Brominated Derivatives of 4-Hydroxy- and 4-Methoxy-6-methyl-2*H*-pyran-2-ones

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Twenty-five different brominated derivatives of 4-hydroxy-6-methyl-2-pyrone (triacetic acid lactone) and 3-acetyl-4-hydroxy-6-methyl-2-pyrone (dehydroacetic acid) have been prepared. Fifteen derivatives have not been previously described and the preparations of a few known products have been improved. Bromination at C-3, C-5, methyl group at C-6 and deacetylations at C-3 have been the types of reactions used.

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Introduction.

3-Acetyl-4-hydroxy-6-methyl-2-pyrone (dehydroacetic acid), **1**, is an industrially available product, and also a natural product [1]. 4-Hydroxy-6-methyl-2-pyrone, **21**, a simple polyketide [2], can be easily prepared by treating **1** with 90% sulfuric acid at 130° [3]. Moreover, many natural products have been isolated which possess the 4-hydroxy (or methoxy)-2-pyrone structure with different substituents at C-3, C-5 and C-6.

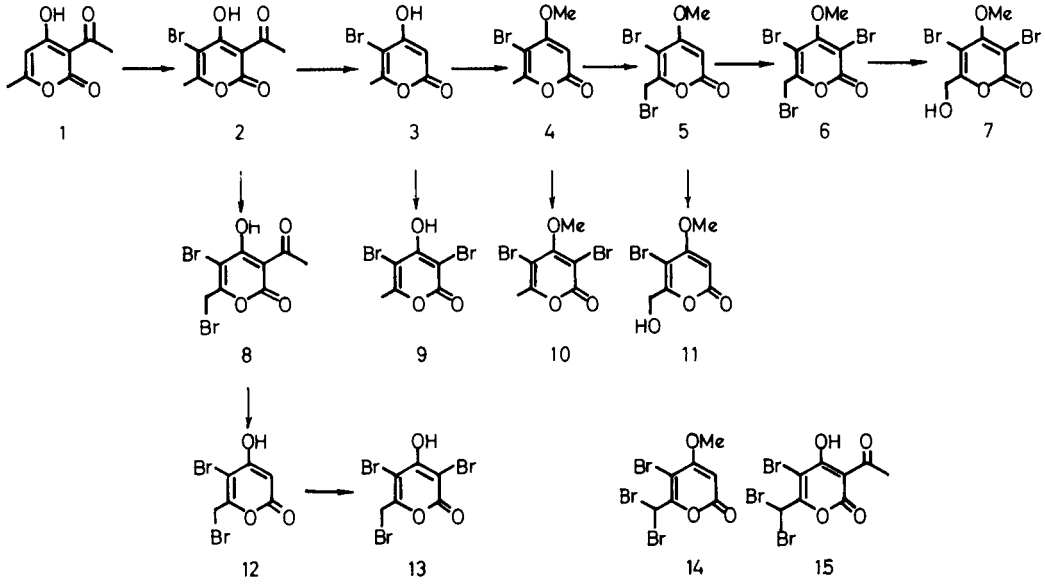
In the course of a synthetic project we needed general methods to functionalize the aforementioned positions. Alkylation at C-3 is now possible, a solution of broad scope having been published [4] by our group. Efforts to alkylate C-5 have met only with limited success [5,6]. Functionalization at C-6 in **1**, **21**, 4-methoxy-6-methyl-2-pyrone, **22**, and related products has been achieved by alkylation [7,8,9], bromination [5,10,11] and selenium dioxide oxidation [5, 12,13].

Introduction of a bromine substituent on a particular carbon atom is the first step of many functionalization sequences. Subsequent replacement by nucleophiles or (with Umpolung, *via* organometallic intermediates) by electrophiles opens a wide range of possibilities.

