Halolactones from 1,4-Dihydrobenzoic Acids

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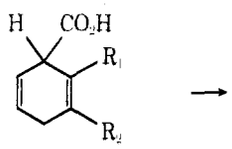
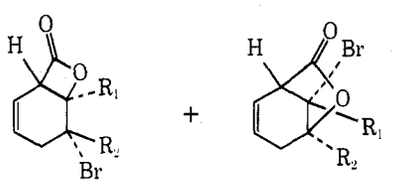
Received February 28, 1975

In an effort to increase the utility of 1,4-dihydrobenzoic acids, which are readily available by the Birch reduction[2] of benzoic acids, and in connection with studies aimed at defining the scope of a new β-lactone synthesis,[3] we have examined the iodolactonization and bromolactonization of 1,4-dihydrobenzoic acids. However, such low yields of lactones have been obtained in the iodolactonization of several 1,4-dihydrobenzoic acids that the reaction cannot be considered as a reliable synthetic method. In contrast, the bromolactonization reaction consistently affords good yields of stable crystalline bromolactones.

The ring size of the lactone formed in the bromolactonization of a 1,4-dihydrobenzoic acid depends upon substitution at the sites of unsaturation. Either a β-lactone or a γ-lactone may be favored. Thus 2-methyl-1,4-dihydrobenzoic acid (**1a**), affords a β-lactone. Of the two possible β-lactones only one is formed, lactone formation in this case being directed toward the more substituted double bond to produce **2a**. In the bromolactonization of the isomeric carboxylate salt, **1b**, lactonization is directed once again toward the more substituted double bond; however, there is a difference in lactone ring size. The major product is γ-lactone **3b**.



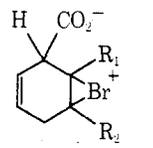
1a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = R_2 = H$
d, $R_1 = R_2 = CH_3$



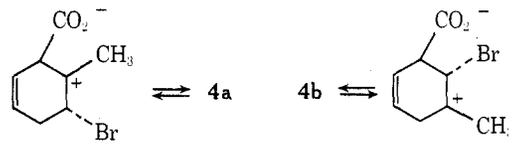
2a, $R_1 = CH_3$; $R_2 = H$ **3a**, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$ **b**, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = R_2 = H$ **c**, $R_1 = R_2 = H$
d, $R_1 = R_2 = CH_3$ **d**, $R_1 = R_2 = CH_3$

This selectivity of halolactonization for the more substituted double bond can be rationalized in terms of a probable mechanism of the reaction.[4] In the addition reactions of bromine to olefinic sites, three-membered cyclic bromonium ions have often been postulated as intermediates in a two-step mechanism, but only until recently have such intermediates received experimental support.[5] The change in lactone ring size which results from the shift of a methyl group from the β to the γ position in dihydrobenzoic acid substrates **1a** and **1b** is consistent with a brominum ion intermediate having more carbonium ion character[6] at the more substituted carbon atom, **4a** → **5**. An intermediate with character as shown by **5** could promote intramolecular Markovnikov-type regiospecificity controlling the formation of **2a** from **1a**.

A similar argument applies to the formation of a γ-lactone in the case of the isomeric acid salt **1b**. An intermediate having carbonium ion character as shown by **6** would tend to promote γ-lactone formation leading to **3b**. In both of the cases, owing to the stability of the tertiary carbonium ions, **5** and **6**, the ring closure step would be expected to possess a great deal of SN1 character.



4a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$

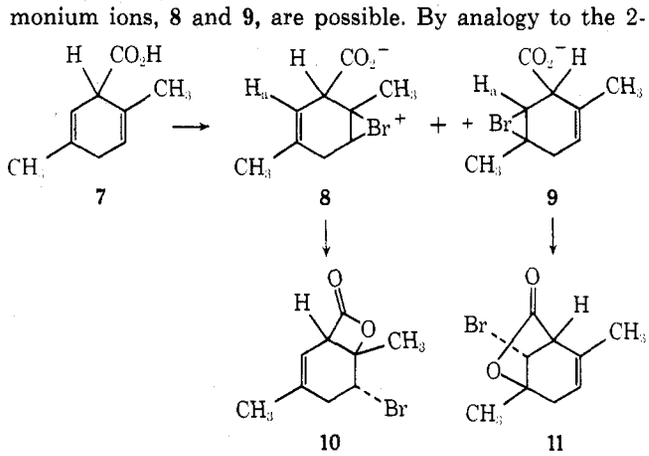


5 **6**

On the other hand, the bromonium ion involved in the reaction of **1c** is not as stable; therefore, the ring closure step would be expected to possess primarily SN2 character. Since it is known that in intramolecular SN2 ring closure reactions the geometry of the molecule is such that the formation of four-membered rings is favored over the formation of five-membered rings,[7] the expected product from **1c** is the β-lactone **2c**; indeed, **2c** is the exclusive lactone product.

