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Note

# The formation of lactams from L-ascorbic acid

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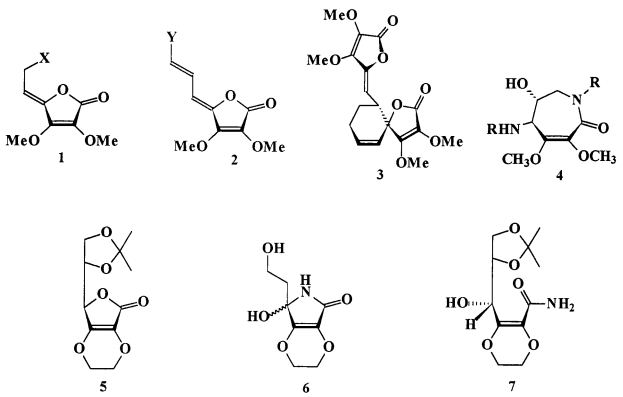
**Abstract**

2,3-*O*-Dimethyl-6-*O*-*p*-toluenesulphonyl-L-ascorbic acid reacted with the primary amines *n*-butylamine, benzylamine and cyclohexylamine at room temperature to give the 1-alkyl-2,3-dimethoxy-4-hydroxy-4-[1′-(2′-aminoalkyl)-ethyl]but-3-enimides in 64, 58 and 60% yields, respectively, after chromatographic purification. However, 2,3-*O*-dimethyl-5,6-di-*O*-*p*-toluenesulphonyl-L-ascorbic acid reacted with *n*-butylamine, benzylamine and cyclohexylamine to give the 1-alkyl-2,3-dimethoxy-4-hydroxy-4-[1′-(2′-aminoalkyl)ethyl]but-3-enimides in 61, 74 and 75% yields, respectively. The absolute configuration for one of the products was established by X-ray crystallography. 

*Keywords:* Lactams; L-Ascorbic acid; (*Z*)-Butenolides; X-ray crystallography

We have previously reported the formation of (*Z*)-butenolides **1** [1], dienes **2** and their Diels–Alder reaction products **3** [2], from the ditosylate **7** obtainable from L-ascorbic acid **8** via the diol **9**. As part of our on-going research on L-ascorbic acid, we now report some interesting products from the reaction of the monotosylate **10** and the ditosylate **11** with reactive primary amines.



In our initial experiment the ditosylate **11** was reacted with a large excess of *n*-butylamine at room temperature to afford compound **15a** and not the anticipated reaction product **4** (Scheme 1). Similar reactions of the ditosylate **11** with neat excess amounts of benzylamine and cyclohexylamine at room temperature yielded products **15b** and **15c**, respectively. The reactions could also be performed in dry organic solvents, such as THF and DCM, but heating was required as the reactions were very slow. The $^1$H NMR spectra for all of the products **15a–c** had similar resonance features, which also fit the azepinone type structure **4** and absolute unambiguous proof of structure was provided by single-crystal X-ray analysis of the only solid product, **15b** (Fig. 1). Performing the above reactions in neat solvent at elevated temperatures produced mixtures of products and the

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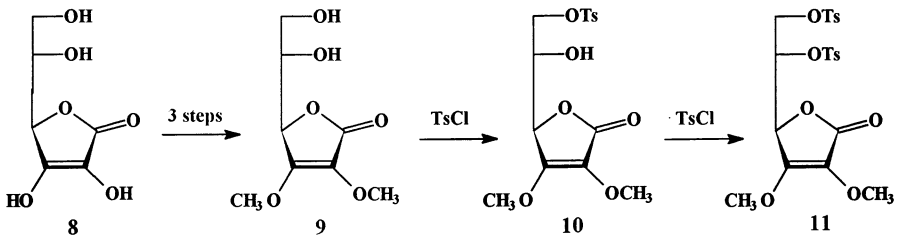



Scheme 1.

best yields of the lactams **15a–c** were obtained when the reactions were performed in a large excess of the amine as the reaction solvent at room temperature. The lactams **15a–c** thus obtained were, however, all optically inactive due to the fact that chirality at C-4 is destroyed during the reaction. The mechanism by which these lactams arise is also quite interesting. It seems that the initial step in the formation of the lactams **15a–c** most probably involves an E2 elimination reaction to give the intermediate allylic tosylate **12**, followed by the nucleophilic displacement reaction of **12** at C-6 to give the intermediate butenolide **13**, which then undergoes ring-opening reactions with the amines to form the enol–keto amides **14** that intramolecularly ring close by a 5-exo-trig process [3] to afford the lactams **15a–c** as racemic modifications (Scheme 2). After completion of our work, we found that racemisation at C-4 had also been observed by Dallacker and Sanders [4], who reported the formation of lactam **6** and amide **7** from the reaction of the isopropylidene L-ascorbic acid derivative **5** with methanolic ammonia and liquefied ammonia.

