Studies on Structurally Simple α,β-Butenolides. VIII. 5-Haloalkyl- and 3-bromo-5-hydroxyalkyl-2(5*H*)-furanones

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Bromine and NBS react with sorbic acid to yield bromohydrin **5** and bromolactones **4**, respectively. The *erythro* and *threo* isomers **4a,b** were separated and the crystal structure of the former was determined. Bromolactone **7**, as a single *erythro* stereoisomer, was prepared by photolactonization of **5**.

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Structurally simple 2(5*H*)-furanones or α,β-butenolides are frequently used in the synthesis of other heterocyclic structures available by thermal [1] and photochemical [2] routes. In addition, their five-membered ring is present in many secondary metabolites with a wide range of biological activities [3,4,5]. In particular 3-bromo-2(5*H*)-furanone derivatives, that can be used in the synthesis of important compounds such as 3-acyltetronic acids [6], have been prepared by a series of methods, depending on the nature of the C-5 substituent: alkyl [7], bromoalkyl [8] or alkoxy [9].

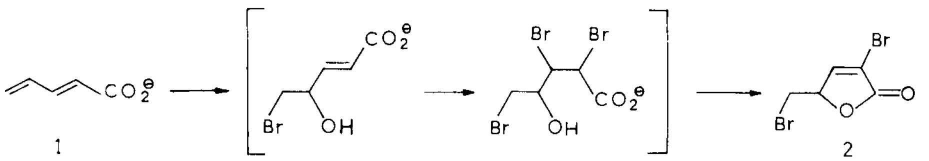
Some time ago we described the simple preparation (although in low yield) of 3-bromo-5-bromomethyl-2(5*H*)-furanone, **2**, by reaction of (*E*)-2,4-pentadienoic acid, **1** with two equivalents of bromine in aqueous sodium bicarbonate [8]. The proposed mechanism for this reaction is given in Scheme 1.

Now, we have found (Scheme 2) that a similar reaction performed on sorbic acid, **3**, gives as the only isolated products: 3-bromo-5-(1-hydroxyethyl)-2(5*H*)-furanone, **4**, (7%), as a mixture of *erythro*/*threo* stereoisomers, and the bromohydrine, (*E*)-(4*RS*,5*SR*)-5-bromo-4-hydroxy-2-hexenoic acid, **5**, (4%). However, **5** is the major identified product (35% yield) in the reaction of **3** with bromine in water [10].

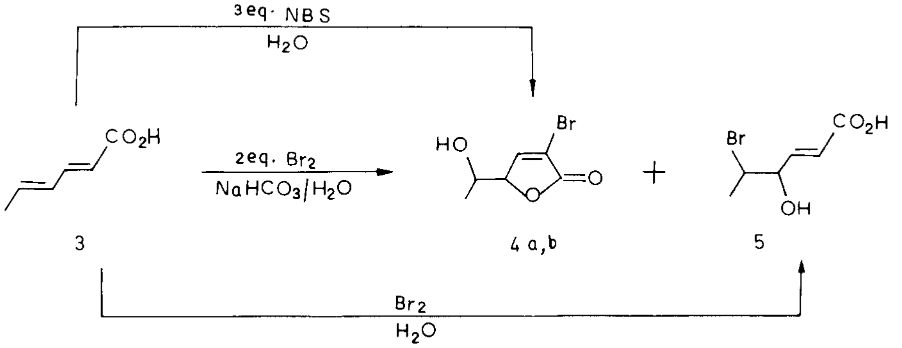
The yield of 2(5*H*)-furanone **4** could be considerably increased using three molar equivalents of *N*-bromosuccinimide (NBS) as brominating agent and water as solvent. Thus, a 20% yield of a 1:1 mixture of *erythro* and *threo*, isomers **4a** and **4b**, could be obtained.