Another example in which Markovnikov control is not operative, but one in which the bromonium ion is stabilized, is 2,3-dimethyl-1,4-dihydrobenzoic acid (**1d**). As expected the γ-lactone **3d** is favored (>80% by quantitative ir); however, it is not the exclusive lactone product.

As an example in which Markovnikov control is operative and competitive β- and γ-lactone formation is conceivable, the bromolactonization of 2,5-dimethyl-1,4-dihydrobenzoic acid (**7**) was studied. In this case two different bromonium ions, **8** and **9**, are possible. By analogy to the 2-methyl- and 3-methyl-1,4-dihydrobenzoic acids, the expected products of Markovnikov addition are **10** and **11**. In practice, γ-lactone formation predominates. The lactone mixture contained 93% of **11** and a small amount of γ-lactone. Since the crude reaction product does not show O=C–O–C**H** absorption in the NMR, this β-lactone must have structure **10**. Both products, **10** and **11**, would be expected to be formed by a SN1 mechanism; however, the entropy factor favors the formation of a five-membered ring over the formation of a four-membered ring.



7 **8** **9** **10** **11**

Although a limited number of examples have been examined, the examples are representative enough to permit several generalizations about the bromolactonization of 1,4-dihydrobenzoic acids. In general, the bromolactonization of alkyl-substituted 1,4-dihydrobenzoic acids is di-

rected to the more substituted olefinic site. The presence of a γ-alkyl group promotes γ-lactone formation and in the absence of any γ-alkyl substituents, β-lactone formation predominates. Within these limitations the bromolactonization reaction appears to be a viable synthetic method which promises to enhance the utility of 1,4-dihydrobenzoic acids as intermediates in organic syntheses.

Experimental Section

NMR spectra were run in CCl_4 unless otherwise indicated. The spectra were recorded with a Hitachi 100 NMR spectrometer. The infrared spectra were run in the media indicated with a Perkin Elmer Model 257 spectrometer, except for the quantitative infrared spectra for 6-bromo-5-hydroxy-5,6-dimethylcyclohex-2-enecarboxylic acid γ-lactone (**3d**) and 2,5-dimethyl-5-hydroxy-6-bromocyclohex-2-enecarboxylic acid γ-lactone (**11**), which were recorded with a Perkin-Elmer Model 261. Melting points were taken on a Reichert hot stage apparatus and are corrected. Analyses were done at the Atlantic Microlab, Inc., Atlanta, Ga.

2-Methyl-1,4-dihydrobenzoic Acid (1a). 2-Methyl-1,4-dihydrobenzoic acid was prepared according to the method of Birch.[2b] *o*-Toluic acid (40.0 g) was reduced by sodium in liquid ammonia to yield 35.0 g (86%) of colorless crystals, mp 74–76° (lit.[2b] mp 74–75°).

1,4-Dihydrobenzoic Acid (1c). 1,4-Dihydrobenzoic acid was prepared according to the method of Kuehne and Lambert,[2a] yield 16.8 g (78%), bp 89° (0.50 mm) [lit. bp[2a,b] 96–98° (0.01 mm)].

3-Methyl-1,4-dihydrobenzoic Acid (1b). To 50 g (0.368 mol) of *m*-toluic acid, 500 ml of absolute methanol, and approximately 1650 ml of liquid ammonia was added 46.3 g (2.0 mol) of sodium which was cut into small pieces. After the addition of sodium had been completed, ammonium chloride (215 g) was added. The reaction mixture was stirred for 3 hr and the ammonia was allowed to evaporate overnight. Water (800 ml) was added and the solution was acidified with 10% HCl. The aqueous layer was extracted four times with 200-ml portions of ether. The combined ether layers were dried (Na_2SO_4) and filtered, and the solvent was evaporated in vacuo, yielding 43.0 g (85%). After one recrystallization from ether–light petroleum ether, the yield was 30.0 g (60%): mp 82.5–84.5°; NMR δ 12.13 (s, 1 H), 5.43–5.75 (m, 3 H), 3.40–3.77 (m, 1 H), 2.48–2.60 (m, 2 H), 1.73 (s, 3 H).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.65; H, 7.37.

2,3-Dimethyl-1,4-dihydrobenzoic Acid (1d). 2,3-Dimethyl-1,4-dihydrobenzoic acid was prepared in the same manner as **1b**. The crude yield from the reduction of 2,3-dimethylbenzoic acid (0.167 mol) was 23.0 g. After recrystallization from ether–light petroleum ether, the yield was 19.2 g (76%): mp 74.5–76.5°; NMR δ 12.12 (s, 1 H), 5.71 (m, 2 H), 3.39–3.67 (m, 1 H), 2.50–2.65 (m, 2 H), 1.68 (s, 6 H).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.11; H, 7.87.

