

Preliminary communication

Studies towards the synthesis of analogues of L-ascorbic acid

ALI H. AL-HAKIM and ALAN H. HAINES*

School of Chemical Sciences, University of East Anglia, University Plain, Norwich NR4 7TJ
(Great Britain)

(Received May 3rd, 1983; accepted for publication, June 15th, 1983)

Interest in L-ascorbic acid (Vitamin C, **1**) continues unabated^{1–3}. In addition to its importance in nutrition, L-ascorbic acid has found application in food preservation and also in non-food areas⁴. Possible uses in medicine⁵, from prevention of bladder carcinoma to treatment of the common cold, have been actively considered. In spite of this extremely widespread interest, surprisingly few analogues have been prepared in which the enolic hydroxyl groups have been replaced by alternative groups⁶. 2-Amino-2-deoxy^{8–10} (**2**) and 2,3-diamino-2,3-dideoxy^{10–12} (**3**) analogues have been obtained by the reduction of appropriate nitrogen derivatives of dehydro-L-ascorbic acid, and the former has high anti-scorbutic activity¹⁰; the preparation and properties of other related compounds is, to our knowledge, a relatively unexplored area. We now report on an investigation directed towards the synthesis of such compounds by suitable modification of the readily available mucochloric acid¹³ [3,4-dichloro-5-hydroxyfuran-2(5*H*)-one, **4**] and mucobromic acid¹⁴ [3,4-dibromo-5-hydroxyfuran-2(5*H*)-one, **5**]. This highly functionalised system is particularly versatile as a synthetic starting-point, since the two halogen atoms in each compound can be replaced by nucleophiles in a double 1,4-addition-elimination reaction¹⁵ and, in the 5-substituted derivatives **6** and **7**, the halogen atom at C-4 may be replaced specifically¹⁶.

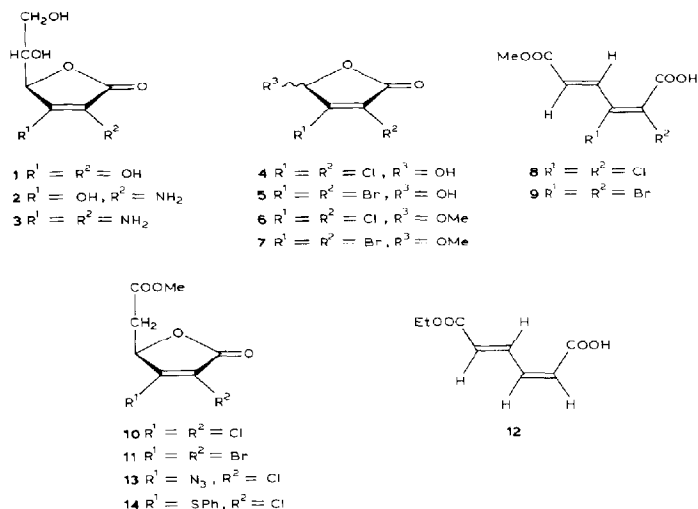
Treatment of **4** with 1 molar equivalent of methyl diethylphosphonoacetate in a Horner–Emmons reaction afforded (2*Z*,4*E*)-2,3-dichloro-5-methoxycarbonyl-2,4-pentadienoic acid (**8**)[†], m.p. 139–141°. N.m.r. data [(CD₃)₂CO]: ¹H, δ 3.96 (CH₃), 6.82 (d, *J* 16 Hz, =CH–), 8.81 (d, =CH–), and 12.27 (br s, COOH); ¹³C, δ 52.4 (CH₃), 127.4 (=CH–), 129.8 (=C–), 137.1 (=CH–), 140.3 (=C–), and 162.3, 166.2 (2 C=O). Similar treatment of **5** gave (2*Z*,4*E*)-2,3-dibromo-5-methoxycarbonyl-2,4-pentadienoic acid¹⁷ (**9**).

On heating a solution of **8** in *m*-xylene under reflux for 30 min, smooth cyclisation occurred by conjugate addition of the carboxylic function to the α,β-unsaturated

*To whom communications should be addressed.

[†]We recognise, of course, the availability of *O*-alkyl¹⁵, *O*-acyl⁶, and *O*-glycosyl¹⁷ derivatives of L-ascorbic acid at positions 2 and 3, as well as such inorganic esters⁸ as the 2-sulphate and 2-phosphate.

