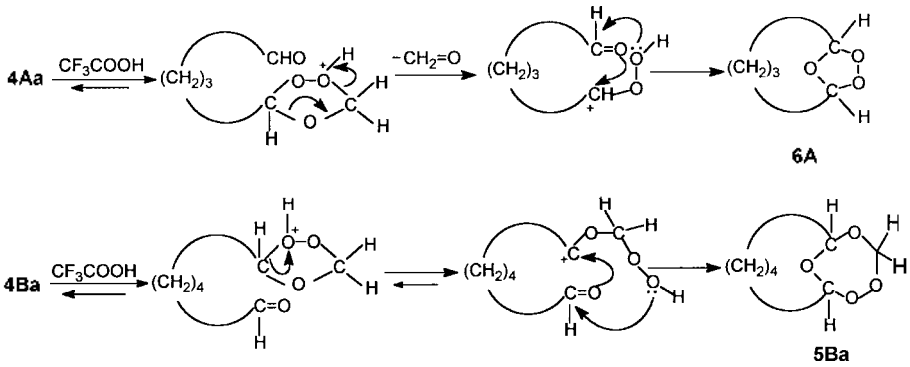
For several of the systems mentioned above, these process appear to be competitive and their respectives contributions influenced by the ring size and the bulky of substituents of ozonide ring.

The structural assignments of the tetroxepanes of structure

Table 1. Acid-Catalyzed Rearrangement of Aldehydo Ozonides

Ozonide	Structural unit				Product (%)[a]	Recovered (%)[a]
	n	R	R^1	R^2		
4Aa	3	H	H	H	**6A** (41), **7a** (20)	
4Ba	4	H	H	H	**5Ba** (31), **7b** (16)	
4Ca	5	H	H	H	**5Ca** (25), **7c** (10)	(5)
4Da	6	H	H	H	**5d** (16), **7d** (11)	(13)
4Ea	10	H	H	H	**7e** (20)	(23)
4Ab	3	H	CH_3	H	**6A** (35), **7a** (30)	
4Bb	4	H	CH_3	H	**5Bb** (22), **7b** (14)	
4Cb	5	H	CH_3	H	**5Cb** (18), **7c** (8)	(8)
4Db	6	H	CH_3	H	**5Db** (16), **7d** (10)	(10)
4Eb	10	H	CH_3	H	**7e** (14)	(30)
4Fa	3	CH_3	H	H	**6F** (18), **7f** (10)	(10)
4Ga	4	CH_3	H	H	**7g** (21)	(26)

[a]Yield of isolated products.



5 are based on characteristic ^{1}H and ^{13}C NMR signals of the CH_2 groups and of the CH groups in the heterocyclic ring systems. In the ^{1}H NMR spectra, the CH_2 groups appeared as two singlet signals, in the range of δ = 5.02-5.05 and δ = 5.17-5.21, and the R-CH groups appeared as two triplets, in the range of δ = 4.84-4.86 and δ = 5.12-5.14. In the ^{13}C NMR spectra, the signals of the CH_2 groups appeared in the range of δ = 93.71-94.41 and those of the two magnetically non-equivalent CH groups appeared in the range of δ = 100.86-101.96 and δ = 103.15-104.19. The structures of all isolated monoozonides **6** were also established by ^{1}H NMR and ^{13}C NMR spectroscopy. Characteristic signals in the ^{1}H NMR spectra were those of CH groups in the ozonide ring appearing in the range δ = 5.19-5.78. Characteristic signals in the ^{13}C NMR spectra were those in range δ = 101.96-108.05.

Experimental Section

All NMR spectra were recored with Bruker FT-NMR (300 MHz), using TMS as an internal reference. The products were isolated by flash chromatography on 80 g silica gel using diethyl ether/*n*-pentane in a ratio of 1 : 2 .

Acid Rearrangement of Ozonide 4Aa. The general procedure is exemplified by the acidolysis of ozonide **4Aa**. An equimolar solution of 1.17 g (8 mmol) of cross ozonide **4Aa** and 0.24 g (8 mmol) of **TFA** in 30 mL of methylene chloride was stirred at room temperature for 2 h. Diethyl ether was added and the resulting reaction mixture was washed with aq. $NaHCO_3$ and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the products were separated by column chromatography to give monoozonide **6A** (0.38 g, 3.3 mmol, 41%) and 1,6-pentanedial **7a** (0.16 g, 1.6 mmol, 20%).

