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Note

Cyclic polyethers derived from 5,6-*O*-isopropylidene-L-ascorbic acid*

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The preparation of 2,3-di-*O*-alkyl derivatives of L-ascorbic acid (vitamin C) was not entirely straightforward until the important discovery by Dallacker and Sanders[1] that treatment of 5,6-*O*-isopropylidene-L-ascorbic acid (**1**) with alkyl halides in *N,N*-dimethylformamide in the presence of anhydrous potassium carbonate led to good yields of 2,3-di-*O*-alkyl-5,6-*O*-isopropylidene-L-ascorbic acids. Interestingly, use of certain 1,*n*-dihalo-alkanes in this type of reaction led to formation of cyclic derivatives (**2**) which, for $n = 2$, 3, and 4, were crystalline. In view of the possible importance of metal-ion complexation in the biological action of L-ascorbic acid in certain metabolic pathways, we wished to adapt this type of synthesis for the preparation of cyclic polyethers (crown polyethers) of L-ascorbic acid. We now report the preparation of 9-crown-3, 15-crown-5, and 18-crown-6 derivatives of the diol **1** and also on elimination products that can arise in the alkylation reactions on **1**, leading to the formation 3,4-dialkoxy-5-(2-hydroxyethylidene)-2(5*H*)-furanones.

Reaction of 5,6-*O*-isopropylidene-L-ascorbic acid (**1**) with diethylene glycol ditosylate in *N,N*-dimethylformamide (Fisons' S.L.R. grade, water $<0.1\%$) at 70° gave (t.l.c.) a mixture of products containing three major components, which were isolated by column chromatography on silica gel. The most mobile component was isolated as a thick oil which, on the basis of its mass spectrum and ^{1}H- and ^{13}C-n.m.r. spectra, was identified as 5,6-*O*-isopropylidene-2,3-di-*O*-[2-(2-tosyloxyethoxy)ethyl]-L-ascorbic acid (**3**). The next most mobile component gave the required cyclic ether, 5,6-*O*-isopropylidene-2,3-*O*-(3-oxa-1,5-pentanediyl)-L-ascorbic acid (**4**), as a crystalline solid in 15% yield. The slowest running component was obtained crystalline in 15% yield and its ^{1}H-n.m.r. spectrum, which clearly indicated the absence of an isopropylidene residue, was relatively simple and contained a one-proton triplet at δ 5.57 (J 7 Hz) that was shown by decoupling experiments to be coupled to a two-proton doublet centred on δ 4.43. The presence of an exchangeable proton on treatment with D_2O, a strong

* Dedicated to Professor Grant Buchanan on the occasion of his 65th birthday.
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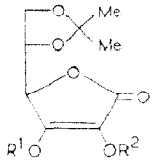
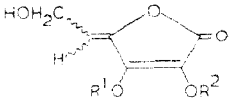
absorption at 3520 cm^{-1} in its i.r. spectrum, and the elemental analysis indicated the compound to be (*Z*)- or (*E*)-5-(2-hydroxyethylidene)-3,4-(3-oxa-1,5-pentanediyloxy)-2(5*H*)-furanone (**5**). The configuration at the alkenic bond could not be ascertained, but elimination without prior isomerisation would favour formation of the (*Z*)-isomer. Interestingly, one CH_2 resonance in the cyclic ether moiety was well separated at δ 4.72 from the other three, which resonated between δ 3.82 and 4.05, presumably because the former CH_2 group lay largely in the deshielding zone of the carbonyl group.

Relatively few elimination reactions of this type have been reported previously with such compounds derived from ascorbic acid. Thus, 5,6-*O*-isoprolylidene-2,3-di-*O*-methyl-L-ascorbic acid (**6**) afforded[2] (*Z*)- and (*E*)-5-(2-hydroxyethylidene)-2,3-dimethoxy-2(5*H*)-furanone (**7** and **8**) on treatment with 1,5-diazabicyclo[4.3.0]non-5-ene or potassium hydride, and 5,6-*O*-isopropylidene-2,3-*O*-ethanediyl-L-ascorbic acid (**2**, n = 2), on treatment with liquid ammonia, yielded[3] the lactam **9**. A reasonable mechanism for the formation of **9** involves[4] initial formation of furanone **10**.