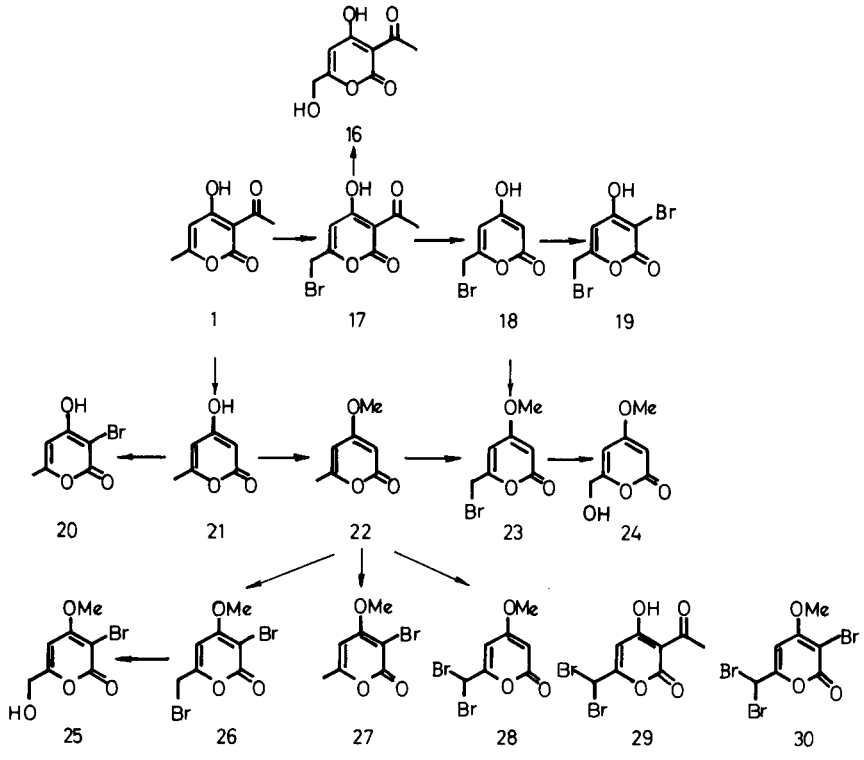
Since we are engaged in a synthetic project in which the pyrones **1** and **21** are starting materials, we became interested in general methods to brominate, and in general to place first oxidation degree functions, at the different positions of our starting materials. Therefore, we have studied methods to prepare twenty-five different brominated products, fifteen of them not previously described, and also to improve the preparation of a few already known compounds.

A very complete study of the bromination of **1** under different experimental conditions, reported by Harris *et al.* [10], describes easily reproducible methods for the preparation of 3-acetyl-5-bromo-4-hydroxy-6-methyl-2-pyrone, **2**, and 3-acetyl-6-bromomethyl-4-hydroxy-2-pyrone, **17**. The

Scheme 1



Scheme 2



former, a C-5 functionalized compound, is obtained by treatment of **1** with bromine in chloroform containing a trace of iodine. On the other hand, reaction of **1** with *N*-bromosuccinimide under radical conditions is the method of choice for the preparation of **17**, although some dibromination takes place also and 3-acetyl-6-dibromomethyl-4-hydroxy-2-pyrone, **29**, is usually isolated as a by-product [10]. Both methods have been used by us [5,6], showing reproducible results. Harris described also the preparation of 3-bromo-4-hydroxy-6-methyl-2-pyrone, **20**, by treatment of the pyrone **21** with *N*-bromosuccinimide.

Bloomer *et al.* [11] reported that bromination of the *O*-methylated derivative **22** under radical conditions affords 6-bromomethyl-4-methoxy-2-pyrone, **23**. We have found some difficulty in reproducing this reaction, in which bromination at C-3 giving 3-bromo-4-methoxy-6-methyl-2-pyrone, **27**, constitutes a seriously competing reaction [5]. High dilution conditions, though favouring formation of **23**, render the method quite difficult to be scaled up [5]. Use of grounded *N*-bromosuccinimide also favors **23** [14]. By varying dilution and NBS/**22** ratio, we could prepare **27**, **23**, 3-bromo-6-bromomethyl-4-methoxy-2-pyrone, **26**, and 6-dibromomethyl-4-methoxy-2-pyrone, **28** [5]. However, as reported below, no special precautions were required to convert 5-bromo-4-methoxy-6-methyl-2-pyrone, **4**, into 5-bromo-6-bromomethyl-4-methoxy-2-pyrone, **5**, by treatment of the former with NBS under radical conditions, as no C-3 brominated by-products were formed.

We have also previously described the preparation of 5-bromo-4-hydroxy-6-methyl-2-pyrone, **3**, by deacetylation of **2** with 90% sulfuric acid [6]. The pyrone **3** was methylated by standard methods to afford 5-bromo-4-methoxy-6-methyl-2-pyrone, **4** [6].

Oxidation of the methyl group of **22** and related compounds with selenium dioxide presents serious problems [5,12,13]. Therefore, replacement of hydroxy group for bromine can be a useful alternative. We have previously reported the conversion of **23** into 6-hydroxymethyl-4-methoxy-2-pyrone, **24** [5], which is a natural product (opuntiol), by adaptations of the method which Caputo *et al.* [15] have applied to a similar case, and which is based on the reaction of water on the substrate adsorbed on silica-gel. This method is superior to the one based on the aqueous sodium hydroxide, as described in the preparation of 3-acetyl-4-hydroxy-6-hydroxymethyl-2-pyrone, **16**, from **17** [5]. The main inconvenience of the latter was the formation of important amounts of the corresponding ether unless high dilution conditions were adopted.

Results.