We have also tried the reaction of a reactive aromatic amine such as *p*-toluidine in excess with the ditosylate **11** in THF for several days at room temperature, but insignificant amounts of the corresponding lactam **15** were produced according to TLC. Performing the reaction at elevated temperatures and for prolonged periods of time produced considerable amounts of the elimination product **1** (X = $NHC_6H_4CH_3$) instead.

The reactions of the monotosylate **10** with the amines *n*-butylamine, benzylamine and cyclohexylamine produced reaction products that corresponded to the lactams **18a–c**. The reaction mechanism must involve the formation of the epoxide **16** as the first intermediate, which undergoes the usual E2 reaction to give the allylic alcohol **17**. The butenolide **17** then undergoes ring opening reaction with the amines (as in Scheme 2) to yield the lactams **18a–c** (Scheme 3).

Compounds **15a–c** and **18a–c** represent lactam derivatives of L-ascorbic acid, which may have some additional biological properties other than the recognised anti-oxidant properties that are associated with the ene–diol system of L-ascorbic acid.

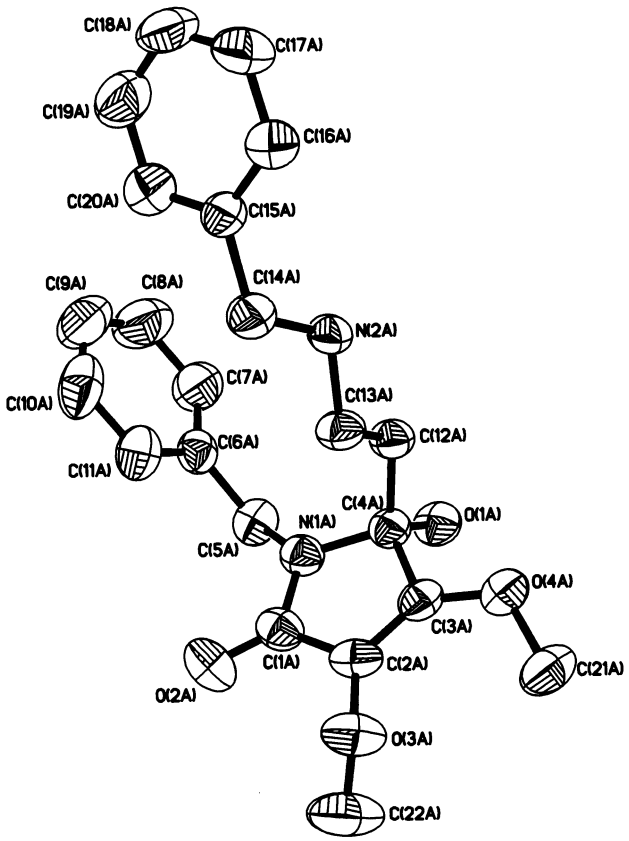
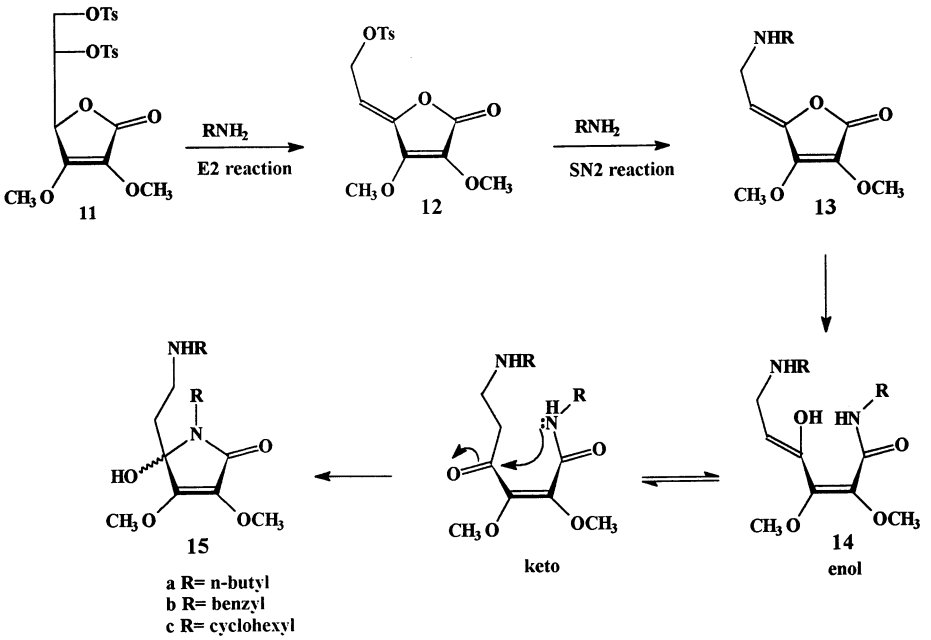
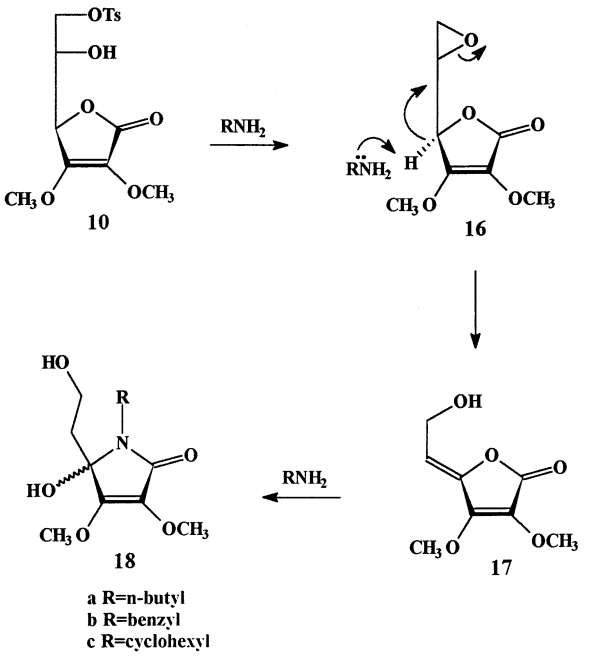