¹All new compounds gave satisfactory elemental analytical analyses.



ester function to afford 3,4-chloro-5-(methoxycarbonylmethyl)furan-2(5*H*)-one (**10**), m.p. 36–37°. N.m.r. data (CDCl_3): ^1H , δ 2.73 (dd, $J_{6,6'} 17, J_{5,6} 7$ Hz, H-6 ‡), 3.15 (dd, $J_{5,6'} 5$ Hz, H-6'), 3.76 (s, OCH_3), and 5.45 (dd, H-5); ^{13}C , δ 36.4 (CH_2), 52.4 (OCH_3), 78.3 (CH), 121.9 ($=\text{C}[3] \text{Cl}-$) * , 151.0 ($=\text{C}[4] \text{Cl}-$) * , and 164.5, 168.2 (2 C=O). Likewise, **9** gave the dibromide **11**, m.p. 56.5–58.5°. N.m.r. data (CDCl_3): ^1H , δ 2.83 (dd, $J_{6,6'} 17, J_{5,6} 7$ Hz, H-6), 3.29 (dd, $J_{5,6'} 5$ Hz, H-6'), 3.90 (s, OCH_3), and 5.65 (dd, H-5); ^{13}C , δ 36.7 (CH_2), 52.5 (CH_3), 81.2 (CH), 115.7 ($=\text{C}[3] \text{Br}-$) $^\star^\star$, 146.8 ($=\text{C}[4] \text{Br}-$) $^\star^\star$, and 165.7, 168.6 (2 C=O). Under similar reaction conditions, (2*Z*,4*E*)-5-ethoxycarbonyl-2,4-pentadienoic acid 17 (**12**) could not be cyclised.

Treatment of a solution of **10** in methanol with 1 molar equivalent of sodium azide at room temperature for 4 h gave, in 86% yield, the 4-azido-3-chloro derivative **13**, m.p. 53–54.5°. N.m.r. data (CDCl_3): ^1H , δ 2.60 (dd, $J_{6,6'} 17, J_{5,6} 7$ Hz, H-6), 2.96 (dd, $J_{5,6'} 5$ Hz, H-6'), 3.76 (s, OCH_3), and 5.15 (dd, H-5); ^{13}C , δ 36.6 (CH_2), 52.4 (OCH_3), 74.6 (CH), 108.4 ($=\text{C}[\text{Cl}]-$), 154.0 ($=\text{C}[\text{N}_3]-$), and 165.9, 168.5 (2 C=O). That the azido group had been introduced at C-4 was indicated by the relatively deshielded position of the resonance for this carbon atom in the substitution product compound to

‡ H-6 and H-6' refer to the protons of the methylene group in the methoxycarbonylmethyl group.

* The assignments are based on the allocation 18 of resonances in the ^{13}C -n.m.r. spectrum of **4** at 122.2 and 149.7 p.p.m. to C-3 and C-4, respectively.

$^\star^\star$ The assignments are based on the allocation 18 of resonances in the ^{13}C -n.m.r. spectrum of **5** at 117.0 and 147.0 p.p.m. to C-3 and C-4, respectively.

that for C-4 in **10** ($\Delta\delta$ +3.0 p.p.m.), and the remarkably shielded position of the resonance for C-3 in the substitution product relative to that for C-3 in **10** ($\Delta\delta$ -13.5 p.p.m.). Such shift differences are entirely analogous to those observed¹⁹ between ¹³C resonances for the corresponding carbon atoms in azidomaleic anhydride (=C[N₃]- at 146.9 p.p.m. and =CH- at 109.3 p.p.m.) and chloromaleic anhydride (=CCl- at 143.3 p.p.m. and =CH- at 129.3 p.p.m.). The shielding effect at the β -carbon atom of an azido-alkene, R¹R²C=C(R³)N₃, may be attributed to a major contribution of the canonical form R¹R²C=C(R³)=N⁺-N⁻=N to the overall resonance hybrid for the molecule.