To prepare the twenty-five compounds, the following methods have been used:

1. Bromination at C-3 (Table 1).

Table 1

Brominations at C-3

No.	Reaction	Experimental Conditions	Yield (%)	Reference
1	**3** → **9**	Bromine (1.1 eq)/dichloromethane/darkness/rt/6 hours	90	This work
2	**4** → **10**	Bromine (4 eq)/dichloromethane/rt/22 hours	65	This work
3	**5** → **6**	Bromine (10 eq)/dichloromethane/rt/20 minutes	92	This work
4	**12** → **13**	Bromine (1.1 eq)/dichloromethane/rt/darkness/1.5 hours	83	This work
5	**18** → **19**	Bromine (1.1 eq)/dichloromethane/rt/darkness/6 hours	95	This work
6	**21** → **20**	NBS (1.1 eq)/*t*-butanol/darkness/30°/2 hours	77	[10]
7	**21** → **20**	NBS (1.1 eq)/dichloromethane/benzoyl peroxide/hν/reflux/2 hours	88	This work
8	**21** → **20**	Bromine (1.1 eq)/dichloromethane/rt/5 hours	73	This work
9	**21** → **20**	Bromine (1.1 eq)/dichloromethane/darkness/rt/3 hours	82	This work
10	**22** → **27**	NBS (1.2 eq)/tetrachloromethane/benzoyl peroxide/reflux/7 hours	86	[5]
11	**22** → **27**	NBS (1.2 eq)/tetrachloromethane/benzoyl peroxide/hν/reflux/7 hours	83	[5]
12	**22** → **27**	NBS (1.1 eq)/tetrachloromethane/darkness/50°/5 hours	49	[10]
13	**22** → **27**	Bromine (1.1 eq)/dichloromethane/rt/30 minutes	74	This work

Position C-3 is very active, both in 4-hydroxy- and in 4-methoxy compounds. Bromine in dichloromethane is a convenient reagent to achieve brominations at C-3, the experimental conditions not being critical (Schemes 1 and 2).

2. Bromination at C-5.

Position C-5 is much less active than C-3. Bromination of **1** to afford **2** takes place under Harris conditions [10] (bromine/cat. iodine/chloroform/5°/72 hours). Fortunately, compound **2** can be converted into a vast array of pyrones brominated at C-5 (Scheme 1).

3. Bromination at the C-6 Methyl Group (Table 2).

Bromination at the C-6 methyl group can be achieved under radical conditions (*N*-bromosuccinimide in carbon tetrachloride). The methyl ethers of triacetic acid lactone and derivatives, such as **22** and **4**, and dehydroacetic acid, **1**, and derivatives such as **2** are convenient substrates. However, lactones with both a free C-3 position and a 4-hydroxy group are too active at C-3 to be regioselectively brominated elsewhere.

Experimental conditions to brominate the methyl group at C-6 are sometimes critical and difficult to reproduce, as it usually happens for reactions in heterophase. Dilution has been found in some cases to help radical bromination at the methyl group at the expense of the competing bromination at C-3 [5] (preparation of **23** and **28**). The use of grounded *N*-bromosuccinimide militates also in favour of bromination at the methyl group [14]. However, neither high dilution nor *N*-bromosuccinimide grinding were required to accomplish the regioselective bromination of **4** into **5** in excellent yield (Table 2, run 17).

4. Deacetylations (Table 3).

The severe conditions used in the pioneering work of Collie to deacetylate **1** into **21** (90% sulfuric acid/130°/15 minutes) are compatible with the presence of bromine atoms at C-5 and at the C-6 methyl group. Thus, **17** has been converted into 6-bromomethyl-4-hydroxy-2-pyrone, **18**, **2** into **3**, and 3-acetyl-5-bromo-6-bromomethyl-4-hydroxy-2-pyrone, **8**, into 5-bromo-6-bromomethyl-4-hydroxy-2-pyrone, **12**.

5. Methylations of Hydroxy Groups at C-4 (Table 4).

They can be achieved easily by treating the 4-hydroxy compounds with the triacetic acid lactone framework under the standard conditions in which **21** was transformed into **22** by Bu'Lock *et al.* (potassium carbonate/butanone/methyl sulfate/reflux) [16].

6. Substitutions of a Hydroxy Group for a Bromine Atom in the Bromomethyl Group at C-6 (Table 5).

A modification of the method of Caputo *et al.* [15] gives very good results. The starting material, adsorbed into silica-gel, is treated with water to afford the hydroxymethyl compounds.

Nine new brominated pyrones, **5-13**, are now available from the 5-bromopyrone **2** previously reported by Harris [10]. Two more, **14** and **15**, have been isolated as by-products in the preparation of **5** and **8** respectively (Scheme 1).