In view of this unexpected elimination under alkylation conditions, we were prompted to reinvestigate the reported[1] benzylation of the diol **1**. When Fisons' S.L.R.





1 $R^1 = R^2 = H$

2 $R^1, R^2 = (CH_2)_n$

3 $R^1 = R^2 = TsOCH_2CH_2OCH_2CH_2$

4 $R^1, R^2 = CH_2CH_2OCH_2CH_2$

5 $R^1, R^2 = CH_2CH_2OCH_2CH_2$

6 $R^1 = R^2 = Me$

7 $R^1 = R^2 = Me$, (*Z*)-isomer

8 $R^1 = R^2 = Me$, (*E*)-isomer

10 $R^1, R^2 = CH_2CH_2$

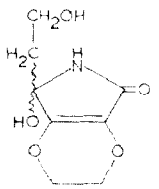
11 $R^1 = R^2 = PhCH_2$

12 $R^1 = R^2 = PhCH_2$

13 $R^1, R^2 = (CH_2CH_2O)_3CH_2CH_2$

14 $R^1, R^2 = (CH_2CH_2O)_4CH_2CH_2$

15 $R^1, R^2 = (CH_2CH_2O)_2CH_2CH_2$



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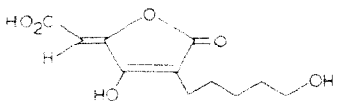

16

Ts = *p*-$MeC_6H_4SO_2$

grade *N,N*-dimethylformamide (water < 0.1%) was used, t.l.c. (dichloromethane–ethyl acetate, 9:1) after reaction for 8 h revealed a mixture of products with one major component having R_F 0.31, but none of the expected* 2,3-dibenzyl ether **11** was detected. Isolation of the major component afforded a thick syrup, identified on the basis of its ^{1}H- and ^{13}C-n.m.r. spectra and its mass spectrum as 3,4-dibenzyloxy-5-(2-hydroxyethylidene)-2-(5*H*)-furanone (**12**), presumably with the (*Z*)-configuration on the basis of the likely mechanism of its formation.

Repetition of the benzylation reaction on **1**, but using Fisons' dried and distilled grade *N,N*-dimethylformamide (water content < 0.02%), gave, without chromatography and in 45% yield, the expected 2,3-dibenzyl ether (**11**) by direct crystallisation from the reaction mixture, in agreement with the reported procedure[1] (which used absolute *N,N*-dimethylformamide), although in somewhat lower yield. Only a small proportion of furanone **12** was present in the crude mixture of products. Treatment of **11** with potassium carbonate in S.L.R. grade *N,N*-dimethylformamide afforded a mixture containing, as the predominant component, the furanone **12**, which could be isolated by chromatography.

Reaction of **1** with tetraethylene glycol ditosylate and with pentaethylene glycol ditosylate in *N,N*-dimethylformamide in the presence of potassium carbonate gave, respectively, as the major product after chromatography, 5,6-*O*-isopropylidene-2,3-*O*-(3,6,9-trioxa-1,11-undecanediyl)-L-ascorbic acid (**13**) and 5,6-*O*-isopropylidene-2,3-*O*-(3,6,9,12-tetraoxa-1,14-tetradecanediyl)-L-ascorbic acid (**14**), the former in only low yield. In contrast, the expected 2,3-*O*-(3,6-dioxa-1,8-octanediyl) derivative **15** could not be isolated from the complex mixture resulting from reaction of **1** with triethylene glycol ditosylate. On replacement of potassium carbonate by lithium carbonate in this reaction, which might reasonably be expected to favour formation of the 12-crown-4 polyether, only starting materials could be detected by t.l.c.