These two isomers, which could be separated by column chromatography, were constitutionally assigned from their analytical and spectroscopic data (see Experimental). However, their configuration could not be deduced from

Scheme 1



Scheme 2



nmr data since differences in chemical shifts and coupling constants were too small. Attempts to correlate coupling constants with *erythro-threo* configurations by means of molecular mechanics [11,12] followed by 3JHH calculations [13] were not carried out because the error accepted for these calculations (±0.5 Hz) is bigger than the observed J differences between both isomers. We therefore resorted to single crystal X-ray diffraction analysis as the only method available for configurational assignment. This was performed on the crystalline isomer **4a** (mp 80.5-82.0°) that was finally identified as the *erythro*.

The formation of **5** can be explained by the same mechanism depicted in Scheme 1, *i.e.* through an attack of the bromine cation to the 4,5-double bond. However, the analogous cyclized by product 3-bromo-5-(1-bromoethyl)-2(5*H*)-furanone was never found. Addition of bromine to the free double bond in bromohydrin **5** seems then precluded. On the other hand, under the action of NBS, sorbic acid, having a more electron-rich conjugation system than pentadienoic acid, prefers to react in a 1,4-addition mode. Therefore, the formation of **4** can be rationalized as shown in Scheme 3.

Eventually, **5** can be cyclized to bromobutenolide **7**, in high yield (70%), by uv irradiation in acidic water (Scheme 4). This photolactonization could also be performed from the corresponding ester **6** (methyl ester) in dichloromethane but the yield of **7** dropped to about 35%. A similar decrease in yield was observed in the case of the photolactonization of the lower homologues, **(E)**-5-bromo-4-hydroxy-2-pentenoic acid and its ester [8].

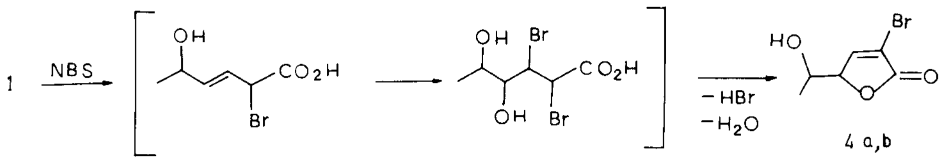
Crystal Structure Determination [14].

Colorless isometric crystals of **4a** were grown from a dichloromethane/pentane solution, a suitable single crystal cut to 0.6 x 0.4 x 0.4 mm having faces {100}, {010}, {0-11}, {0-1-1} was mounted on an Enraf-Nonius CAD4 diffractometer with Nb filtered MoKα radiation (λ = 0.71069 Å). The tetragonal unit cell and orientation matrix were defined by a least-squares refinement of 25 centered reflections in the 16-20° 2θ range. Cell parameters are a = b = 16.511(2) c = 5.5165(9)Å, $\alpha = \beta = \gamma = 90°$, V = 1503.8(6)Å^3, Z = 8, D_x = 1.824 g.cm^{-3}. Intensity data were collected at room temperature for $h \geq 0$, $k \geq 0$, $l \geq 0$; (the maximum values of h, k, l were 19, 19 and 6 respectively). Space group $p4_2/n$ deduced from systematic extinctions. Absorption corrections were applied (μ = 53.56 cm^{-1}) and gave minimum and maximum transmission factors 0.117 and 0.203 respectively. Tree standard reflections were monitored every 6000 seconds with no appreciable variations. A variable speed from 0.8 to 2.0 degrees/minute was used. Total reflections with $2\theta < 50°$, 1407 unique reflections with 861 having $F \geq 2.5\,\sigma(F)$. The structure was solved by the heavy atom method, locating the bromine by Patterson synthesis. The lactonic ring was found on subsequent weighted Fourier maps. The refinement (on F) was carried out using the program UPALS [15]. Anisotropic thermal parameters were used for all non-H atoms and isotropic temperature factors for hydrogens bonded to C4, C5 and C6; an isotropic extinction factor (2.565 x 10^{4}rad^{-1}) was used. The (200) reflection was excluded from the refinement due to poor measurements of very low angle peak and backgrounds. Final conventional R value was R = 0.058 and wR = 0.059, s = 1.292.