The new 6-bromomethyl derivatives **18** and **19** can be prepared from Harris' pyrone **17** [10] (Scheme 2). The methyl ether **23**, previously reported *via* **1** → **21** → **22** → **23** [5,11], was more comfortably obtained *via* **1** → **17** → **18** → **23**. This alternative route circumvents the radical bromination of **22**, so difficult to reproduce [5] and is more easily scaled up. However, all our radical brominations of 6-methylpyrones to 6-bromomethylpyrones have always yielded in addition minor amounts of dibrominated compounds, 6-dibromomethylpyrones (reactions 14-17, 19 and 23, Table 2) or the product of dibromination at both, the methyl group and C-3 (reaction 18, Table 2).

Table 2

Brominations at the C-6 Methyl Group

No.	Reaction	Experimental Conditions	Yield of main product (%)	By-product (yield)	Reference
14	**1** → **17**	NBS (1.1 eq)/tetrachloromethane/hν/rt/7 hours	23	**29**	[10]
15	**1** → **17**	NBS (1.1 eq)/tetrachloromethane/hν/rt/7 hours	59	**29**	[5]
16	**2** → **8**	NBS (1.2 eq)/tetrachloromethane/hν/rt/20 hours	61	**15** (5%)	This work
17	**4** → **5**	NBS (1.3 eq)/tetrachloromethane/benzoyl peroxide/reflux/24 hours	78	**14** (10%)	This work
18	**22** → **23**	NBS (1.2 eq)/tetrachloromethane/high dilution/benzoyl peroxide/hν/-reflux/2 hours	68	**26** (9%)	[5]
19	**22** → **23**	NBS (1.1 eq)/tetrachloromethane/high dilution/AIBN/hν/reflux/1.5 hours	63	**28** (14%)	[5]
20	**22** → **23**	NBS/tetrachloromethane/*t*-butyl peroxide/reflux	70		[11]
21	**22** → **26**	NBS (2.3 eq)/benzene/AIBN/hν/rt/6 hours	86		[5]
22	**22** → **26**	NBS (2.2 eq)/tetrachloromethane/benzoyl peroxide/hν/reflux 2 hours	82		[5]
23	**22** → **26**	NBS (2.2 eq)/tetrachloromethane/benzoyl peroxide/hν/reflux/2 hours	69	**30** (8%)	This work
24	**22** → **28**	NBS (2.2 eq)/tetrachloromethane/high dilution/benzoyl peroxide/hν/reflux/1 hour	81		[5]

Table 3

Deacetylations

No.	Reaction	Experimental Conditions	Yield (%)	Reference
25	**2** → **3**	90% sulfuric acid/130°/25 minutes	50	[6]
26	**17** → **18**	90% sulfuric acid/132°/18 minutes	72	This work
27	**8** → **12**	90% sulfuric acid/132°/18 minutes	70	This work

Table 4

Methylations

No.	Reaction	Experimental Conditions	Yield (%)	Reference
28	**3** → **4**	Potassium carbonate/butanone/methyl sulfate/reflux/5 hours	80	[6]
29	**18** → **23**	Potassium carbonate/acetone/methyl sulfate/reflux/1 hour	80	This work

Table 5

Substitution of OH for Br

No.	Reaction	Experimental Conditions	Yield (%)	Reference
30	**23** → **24**	Silica-gel/water/rt/18 hours	83	[5]
31	**26** → **25**	Silica-gel/water/reflux/21 hours	70	This work
32	**5** → **11**	Silica-gel/water/reflux/19 hours	67	This work
33	**6** → **7**	Silica-gel/water/reflux/7 hours	30	This work
34	**17** → **16**	Excess sodium hydroxide/water/50°/25 hours	67	[5]

EXPERIMENTAL

The ir spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. The pmr and cmr spectra were recorded on a Bruker WP80SY spectrometer. The ms were run on a Hewlett-Packard 5985-B spectrometer; peaks with an intensity lower than 20% are not described (except molecular ions).

5-Bromo-6-bromomethyl-4-methoxy-2-pyrone (**5**) and 5-Bromo-6-dibromomethyl-4-methoxy-2-pyrone (**14**) (Reaction 17, Table 2).

The pyrone **4** [6] (2.19 g, 10.0 mmoles), *N*-bromosuccinimide (2.31 g, 13 mmoles) and benzoyl peroxide (catalytic amount) were refluxed in anhydrous tetrachloromethane (75 ml) for 24 hours. The mixture was filtered and the solvent was evaporated. The residue was partitioned between dichloromethane and 1*N* sodium hydroxide. The organic layer was dried over sodium sulfate and evaporated to afford a residue, which recrystallized from ethanol afforded 1.96 g of pure **5**, mp 137-138°; ir (potassium bromide): 1720 cm^{-1}; pmr (deuteriochloroform): δ 3.9 (s, 3H), 4.4 (s, 2H), 5.6 (s, 1H); cmr (deuteriochloroform): δ 166.2, 161.1, 156.3, 98.9, 90.3, 57.2, 26.1; ms: 300 (15), 298 (40), 296 (M^+, 15), 219 (67), 217 (67), 191 (100), 189 (96), 149 (51), 111 (20), 69 (90), 53 (52), 43 (41).