The elimination reaction leading to the furanoses **5, 7, 8,** and **12**, which, under the alkylation conditions described, is clearly promoted by the presence of a small concentration of water, is worthy of further exploitation for synthesis. Such compounds are closely related in structure to the naturally occurring 4-ylidenebutenolides and 4-ylidenetetronic acids[5], multicolic acid (**16**) being an example of the latter class of compounds. Some ylidenebutenolides and ylidenetetronic acids show a useful spectrum of biological activity[5].

EXPERIMENTAL

^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) at 60 or 90 MHz with JEOL PMX60si or EX90 FT spectrometers, respectively, and ^{13}C-n.m.r.

* We are indebted to Professor Dr. Dallacker for generously supplying an authentic sample of **11**, the corresponding dimethyl ether, a copy of the Dissertation of J. Sanders, and for very helpful correspondence on this matter.

spectra were recorded with the latter instrument. T.l.c. was performed on silica gel (Machery–Nagel, SIL G-25UV$_{254}$) and column chromatography on Silica Gel 60 (Merck, 70–230 mesh). The two grades of Fisons' *N,N*-dimethylformamide used were (*a*) specified laboratory reagent (S.L.R.; water < 0.1%) and (*b*) dried and distilled (water < 0.02%). 5,6-*O*-Isopropylidene-L-ascorbic acid (**1**) was prepared by the method of Dallacker and Sanders[5].

Reactions of 5,6-O-isopropylidene-L-ascorbic acid (**1**). — (*a*) *With diethylene glycol di-p-toluenesulphonate.* A mixture of **1** (2.16 g), diethylene glycol di-*p*-toluenesulphonate[6,7] (4.14 g), and anhydrous potassium carbonate (1.52 g) in S.L.R. grade *N,N*-dimethylformamide (50 mL) was stirred for 5 h at 70° under nitrogen. The mixture was concentrated, and a solution of the residue in dichloromethane (40 mL) was washed with water (4 × 30 mL), then dried. Concentration of the solution afforded a syrup (1.5 g) which consisted (t.l.c.; dichoromethane–ethyl acetate, 3:1) of three major components with R_F 0.52, 0.42, and 0.20. The syrup was subjected to column chromatography (dichloromethane–ethyl acetate, 3:1), and fractions containing the fastest running component were combined and concentrated to give, as a thick syrup, 5,6-*O*-isopropylidene-2,3-di-*O*-[2-(2-*p*-toluenesulphonyloxyethoxy)ethyl]-L-ascorbic acid (**3**; 0.12 g, 1.7%); υ_{max}^{film} 1740 (C=O), 1670 (C=C), and 1330 cm^{-1} (OSO$_2$O–). ^{1}H-N.m.r. data (90 MHz): ^{1}H, δ 1.34, 1.38 (2 s, each 3 H, CMe$_2$), 2.44 (s, 6 H, 2 Ar*Me*), 3.50–4.70 (cm, 20 H, H-4,5,6a,6b and 4 OCH$_2$CH$_2$O), 7.20–7.95 (m, 8 H, 2 AA'BB' systems of Ar*H*). Mass spectrum (c.i. with NH$_3$): *m/z* 718.2203 [M + NH$_4$]$^+$.

Fractions containing the component with R_F 0.42 yielded material which crystallised from methanol to give 5,6-*O*-isopropylidene-2,3-*O*-(3-oxa-1,5-pentanediyl)-L-ascorbic acid (**4**; 0.43 g, 15%), m.p. 144–145°, $[\alpha]_D$ −4.1° (*c* 0.44, chloroform); υ_{max}^{film} 1755 (C=O) and 1670 cm^{-1} (C=C). ^{1}H-N.m.r. data: δ 1.42, 1.44 (2 s, each 3 H, CMe$_2$), 3.60–5.10 (cm, 12 H, H-4,5,6a,6b and 2 OCH$_2$CH$_2$O).