Treatment of **10** with 1 molar equivalent of the potassium salt of thiophenol in methanol proceeded analogously, to afford the 3-chloro-4-phenylthio derivative **14** (72%), m.p. 68.5-70°. N.m.r. data (CDCl₃): ¹H, δ 2.35 (dd, $J_{6,6'}$ 17, $J_{5,6}$ 8 Hz, H-6), 2.75 (dd, $J_{5,6}$ 4 Hz, H-6'), 3.65 (s, OCH₃), 5.27 (dd, H-5), and 7.53 (br.s., Ar H). ¹³C, δ 37.6 (CH₂), 52.3 (CH₃), 77.7 (ClH), 117.8 (=CCl-), 125.9, 130.2, 130.6, 134.4 (aromatic C), 157.3 (=C[SPh]-), and 165.7, 168.5 (2 C=O). The position of the phenylthio substituent in **14** was confirmed by the deshielded position of the ¹³C resonance for C-4 relative to that for C-4 in **10** ($\Delta\delta$ +6.3 p.p.m.). This deshielding effect on replacement of a chlorine atom by a phenylthio group is analogous to that observed between chloroethylene (=CHCl at 124.9 p.p.m.)²⁰ and phenylthioethylene (=CHSPh at 131.6 p.p.m.)²¹.

On treatment with such oxygen nucleophiles as sodium methoxide or sodium benzoate in methanol, **10** gave mixtures of polar products which we have not succeeded in separating.

With the availability of the 3,4-disubstituted 5-(methoxycarbonylmethyl)furan-2(5H)-ones **10**, **11**, **13**, and **14**, achievement of our ultimate objective requires transformation of the methoxycarbonylmethyl side-chain into an α,β -dihydroxyethyl group so that the relative stereochemistry at the two chiral centres is *threo*, followed by resolution of the racemic materials. Both of these problems are currently being investigated.

REFERENCES

- 1 C. G. King and J. J. Burns (Eds.), *Ann. N.Y. Acad. Sci.*, 258 (1975) 1-552.
- 2 P. A. Seib and B. M. Tolbert (Eds.), *Ascorbic Acid: Chemistry, Metabolism, and Uses*, Adv. Chem. Ser., 200 (1982).
- 3 T. C. Crawford and S. A. Crawford, *Adv. Carbohydr. Chem. Biochem.*, 37 (1980) 79-155.
- 4 C. G. King, in ref. 1, pp. 540-545.
- 5 Ref. 1, *Part IV: Pharmacological Aspects*, pp. 355-437.
- 6 B. M. Tolbert, M. Downing, R. W. Carlson, M. K. Knight, and E. M. Baker, in ref. 1, pp. 48-69.
- 7 W. A. Szarek and K. S. Kim, *Carbohydr. Res.*, 67 (1978) C13-C16.
- 8 F. Micheel and R. Mittag, *Naturwissenschaften*, 25 (1937) 158-159.
- 9 F. Micheel and R. Mittag, *Hoppe-Seyler's Z. Physiol. Chem.*, 247 (1937) 34-42.
- 10 F. Smith, *Adv. Carbohydr. Chem.*, 2 (1946) 79-106.
- 11 F. Micheel, G. Bode, and R. Siebert, *Ber.*, 70 (1937) 1862-1866.
- 12 B. Gross, M. El Sekily, S. Mancy, and H. S. El Khadem, *Carbohydr. Res.*, 37 (1974) 384-389.
- 13 S. Beattie, I. M. Heilbron and F. Irving, *J. Chem. Soc.*, (1932) 260-268.
- 14 *Org. Synth. Coll. Vol. IV*, (1963) 688-689.
- 15 T. I. Bobrova, S. D. Volodkovich, and S. S. Kukalenko, *J. Gen. Chem. USSR*, 44 (1974) 370-372.
- 16 H. H. Wasserman and F. M. Precopio, *J. Am. Chem. Soc.*, 76 (1954) 1242-1243.

- 17 A. H. Al-Hakim and A. H. Haines, *Tetrahedron Lett.*, 23 (1982) 5295–5298.
- 18 E. Lippmaa, T. Peltk, K. Andersson, and C. Rappe, *Org. Magn. Reson.*, 2 (1970) 109–121.
- 19 A. H. Al-Hakim and A. H. Haines, unpublished observations.
- 20 G. Miyajima and K. Takahashi, *J. Phys. Chem.*, 75 (1971) 331–334.
- 21 O. Kajimoto, M. Kobayashi, and T. Fueno, *Bull. Chem. Soc. Jpn.*, 46 (1973) 1422–1425.