Maximum and minimum heights in the final difference Fourier map 0.4 and −0.3 e.Å^{-3}. All calculations were performed on a Digital Vax 750.

Final atomic coordinates and temperature factors are given in Table 1. Bond lengths and bond angles are given in Table 2. Figure 1 and Figure 2 show, respectively a perspective view of molecule 4a and a stereoscopic view [16].

Scheme 3



Scheme 4

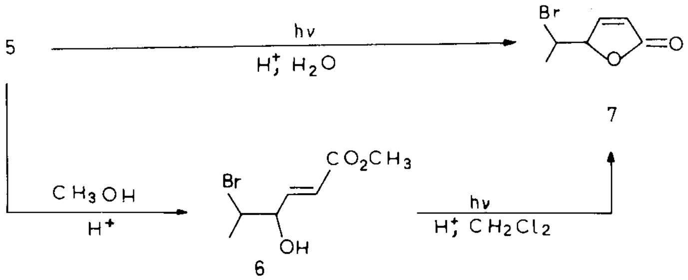


Table 1

Final fractional atomic coordinates and anisotropic temperature factors ($\times 10^5$), e.s.d.'s in parentheses

	X/A	Y/B	Z/C	β_{11}	β_{22}	β_{33}	β_{23}	β_{13}	β_{12}
O1	0.05983(28)	0.02651(30)	−0.30088(94)	195(21)	299(24)	3514(244)	21(18)	48(58)	71(62)
C2	0.09770(47)	0.07003(47)	−0.13273(151)	275(35)	229(34)	3005(337)	61(29)	142(90)	112(85)
C3	0.18471(43)	0.05755(46)	−0.15864(139)	198(31)	320(36)	2353(289)	−36(27)	−15(77)	134(87)
C4	0.19831(48)	0.00630(51)	−0.33425(148)	217(35)	357(38)	2779(321)	−46(31)	148(88)	−19(94)
C5	0.11847(43)	−0.02145(48)	−0.43356(170)	248(31)	368(36)	1939(308)	−13(27)	−55(90)	221(91)
C6	0.09959(48)	−0.11093(50)	−0.39961(158)	199(35)	390(39)	3216(397)	15(32)	−217(89)	184(92)
C7	0.15878(54)	−0.16558(51)	−0.53732(158)	415(39)	416(41)	3221(326)	78(34)	−13(103)	−360(100)
O8	0.06218(35)	0.11053(34)	0.00893(110)	353(26)	400(27)	4954(325)	26(22)	429(72)	−169(74)
Br9	0.25747(5)	0.10981(7)	0.04647(19)	326(5)	621(6)	4601(47)	−73(4)	−120(12)	−594(13)
O10	0.10038(32)	−0.12904(31)	−0.14880(95)	379(27)	332(25)	2332(213)	51(20)	80(57)	237(55)

Table 2

Bond distances (A) and bond angles (°) e.s.d.'s. in Parentheses

Bond Distances

C2---O1	1.330(9)	Br9--C3	1.862(7)
C5---O1	1.449(9)	C5---C4	1.499(11)
C3---C2	1.458(11)	C6---C5	1.522(11)
O8---C2	1.184(10)	C7---C6	1.532(12)
C4---C3	1.306(11)	O10--C6	1.416(10)

Bond Angles

C2---O1---C5	109.5(5)	C3---C4---C5	108.5(1)
O1---C2---C3	108.6(6)	O1---C5---C4	103.6(6)
O1---C2---O8	122.2(7)	O1---C5---C6	109.4(6)
C3---C2---O8	129.2(7)	C4---C5---C6	115.6(6)
C2---C3---C4	109.5(7)	C5---C6---C7	112.3(7)
C2---C3---Br9	120.7(5)	C5---C6---O10	108.9(7)
C4---C3---Br9	129.8(6)	C7---C6---O10	110.7(6)

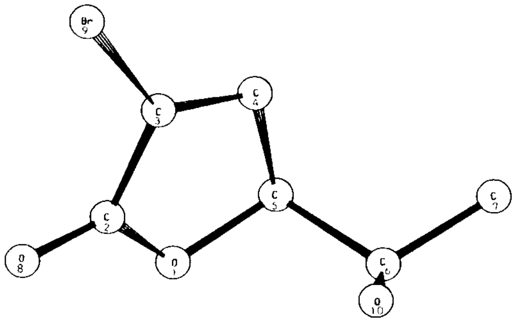


Figure 1. A perspective view of the molecule **4a** with atom labelling.