Anal. Calc. for C$_{13}$H$_{18}$O$_7$: C, 54.5; H, 6.3. Found: C, 54.6; H, 6.4.

The residue obtained by concentration of fractions containing the component R_F 0.20 was crystallised from methanol to afford (*Z*)- or (*E*)-5-(2-hydroxyethylidene)-3,4-(3-oxapentane-1,5-diyloxy)-2(5*H*)-furanone (**5**; 0.34 g, 15%), m.p. 175–177°; υ_{max}^{Nujol} 3520 (OH), 1780 (C=O), and 1650 cm^{-1} (C=C). N.m.r. data: ^{1}H (90 MHz), δ 1.61 (bs, OH), 3.82–4.05 (cm, 6 H, 3 OCH$_2$), 4.43 (d, 2 H, *J* 7 Hz, CH$_2$OH), 4.67–4.76 (m, 2 H, OCH$_2$), 5.57 (t, 1 H, =C*H*CH$_2$OH); ^{13}C, δ 56.6 (CH$_2$OH), 69.2, 72.2, 72.6, 73.2 (2 OCH$_2$CH$_2$O–), 108.2 (=CH–), 124.7 (C=C–C=O), 142.1 (C=C–O–C=O), 152.1 (C=C–C=O); the signal for C=O could not detected.

Anal. Calc. for C$_{10}$H$_{12}$O$_6$: C, 52.6; H, 5.3. Found: C, 52.25; H, 5.4.

(*b*) *With tetraethylene glycol di-p-toluenesulphonate.* Reaction of **1** (2.16 g) with tetraethylene glycol di-*p*-toluenesulphonate[6] (5.02 g) and anhydrous potassium carbonate (1.52 g) in dried and distilled *N,N*-dimethylformamide (40 mL) at 40° for 7 h under nitrogen, with work-up as in (*a*), gave a syrup which contained (t.l.c.; dichloromethane–ethyl acetate, 3:1) a major and two minor components. Isolation of the major product (R_F 0.28) by column chromatography gave, as a thick syrup, 5,6-*O*-isopropylidene-2,3-*O*-(3,6,9-trioxa-1,11-undecanediyl)-L-ascorbic acid (**13**; 0.045 g, 1.2%); υ_{max}^{film} 1765

(C=O), 1680 cm^{-1} (C=C). ^{1}H-N.m.r. data: δ 1.29, 1.32 (2 s, each 3 H, CMe_2), 3.20–5.10 (cm, 20 H, H-4,5,6a,6b and 4 OCH_2CH_2O). Mass spectrum (c.i. with NH_3): m/z 375.1655 $[M + H]^+$.

Repetition of the reaction with either sodium or caesium carbonate gave no advantage.

(*c*) *With pentaethylene glycol di-*p*-toluenesulphonate.* Treatment of **1** (2.16 g) with pentaethylene glycol di-*p*-toluenesulphonate[8] (5.46 g) and potassium carbonate (1.52 g) in *N,N*-dimethylformamide, as described in (*b*), gave (t.l.c.; dichloromethane–ethyl acetate, 1:1) a major product, with R_F 0.23, which was isolated by column chromatography in the same solvent system to give, as a thick syrup, 5,6-*O*-isopropylidene-2,3-*O*-(3,6,9,12-tetraoxa-1,14-tetradecanediyl)-L-ascorbic acid (**14**; 0.83 g, 20%), $[\alpha]_D$ +22° (*c* 0.55, chloroform); ν_{max}^{film} 1765 (C=O), 1675 cm^{-1} (C=C). ^{1}H-N.m.r. data: δ, 1.40 (s, 6 H, CMe_2), 3.40–4.90 (cm, 24 H, H-4,5,6a,6b and 5 OCH_2CH_2O). Mass spectrum (c.i. with NH_3): m/z 419.1917 $[M + H]^+$.