Anal. Calcd. for $C_7H_6Br_2O_3$: C, 28.22; H, 2.03. Found: C, 28.31; H, 2.05.

The evaporated mother liquor gave a residue which was chromatographed through silica-gel with hexane/ethyl acetate as eluent to afford a second crop of 377 mg of **5** (overall yield, 78%), and 370 mg (10%) of 5-bromo-6-dibromomethyl-4-methoxy-2-pyrone, **14**, mp 157-161° (from ethanol); ir (potassium bromide): 1740 cm^{-1}; pmr (deuteriochloroform): δ 6.84 (s, 1H), 5.60 (s, 1H), 3.94 (s, 1H); cmr (deuteriochloroform): δ 165.2, 160.0, 154.5, 94.5, 91.1, 57.4, 30.2; ms: 380 (3), 378 (11), 376 (11), 374 (M^+, 4), 299 (45), 297 (100), 295 (53).

Anal. Calcd. for $C_7H_5Br_3O_3$: C, 22.25; H, 1.33. Found: C, 22.27; H, 1.35.

3,5-Dibromo-6-bromomethyl-4-methoxy-2-pyrone (**6**) (Reaction 3, Table 1).

The dibromopyrone **5** (298 mg, 1.0 mmole) in dichloromethane (3 ml) was added in 5 minutes to a solution of bromine (1.6 g, 10 mmoles) in dichloromethane (2 ml). The solution was washed with aqueous 50% sodium bisulfite. The organic layer was washed with water, dried over sodium sulfate and evaporated to afford 348 mg (92%) of the tribromopyrone **6**, which was recrystallized from ethanol to afford 328 mg (84%) of pure **6**, mp 114-117°; ir (potassium bromide): 1720 cm^{-1}; pmr (deuteriochloroform): δ 4.38 (s, 2H), 4.13 (s, 3H); cmr (deuteriochloroform): δ 164.6, 158.0, 154.9, 101.2, 99.2, 61.5, 25.8; ms: 380 (7), 378 (21), 376 (20), 374 (M^+, 6), 299 (52), 297 (100), 295 (52), 269 (34), 255 (20), 253 (60), 251 (40), 241 (26), 227 (25), 225 (28), 147 (22), 133 (37), 131 (38), 93 (24).

Anal. Calcd. for $C_7H_5Br_3O_3$: C, 22.25; H, 1.33. Found: C, 22.61; H, 1.11.

3,5-Dibromo-6-hydroxymethyl-4-methoxy-2-pyrone (**7**) (Reaction 33, Table 5).

A mixture of the tribromopyrone **6** (754 mg, 2 mmoles), dichloromethane (80 ml) and silica-gel (40 g) was evaporated to dryness. Water (100 ml) was added and the mixture was refluxed under mechanical stirring for 7 hours, then cooled and extracted with ethyl acetate. The organic layer was evaporated and the residue passed through a silica-gel column to afford 190 mg (30%) of pyrone **7**, mp 105-109° (from ethanol); ir (potassium bromide): 3600-3100, 1680 cm^{-1}; pmr (deuteriochloroform + hexadeuteriodimethyl sulfoxide): δ 4.47 (s, 2H), 4.00 (s, 3H); ms: 316 (18), 314 (43), 312 (M^+, 23), 287 (48), 285 (100), 283 (69), 255 (50), 253 (25), 229 (40), 227 (79), 225 (36), 133 (42), 131 (44), 93 (26).

This product was too unstable to obtain any analytical data.

3-Acetyl-5-bromo-6-bromomethyl-4-hydroxy-2-pyrone (**8**) and 3-Acetyl-5-bromo-6-dibromomethyl-4-hydroxy-2-pyrone (**15**) (Reaction 16, Table 2).

The bromopyrone **2** [10] (4.94 g, 20 mmoles) and *N*-bromosuccinimide (4.28 g, 24 mmoles) in tetrachloromethane (75 ml) were irradiated at room temperature for 20 hours with a 500 W bulb. The mixture was filtered and the solution was evaporated to give a residue which was recrystallized from ethanol to afford 3.97 g (61%) of **8**, mp 122-124°; ir (potassium bromide): 1720, 1605 cm^{-1}; pmr (deuteriochloroform): δ 18.05 (s, 1H), 4.39 (s, 2H), 2.74 (s, 3H); cmr (deuteriochloroform): δ 204.8, 177.9, 162.1, 158.2, 100.9, 99.8, 28.5, 25.7; ms: 328 (14), 326 (27), 324 (M^+, 14), 245 (100), 43 (38).