Figure 2. Stereoscopic view of the molecule **4a**.

The bond distances and angles are in the normally observed ranges for this type of molecules [17]. The lactonic ring is planar (average of intra-annular torsion angles in absolute value: 3.5°). The maximum deviation from the mean plane of the ring is 0.03 Å at oxygen O1.

The bromines lying on symmetry codes X,Y,Z; Y,0.5-X,-0.5-Z; 0.5-Y,X,-0.5-Z and 0.5-X,0.5-Y,Z are the vertices of a tetrahedron, one of whose binary axis is coincident with the 4-inversion symmetry axis; the distance between these bromines is 4.629(2) Å.

Both enantiomers are present in the crystal lattice as centrosymmetric space group suggests. The stereochemistry at the chiral centers C5 and C6 is 5R, 6S for one of the enantiomers.

EXPERIMENTAL

General Methods.

Melting points were determined on a Kofler and are uncorrected. The pmr (80 MHz) spectra were recorded on a Bruker WP 80 SY spectrometer and the cmr spectra on a Varian 400 VXR. Mass spectra were obtained on a Hewlett Packard 5985 B spectrometer. The ir spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. The uv spectra were recorded on a Perkin-Elmer 550 spectrophotometer. The irradiations were performed using a 400W medium pressure mercury lamp (Applied Photophysics mod 3040), refrigerated with a water-cooled quartz jacket, on standard uv cells containing the solution to be irradiated under argon bubbling. Elemental analyses were performed by Centro de Investigacion y Desarrollo (CSIC) in Barcelona.

General Procedure.

Synthesis of 3-Bromo-5-(1-hydroxyethyl)-2(5*H*)-furanones, **4a,b**.

To an emulsion of 2,4-hexadienoic acid (3.0 g) in water (100 ml), *N*-bromosuccinimide (14.310 g) was added portionwise at 37° and the mixture was stirred for 18.5 hours at this temperature. After cooling, the mixture was extracted with dichloromethane, and the organic phase was kept. The aqueous phase was concentrated to dryness by azeotropic elimination of water with benzene (Dean-Stark) and the residue was taken up with ether.

The combined organic extracts were washed with aqueous sodium hydrogenosulfite, dried over sodium sulfate and the solvents were evaporated. Chromatography of the residue on silica gel, eluting with hexane/ethyl acetate, yielded the following in order of elution:

(5*RS*)-3-Bromo-5-[(1*SR*)-1-hydroxyethyl]-2(5*H*)-furanone (*erythro*, **4a**).

The yield was 560 mg (10%), mp 80.5-82°; uv (methanol): λ max (log ε) 225 nm (3.95) and 208 nm (3.83); ir (potassium bromide): 3435, 3095, 2985, 2925, 1750, 1601, 1455, 1425, 1390, 1365, 1328, 1310, 1280, 1267, 1173, 1150, 1097, 1074, 1023, 999, 975, 920, 888 and 840 cm^{-1}; pmr (deuteriochloroform): 1.35, H(7) [d, J (7,6) = 6.5 Hz, 3H]; 4.05, H(6) [m, 1H], 4.84, H(5) [dd, J(5,4) = 1.8 Hz, J(5,6) = 5.1 Hz, 1H] and 7.60, H(4) [dd, J(4,6) = 0.4 Hz, 1H]; cmr (deuteriochloroform): 19.0, 67.7, 85.9, 114.2, 149.9 and 168.3; ms: m/z 207-209 ($M^+ + 1$, 2.04:2.40), 162-164 (48.7:56.2), 105-107 (11.0:10.8), 53 (26.5) and 45 (100).