(*d*) *With triethylene glycol di-*p*-toluenesulphonate.* Treatment of **1** (2.16 g) with triethylene glycol di-*p*-toluenesulphonate[6] (4.58 g) and anhydrous potassium carbonate (1.52 g) in *N,N*-dimethylformamide, as described in (*b*), yielded a multicomponent mixture which could not be fractionated. When lithium carbonate was used, only starting materials were detected.

(*e*) *With benzyl bromide–potassium carbonate in* N,N-*dimethylformamide.* — (*i*) A mixture of **1** (2.16 g), benzyl bromide (3.75 g), and anhydrous potassium carbonate (1.52 g) in S.L.R. grade *N,N*-dimethylformamide (40 mL) was stirred at 60° under nitrogen for 8 h, then worked-up as in (*a*). T.l.c. (dichloromethane–ethyl acetate, 9:1) revealed a mixture of products with that having R_F 0.31 preponderating, but none of the expected 2,3-dibenzyl ether **11**. Isolation of the major component by repeated column chromatography with dichloromethane–ethyl acetate (first 10:1, then 3:1) afforded, as a thick syrup, (*E*)- or (*Z*)-3,4-dibenzyloxy-5-(2-hydroxyethylidene)-2(5*H*)-furanone (**12**; 0.17 g, 5%); ν_{max}^{film} 3400 (OH), 1770 (C=O), and 1650 cm^{-1} (C=C). N.m.r. data: ^{1}H, δ 1.80 (bs, 1 H, OH), 4.35 (d, 2 H, *J* 7.2 Hz, CH_2OH), 5.10 and 5.20 (2 s, each 2 H, 2 $PhCH_2$), 5.50 (t, 1 H, $=CHCH_2OH$), 7.18–7.60 (m, 10 H, 2 Ph); ^{13}C, δ 56.5 (CH_2OH), 73.2 and 74.0 (2 $PhCH_2$), 107.5 ($=CHCH_2OH$), 123.2 (C=C–C=O), 142.4 (C=C–O–C=O), 148.2 (C=C–C=O), 164.3 (C=O) (besides aromatic-C resonances (not listed), peaks at δ 53.4 and 113.0 were observed that were relatively weak compared to those at δ 56.5 and 107.5, which might indicate the presence of a minor proportion of the alternative geometrical isomer). Mass spectrum (c.i. with NH_3): m/z 356.1498 $[M + NH_4]^+$.

(*ii*) The method was essentially that described by Dallacker and Sanders[1] except that benzyl bromide was used in place of benzyl chloride and the reaction was conducted at 40° instead of 60° in an attempt to minimise elimination. Treatment of **1** (2.16 g) with benzyl bromide (3.75 g) and anhydrous potassium carbonate (1.52 g) in dried and distilled *N,N*-dimethylformamide at 40° for 7 h under a nitrogen atmosphere, with crystallisation of the crude product from methanol, afforded 2,3-di-*O*-benzyl-5,6-*O*-isopropylidene-L-ascorbic acid (**11**; 1.8 g, 45%), m.p. 128°, $[\alpha]_D$ +63° (*c* 0.58, acetone); lit.[1] m.p. 123–125°, $[\alpha]_D$ +59.3° (acetone). T.l.c. (dichloromethane–ethyl acetate, 9:1) revealed a small proportion of **12** in the crude reaction product.

Treatment of **11** *with potassium carbonate in* N,N-*dimethylformamide*. — A mixture of **11** (0.396 g) and anhydrous potassium carbonate (0.152 g) in S.L.R. grade *N*,*N*-dimethylformamide (4 mL) was stirred for 5 h at 40° under nitrogen. Isolation of the product in the usual manner gave a syrup which contained (t.l.c.; dichloromethane–ethyl acetate, 9:1) a minor proportion of **11** and the elimination product **12**, which could be isolated by column chromatography. On repeating the reaction in dried and distilled *N*,*N*-dimethylformamide, the proportion of **12** in the mixture of products, as judged by t.l.c., was significantly lower.

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