Anal. Calcd. for $C_8H_6Br_2O_4$: C, 29.48; H, 1.85. Found: C, 29.68; H, 1.69.

The evaporated mother liquor gave a residue which was recrystallized twice from ethanol to afford 380 mg of a pure sample of the unstable 3-acetyl-5-bromo-6-dibromomethyl-4-hydroxy-2-pyrone, **15** (5%), mp 164-166°; ir (potassium bromide): 1730, 1600 cm^{-1}; pmr (deuteriochloroform): δ 17.93 (s, 1H), 6.62 (s, 1H), 2.69 (s, 3H); ms: 408 (3), 406 (10), 404 (9) 402 (M^+, 3), 327 (51), 325 (100), 323 (53), 43 (41).

3,5-Dibromo-4-hydroxy-6-methyl-2-pyrone (**9**) (Reaction 1, Table 1).

A mixture of the bromopyrone **3** [6] (819 mg, 4.0 mmoles), bromine (703 mg, 4.4 mmoles) and dichloromethane (30 ml) was stirred in the darkness at room temperature for 6 hours it was evaporated and the residue recrystallized from chloroform to afford 1.017 g (90%) of **9**, mp 181-192° dec; ir (potassium bromide): 3400-3100 (broad), 1695, 1680, 1600 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): δ 2.32 (s, 3H); ms: 286 (43), 284 (100), 282 (M^+, 52), 258 (47), 256 (92), 254 (44), 165 (23), 133 (31), 43 (47).

Anal. Calcd. for $C_6H_4Br_2O_3$: C, 25.38; H, 1.42. Found: C, 25.65; H, 1.25.

3,5-Dibromo-4-methoxy-6-methyl-2-pyrone (**10**) (Reaction 2, Table 1).

A mixture of the bromopyrone **4** [6] (219 mg, 1.0 mmole), bromine (640 mg, 4 mmoles) and dichloromethane (10 ml) was stirred at room temperatre for 22 hours. Air was bubbled to eliminate the excess of bromine and the residual solution was dried with sodium sulfate, filtered and evaporated to afford a residue which was recrystallized from ethanol to afford 195 mg (65%) of **10**, mp 57-59°; ir (potassium bromide): 1710 cm^{-1}; pmr (deuteriochloroform): δ 2.4 (s, 3H), 4.1 (s, 3H); cmr (deuteriochloroform): δ 165.5, 159.4, 158.8, 99.3, 96.9, 61.2, 19.9.

Anal. Calcd. for $C_7H_6Br_2O_3$: C, 28.21; H, 2.00. Found: C, 28.29; H, 2.04.

5-Bromo-6-hydroxymethyl-4-methoxy-2-pyrone (**11**) (Reaction 32, Table 5).

A mixture of 5-bromo-6-bromomethyl-4-methoxy-2-pyrone, **5**, (596 mg, 2.0 mmoles), silica-gel (30 g) and dichloromethane (60 ml) was evaporated to dryness. Water (80 ml) was then added and the mixture was refluxed for 19 hours under efficient mechanical stirring. After cooling, the mixture was thoroughly extracted with ethyl acetate, the organic phase was separated and dried over anhydrous sodium sulfate. Solvent removal gave 314 mg (67%) of crude **11**, which after recrystallization (ethanol) showed mp 198° (sublimes); ir (potassium bromide): 3500-3300 (broad), 1710 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): δ 8.3 (s, 1H), 5.75 (s, 1H), 4.4 (s, 2H), 3.9 (s, 3H); cmr (hexadeuteriodimethyl sulfoxide): δ 165.9, 161.3, 160.2, 95.6, 88.9, 59.6, 57.4; ms: 236 (28), 234 (M^+, 29), 205 (100), 203 (84), 177 (20), 175 (20), 149 (55), 147 (60).

Anal. Calcd. for $C_7H_7BrO_4$: C, 35.77; H, 3.00. Found: C, 36.17; H, 2.94.

5-Bromo-6-bromomethyl-4-hydroxy-2-pyrone (**12**) (Reaction 27, Table 3).

A solution of **8** (977 mg, 3.0 mmoles) in 90% sulfuric acid (2.93 g) was stirred at 132° for 18 minutes and was immediately poured on ice-water (20 ml). The precipitate was filtered, washed with ice-cold water and air-dried. Crystallization from ethanol containing a few drops of water afforded 600 mg (70%) of **12**, mp 175-185° dec; ir (potassium bromide): 3600-3100 (broad), 1650 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): δ 5.50 (s, 1H), 4.54 (s, 2H); cmr (hexadeuteriodimethyl sulfoxide): δ 166.4, 161.3, 157.3, 99.9, 90.9, 28.1; ms: 286 (27), 284 (54), 282 (M^+, 22), 242 (31), 205 (51), 203 (53), 191 (21), 177 (83), 175 (100), 149 (53), 147 (40), 135 (30), 133 (46), 121 (24), 107 (34), 105 (32), 95 (33), 93 (29), 81 (30), 79 (39), 69 (64), 53 (53), 42 (61), 41 (35).