Anal. Calcd. for $C_6H_7BrO_3$: C, 34.81; H, 3.41. Found: C, 34.89; H, 3.56.

(5*RS*)-3-Bromo-5-[(1*RS*)-1-hydroxyethyl]-2-(5*H*)-furanone (*threo*, **4b**).

The yield was 560 mg (10%), oil, bp 134-137° at 0.02 mm Hg; uv (methanol): λ max (log ε) 224 nm (3.88); ir (film): 3428, 3087, 2975, 2930, 1760, 1607, 1456, 1405, 1385, 1360, 1290, 1170, 1142, 1075, 1063, 1038, 1015, 926, 887 and 840 cm^{-1}; pmr (deuteriochloroform): 1.32, H(7) [d, J(7,6) = 6.5 Hz, 3H], 4.00, H(6) [dq, J(6,5) = 5.0 Hz, 1H], 4.89, H(5) [dd, J(5,4) = 1.8 Hz, 1H] and 7.55, H(4) [d, 1H]; cmr (deuteriochloroform): 18.7, 68.1, 86.2, 114.3, 149.9 and 168.2; ms: m/z 207-209 ($M^+ + 1$, 0.3:0.3), 162-164 (41.7:39.9), 105-107 (7.7:5.4) and 45 (100).

Anal. Calcd. for $C_6H_7BrO_3$: C, 34.81; H, 3.41. Found: C, 34.52; H, 3.34.

Preparation of (*E*)-(4*RS*,5*SR*)-5-Bromo-4-hydroxy-2-hexenoic Acid, **5**.

To a solution of 5.60 g (50 mmoles) of **3** in 1.0 ℓ of water, 3.2 ml (10.0 g, 62.5 mmoles) of bromine dissolved in 0.5 ℓ of cold water, was added dropwise over 1 hour at 85°, under stirring. Mixture was stirred for two further hours at room temperature. The extraction with dichloromethane yielded 1.85 g (33%) of starting material, **3**. A new extraction with diethyl ether gave 3.26 g of oil, which by column chromatography yielded 2.43 g (35%) of **5**, mp 104-105° (chloroform) (lit [10] 110°). The unpublished spectra of this compound are: uv (methanol): λ max (log ε) 206 nm (4.12); ir (potassium bromide): 3284, 2984, 2674, 2579, 1696, 1664, 1447, 1400, 1316, 1292, 1272, 1219, 1201, 1148, 1109, 1084, 989, 951, 874 and 844 cm^{-1}; pmr (deuterioacetone): 1.67, H(6) [d, J(6,5) = 6.7 Hz, 3H], 4.38, H(5) [dq, J(5,4) = 4.7 Hz, 1H], 4.74, (H(4) [m, 1H], 6.15, H(2) [dd, J(2,3) = 15.6 Hz, J(2,4) = 1.5 Hz, 1H] and 6.98, H(3) [dd, J(3,4) = 4.8 Hz, 1H]; cmr (deuterioacetone): 21.4, 54.0, 75.1, 123.5, 147.7 and 167.3; ms: m/z 190-192 (0.7:0.4), 163-165 (0.9:0.6), 129 (1.3), 107-109 (26.0:16.7), 101 (100), 84 (28.8), 73 (40.3) and 45 (97.9).

Reaction of Sorbic Acid, **3**, with Bromine in Aqueous Medium.

To 0.900 ℓ of an aqueous saturated solution of sodium bicarbonate, containing 39.2 g (0.35 mole) of **3**, 19.6 ml (67.8 g, 0.42 mole) of bromine, was added dropwise over 3 hours at room temperature under stirring. Extraction with dichloromethane yielded 6.7 g of an oil. Acidification to *p*H 2 with sulfuric acid and a new extraction with dichloromethane yielded 20.9 g (53%) of starting material **3**. Repeated extractions with diethyl ether gave a further amount of 17.55 g of oil. Column chromatography of the combined oils yielded 2.40 g (7.1%) of a mixture of **4a,b** and 2.63 g (7.7%) of **5**, identical with those described above.