6,7,8-Trioxabicyclo[3,2,1]octane (6A): Colorless solid, m.p. 74 °C; ^{1}H NMR: δ = 1.64 (m, 1H), 1.77 (m, 4H), 2.18 (m, 1H), 5.78 (s, 2H); ^{13}C NMR: δ = 15.00, 29.85, 101.96. The data are identical to those of reported.[8]

7,8,10,11-Tetraoxabicyclo[4,4,1]undecane (5Ba): Yield, 31%; Colorless liquid; ^{1}H-NMR: δ = 1.46-1.50 (m, 4H), 1.67-1.75 (m, 4H), 4.84 (t, J = 5 Hz, 1H), 5.03 (s, 1H), 5.12 (t, J = 5 Hz, 1H), 5.17 (s, 1H); ^{13}C NMR(BB): δ = 23.30, 23.33, 30.59, 33.04, 93.71, 100.86, 103.15; ^{13}C NMR(CB): δ = 23.30 (t, J = 480 Hz), 23.33 (t, J = 510 Hz), 30.59 (t, J = 515 Hz), 33.04 (t, J = 530 Hz), 93.87 (t, J = 630 Hz), 100.95 (d, J = 640 Hz), 103.15 (d, J = 685 Hz).[8]

8,9,11,12-Tetraoxabicyclo[5,4,1]dodecane (5Ca): Yield, 11%; Colorless liquid; ^{1}H NMR: δ = 1.40-1.55 (m, 6H), 1.60-1.77 (m, 4H), 4.86 (t, J = 5 Hz, 1H), 5.03 (s, 1H), 5.13 (t, J = 5 Hz, 1H), 5.20 (s, 1H); ^{13}C NMR: δ = 23.69, 24.07, 29.48, 31.38, 34.57, 94.41, 101.83, 104.13.[8]

9,10,12,13-tetraoxabicyclo[6,4,1]tridecane (5Da): Yield, 11%; Colorless liquid; ^{1}H NMR: δ = 1.35-1.42 (m, 8H), 1.52-1.75 (m, 4H), 4.84 (t, J = 5 Hz, 1H), 5.05 (s, 1H), 5.14 (t, J = 5 Hz, 1H), 5.21 (s, 1H); ^{13}C NMR: δ = 23.76, 24.14, 29.53, 29.60, 31.45, 34.71, 94.41, 101.96, 104.19.[8]

9-Methyl-7,8,10,11-tetraoxabicyclo[4,4,1]undecane (5Bb): Yield, 12% Colorless liquid; ^{1}H NMR: δ = 1.30-1.48 (m, 4H), 1.38 (d, J = 6.14 Hz, 3H), 1.65-1.70 (m, 4H), 4.83 (m, 3H); ^{13}C NMR(BB): δ = 16.69, 18.51, 23.79, 30.89, 32.63, 34.47, 101.54, 101.66, 104.50; ^{13}C NMR(CB): 100.36, 100.40, 101.75, 101.79, 103.21, 104.64. The data are identical to those of reported.[8]

10-Methyl-8,9,11,12-tetraoxabicyclo[5,4,1]dodecane (5Cb): Yield, 8% Colorless liquid; ^{1}H NMR: δ = 1.32-1.49 (m, 6H), 1.37 (d, J = 6.12 Hz, 3H), 1.60-1.67 (m, 4H), 4.83 (m, 3H); ^{13}C NMR(BB): δ = 16.69, 18.51, 23.79, 30.89, 32.63, 34.47, 101.54, 101.66, 104.50; ^{13}C NMR(CB): 100.36, 100.40, 101.75, 101.79, 103.21, 104.64.[8]

11-Methyl-9,10,12,13-tetraoxabicyclo[6,4,1]tridecane (5Db): Yield, 10%; Colorless liquid; ^{1}H NMR: δ = 1.34-1.43 (m, 8H), 1.39 (d, J = 6 Hz, 3H), 1.62-1.69 (m, 4H), 4.84 (m, 3H); ^{13}C NMR(BB): δ = 16.29, 18.18, 23.31, 29.11, 30.67, 32.57, 34.29, 101.14, 101.24, 101.52, 104.58; ^{13}C NMR(CB): δ = 100.52, 100.87, 101.95, 102.14, 103.58, 104.96.[8]

1-Methyl-6,7,8-Trioxabicyclo[3,2,1]octane (6F): Yield, 18%; Colorless liquid; ^{1}H NMR: δ = 1.43 (s, 3H), 1.54-1.75 (m, 5H), 2.08-2.15 (m, 1H), 5.19 (s, 1H); ^{13}C NMR: δ = 15.00, 29.85, 101.96.[8]

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