Anal. Calcd. for $C_6H_4Br_2O_3$: C, 25.38; H, 1.42. Found: C, 25.32; H, 1.72.

3,5-Dibromo-6-bromomethyl-4-hydroxy-2-pyrone (**13**) (Reaction 4, Table 1).

A solution of **12** (851 mg, 3.0 mmoles) and bromine (528 mg, 3.3 mmoles) in dichloromethane (20 ml) was stirred in darkness for 1.5 hours at room temperature. Solvent removal and crystallization of the residue from chloroform yielded 900 mg (83%) of **13**, mp 163-174° dec; ir (potassium bromide): 3300-2700 (broad), 1675 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): δ 10.78 (broad s, 1H), 4.53 (s, 2H); cmr (hexadeuteriodimethyl sulfoxide + hexadeuterioacetone): δ 163.2, 158.4, 155.4, 100.1, 89.3, 27.9; ms: 366 (7), 364 (24), 362 (24), 360 (M^+, 8), 285 (54), 283 (100), 281 (63), 255 (23), 227 (31), 133 (25), 131 (26), 119 (21), 117 (21), 95 (21), 93 (31), 81 (30), 79 (24), 66 (24), 53 (23), 50 (21), 42 (25).

Anal. Calcd. for $C_6H_3Br_3O_3$: C, 19.86; H, 0.83. Found: C, 19.93; H, 0.87.

6-Bromomethyl-4-hydroxy-2-pyrone (**18**) (Reaction 26, Table 3).

A solution of **17** [5,10] (6.17 g, 24.9 mmoles) in 90% aqueous sulfuric (18.5 g) was stirred at 132° for 18 minutes and was immediately poured

on ice-water (75 ml). The precipitate was filtered, washed with ice-cold water and air-dried. Crystallization from chloroform yielded 3.69 g (72%) of **18**, mp 112-114°; ir (potassium bromide): 3200-2300 (broad, 1690 (shoulder), 1650 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): δ 11.80 (broad s, 1H), 6.32 (d, J = 2.5 Hz, 1H), 5.30 (d, J = 2.5 Hz, 1H), 4.40 (s, 2H); cmr (hexadeuteriodimethyl sulfoxide): δ 169.8, 163.1, 159.7, 102.5, 90.5, 28.3; ms: 206 (9), 204 (M^+, 10), 111 (61), 97 (57), 69 (100), 55 (47), 42 (49), 41 (24).

Anal. Calcd. for $C_6H_5BrO_3$: C, 35.15; H, 2.45. Found: C, 35.00; H, 2.36.

3-Bromo-6-bromomethyl-4-hydroxy-2-pyrone (**19**) (Reaction 5, Table 1).

A solution of **18** (819 mg, 4.0 mmoles) and bromine (703 mg, 4.4 mmoles) in dichloromethane (30 ml) was stirred in darkness for 6 hours at room temperature. Solvent removal and crystallization of the residue from ethanol afforded 1.078 g (95%) of **19**, mp 184-192° dec; ir (potassium bromide): 3100-2400 (broad), 1615 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): δ 6.46 (s, 1H), 4.51 (s, 2H); cmr (hexadeuteriodimethyl sulfoxide): 165.9, 159.6, 157.8, 101.6, 87.4, 27.8; ms: 286 (23), 284 (43), 282 (M^+, 22), 205 (95), 203 (100), 177 (33), 175 (47), 149 (24), 147 (21), 135 (20), 133 (22), 53 (25).

Anal. Calcd. for $C_6H_4Br_2O_3$: C, 25.38; H, 1.42. Found: C, 25.18; H, 1.11.

3-Bromo-4-hydroxy-6-methyl-2-pyrone (**20**) (Reactions 7, 8 and 9, Table 1).

A mixture of *N*-bromosuccinimide (700 mg, 3.9 mmoles) and a catalytic amount of benzoyl peroxide in dichloromethane (25 ml) was illuminated with a 500 W bulb until onset of boiling. Then, **21** (500 mg, 3.9 mmoles) was added and the illuminated mixture was kept boiling for 2 hours. The warm reacted mixture was filtered, the filtrate was concentrated to yield more solid, and recrystallization of both crops from water containing a few drops of ethanol gave 720 mg (88%) of **20**, mp 214-217° (lit [10] 203-204°).