Preparation of Methyl (*E*)-(4*RS*,5*SR*)-5-Bromo-4-hydroxy-2-hexenoate, **6**.

A solution of 1.045 g (5 mmoles) of **5** in 20 ml of dry methanol, containing 3 drops of sulfuric acid, was refluxed under stirring for 20 hours. After neutralization with aqueous sodium bicarbonate and solvent removal, the residue was taken up with dichloromethane yielding 0.941 g (84%) of an ester, **6**, bp 101-106°/0.02 mm Hg. The unpublished spectra of this compound are: uv (methanol): λ max (log ε) 224 nm (3.70); ir (film): 3600-3200, 2975, 2944, 2923, 1715, 1657, 1510, 1443, 1384, 1323, 1287, 1208, 1185, 1148, 1105, 1077, 1052, 1002, 985, 934, 890 and 866 cm^{-1}; pmr (deuteriochloroform): 1.66, H(6) [d, J(6,5) = 6.8 Hz, 3H]; 3.76, OCH_3 [s, 3H]; 4.31, H(5) [dq, J(5,4) = 3.7 Hz, 1H]; 4.46, H(4) [m, 1H]; 6.16, H(2) [dd, J(2,3) = 15.6 Hz, J(2,4) = 1.6 Hz, 1H] and 6.91, H(3) [dd, J(3,4) = 4.5 Hz, 1H]; cmr (deuteriochloroform): 20.2, 51.7, 53.6, 74.3, 123.0, 144.8 and 166.4; ms: m/z 223-225 ($M^+ + 1$, 3.4:3.5), 191-193 (5.9:5.8), 115 (100), 87 (48.8), 83 (54.7) and 55 (62.1).

Preparation of (5*RS*)-5-[(1*SR*)-1-Bromoethyl]-2(5*H*)-furanone, **7**.

(a) By Photolactonization of **5**.

A solution of 104 mg (0.5 mmole) of **5** in 3.5 ml of water, containing 1 ml of 0.3*N* hydrochloric acid was irradiated for 30 minutes. Extraction with dichloromethane yielded 67 mg (70%) of **7**, mp 51-52° (dichloromethane/pentane); uv (chloroform): λ max (log ε) 241 nm (2.10); ir (potassium bromide): 3105, 2992, 2980, 2968, 1748, 1603, 1443, 1383, 1334, 1298, 1276, 1206, 1163, 1098, 1023, 1006, 897, 883 and 834 cm^{-1}; pmr (deuteriochloroform): 1.84, H(7) [d, J(7,6) = 6.7 Hz, 3H], 3.94, H(6) [dq, J(6,5) = 7.7 Hz, 1H], 4.98, H(5) [ddd, J(5,3) = 2.0 Hz, J(5,4) = 1.5 Hz, 1H], 6.22, H(3) [dd, J(3,4) = 5.8 Hz, 1H] and 7.62, H(4) [dd, 1H]; cmr (deuteriochloroform): 22.6, 46.3, 85.4, 123.4, 154.1 and 171.9; ms; m/z 190-192 (M^+, 1.4:1.4), 161-163 (13.2:12.7), 133-135 (2.0:2.0), 107-109 (6.7:6.5), 84 (100), 83 (28.5).

Anal. Calcd. for $C_6H_7BrO_2$: C, 37.72; H, 3.69. Found: C, 37.65; H, 3.55.

(b) By Photolactonization of **6**.

A solution of 0.5 mg of 4-methylbenzenesulfonic acid in 4.5 ml of dichloromethane, containing 36 mg (0.16 mmole) of **6**, was irradiated for 10 minutes. The solvent was evaporated and column chromatography yielded 6 mg (17%) of starting material **6** and 9 mg (35%) of **7**, identical with that described above.

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