2,5-Dimethyl-1,4-dihydrobenzoic Acid (7). 2,5-Dimethyl-1,4-dihydrobenzoic acid was prepared in the same manner as **1b**. The crude yield from the reduction of 2,5-dimethylbenzoic acid (0.167 mol) was 23.2 g (91.5%). After recrystallization from ether–light petroleum ether, the yield was 17.8 g (72%): mp 82–83°; NMR δ 12.02 (s, 1 H), 5.35–5.50 (m, 2 H), 3.27–3.67 (m, 1 H), 2.42–2.65 (m, 2 H), 1.70 (s, 6 H).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03, H, 7.95. Found: C, 70.90; H, 8.00.

5-Bromo-6-hydroxy-6-methylcyclohex-2-enecarboxylic Acid β-Lactone (2a). To 1.38 g (0.01 mol) of **1a**, which was dissolved in 40 ml of a saturated $NaHCO_3$ solution, was added 1.60 g (0.01 mol) of bromine in 50 ml of methylene chloride. The stirring was continued at room temperature until the disappearance of the bromine color (about 1 min). The layers were separated and the aqueous layer was extracted with 25 ml of methylene chloride. The combined organic layers were washed with 25 ml of water. The organic layer was dried (Na_2SO_4), and then the solvent was evaporated in vacuo, yielding 1.13 g (52%), ir (film) 1827 (C=O), 1642 cm^{-1} (C=C). Recrystallization from ether–light petroleum ether yielded 0.74 g (29.5%): mp 51–53°; NMR δ 5.85–5.98 (m, 2 H), 4.31–4.45 (t, 1 H), 3.79–3.88 (d, 1 H), 2.64–2.80 (m, 2 H), 1.84 (s, 3 H).

Anal. Calcd for $C_8H_9BrO_2$: C, 44.27; H, 4.18; Br, 36.70. Found: C, 44.31; H, 4.26; Br, 36.54.

5-Bromo-6-hydroxycyclohex-2-enecarboxylic Acid β-Lactone (2c). A procedure similar to that used for the preparation of **2a** was used. The crude yield from **1c** (0.01 mol), bromine (0.01 mol), and $NaHCO_3$ reaction mixture was 1.20 g (59.6%), ir (film) 1825 (C=O), 1643 cm^{-1} (C=C). Recrystallization from ether–light petroleum ether yielded 0.85 g (42%): mp 84–85°; NMR ($CDCl_3$) δ 5.68–6.18 (m, 2 H), 4.17–4.96 (m, 3 H), 2.64–2.75 (m, 2 H).

Anal. Calcd for $C_7H_7BrO_2$: C, 41.41; H, 3.48; Br, 39.35. Found: C, 41.36; H, 3.58; Br, 39.15.

6-Bromo-5-hydroxy-5-methylcyclohex-2-enecarboxylic Acid β-Lactone (3b). A procedure similar to that used for the preparation of **2a** was used. The crude yield from **3b** (0.01 mol), bromine (0.01 mol), and $NaHCO_3$ reaction mixture was 1.55 g (71.4%), ir (film) 1785 (C=O), 1638 cm^{-1} (C=C). Recrystallization from ether–light petroleum ether yielded 1.33 g (61.3%): mp 70–71°; NMR δ 5.78–5.84 (m, 2 H), 4.24–4.28 (d, 1 H), 3.12–3.24 (m, 1 H), 2.40–2.50 (m, 2 H), 1.45 (s, 3 H).

Anal. Calcd for $C_8H_9BrO_2$: C, 46.78; H, 4.80; Br, 34.58. Found: C, 46.74; H, 4.83; Br, 34.51.

The infrared spectrum of the residue from the combined mother liquors vs. the spectrum of the pure γ-lactone indicated that the mother liquor contained 80 ± 3% γ-lactone (ratio of γ- to β-lactone in crude product ~93:7).

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

Registry No.—**1a**, 55886-48-1; **1b**, 31673-44-6; **1c**, 4794-04-1; **1d**, 31673-37-7; **2a**, 55886-49-2; **2c**, 55886-50-5; **3b**, 55886-51-6; **7**, 31673-39-9; *m*-toluic acid, 99-04-7; 2,3-dimethylbenzoic acid, 603-79-2; 2,5-dimethylbenzoic acid, 610-72-0.

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(6) For a discussion of unsymmetrical halonium ions see G. A. Olah and J. M. Bollinger, *J. Am. Chem. Soc.*, **90**, 947 (1968); B. Capon, *Q. Rev., Chem. Soc.*, **18**, 45 (1964).
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