A mixture of **21** (1.00 g, 7.9 mmoles) and bromine (1.40 g, 8.7 mmoles) in dichloromethane (50 ml) was stirred at room temperature for 5 hours. Then, solvent removal and crystallization of the residue from ethanol yielded 1.18 g (73%) of **20**, mp 213-216°.

A mixture of **21** (500 mg, 3.9 mmoles) and bromine (700 mg, 4.3 mmoles) in dichloromethane (30 ml) was stirred in darkness at room temperature for 3 hours. Then solvent removal and crystallization of the residue from ethanol yielded 670 mg (82%) of **20**, mp 214-217°.

6-Bromomethyl-4-methoxy-2-pyrone (**23**) (Reaction 29, Table 4).

To a stirred mixture of potassium carbonate (8.87 g, 64.3 mmoles), dimethyl sulfate (1.38 ml, 1.83 g, 14.5 mmoles) and anhydrous acetone (30 ml), kept under reflux, was added over one hour a solution of **18** (2.317 g, 11.3 mmoles) in anhydrous acetone (15 ml) under rigorous exclusion of moisture. After cooling and filtering, solvent removal yielded a crude mixture (2.895 g) which was chromatographed through silica-gel, eluting with hexane-ethyl acetate (70:30), to afford 1.983 g (80%) of pure **23**, mp 93-95° (lit [5] 93-95°).

3-Bromo-6-hydroxymethyl-4-methoxy-2-pyrone (**25**) (Reaction 31, Table 5).

A mixture of **26** [5] (596 mg, 2.0 mmoles), chloroform (70 ml) and silica-gel (30 g) was evaporated to dryness. Then water (50 ml) was added and the mixture was refluxed for 21 hours under efficient stirring. Extractive isolation (ethyl acetate) yielded 330 mg (70%) of pure **25**, which after crystallization from chloroform showed mp 134-140° dec; ir (potassium bromide): 3600-3100 (broad), 1720, 1700 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): δ 6.6 (s, 1H), 5.8 (t, J = 6 Hz, 1H), 4.3 (d, J = 6 Hz, 2H), 4.0 (s, 3H); cmr (hexadeuteriodimethyl sulfoxide): δ 167.5, 165.9, 159.6, 93.8, 87.3, 59.6, 57.9; ms: 236 (37), 234 (M^+, 34), 205 (52), 203 (54), 149 (92), 147 (100), 93 (34), 81 (21), 69 (46), 53 (72).

Anal. Calcd. for $C_7H_7BrO_4$: C, 35.77; H, 3.00. Found: C, 35.85; H, 3.16.

3-Bromo-4-methoxy-6-methyl-2-pyrone (**27**) (Reaction 13, Table 1).

To a stirred solution of **22** [16] (420 mg, 3.0 mmoles) in dichloromethane (10 ml) was added dropwise over a 30 minute period a solution of bromine (528 mg, 3.3 mmoles) in dichloromethane (5 ml). No excess bromine was observed. Solvent removal and crystallization of the residue from ethanol yielded 498 mg (74%) of **27**, mp 155-156° (lit [5] 154-155°, [10] 155-156°).

3-Bromo-6-dibromomethyl-4-methoxy-2-pyrone (**30**) (Reaction 23, Table 2).

A stirred mixture of **22** [16] (2.8 g, 20 mmoles) and dry *N*-bromosuccinimide (7.8 g, 44 mmoles) in anhydrous tetrachloromethane (190 ml) containing a catalytic amount of benzoyl peroxide was irradiated with a 500 W bulb for 2 hours under reflux, with rigorous exclusion of moisture. Solvent was eliminated *in vacuo* and the residue was taken up in chloroform (250 ml) and washed with 1*M* potassium carbonate. The organic phase was separated, dried over anhydrous sodium sulfate and after solvent removal the residue was chromatographed through silica-gel, eluting with hexane/dichloromethane mixtures. The first compound eluted was **30** (616 mg, 8%) as a white solid, which after crystallization from acetone/pentane showed mp 180-185° dec; ir (potassium bromide): 1730, 1710 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): δ 6.88 (s, 1H), 6.78 (s, 1H), 3.87 (s, 3H); cmr (hexadeuteriodimethyl sulfoxide): δ 168.9, 158.0, 156.7, 94.6, 90.1, 58.1, 32.6; ms: 380 (4), 378 (15), 376 (15), 374 (M^+, 4), 299 (54), 297 (100), 295 (52), 149 (20), 147 (27), 59 (27), 53 (34).

Anal. Calcd. for $C_7H_5Br_3O_3$: C, 22.31; H, 1.33. Found: C, 22.47; H, 1.42.

The second product eluted was **26** (4.1 g, 69%), mp 162-164° (lit [5] 162-164°).

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