Fig. 1. ORTEP diagram for compound **15b**.




Scheme 2.




Scheme 3.

## 1. Experimental

*General methods.*—Melting points are uncorrected and were determined on Gallenkamp electrothermal apparatus. Infrared spectra were recorded with a Perkin–Elmer 783 spectrophotometer with a data station. $^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ using a Brucker AC 250 spectrometer operating at 250 and 62.9 MHz, respectively. Chemical shifts ($\delta$) are in ppm downfield from $Me_4Si$ as internal standard and $J$ values are given in Hz. Mass spectra were recorded with either a VG 7070 or VG Trio-1 quadrupole mass spectrometer fitted with a Hewlett–Packard 5890 GC. Microanalyses were performed by the University of Sheffield microanalytical laboratory. All solvents were dried and distilled by standard techniques. All organic solutions were dried over anhydrous $MgSO_4$. Petrol refers to a light petroleum fraction boiling in the range 40–60 °C.

*Typical experimental procedure for the formation of lactams* **15a–c** *and* **18a–c**.—To the ditosylate **11** (2.60 g, 5 mmol) was added benzylamine (15 mL), whence an exothermic occurred. The reaction mixture, after overnight stirring at room temperature, was diluted with a little THF and purified by flash chromatography (EtOAc, followed by 10:1 EtOAc–MeOH) to give product 1-benzyl-2,3-dimethoxy-4-hydroxy-4-[1′-(2′-aminobenzyl)-ethyl]but-3-enimide (**15b**) (1.44 g, 74%) as a light brown glass that solidified later. Recrystallisation (DCM–petrol) afforded single triclinic crystals, mp 72–74 °C.

*1-Benzyl-2,3-dimethoxy-4-hydroxy-4-[1′-(2′-aminobenzyl)ethyl]but-3-enimide* (**15b**). IR (thin film): $\nu$ 3120–3650 (OH), 3260 (NH),

1665 $cm^{-1}$ (C=O); $^1H$ NMR: $\delta$ 1.60–1.72 (1 H, m, 5-H), 1.72–1.87 (1 H, m, 5-H), 2.42–2.58 (1 H, m, 6-H), 2.83–2.98 (1 H, m, 6-H), 3.62 (2 H, s, $-NCH_2-$), 3.83 (3 H, s, $OCH_3$), 4.04 (3 H, s, $OCH_3$), 4.20 (1 H, d, $J$ 16, >NCH–), 4.76 (1 H, d, $J$ 16, >NCH–), 7.13–7.49 (10 H, m, 2Ph); $^{13}C$ NMR: $\delta$ 32.43, 34.35, 36.39, 39.22, 41.39, 42.21, 43.61, 44.33, 46.45, 51.27, 53.59, 55.74, 58.41, 60.16, 60.72, 62.38, 87.18, 125.13. 126.00, 126.67, 127.53, 128.54, 129.15, 130.02, 139.00, 139.64, 155.42, 168.14; MS: $m/z$, 382 [$M^+$], 364 [$M-H_2O$], 350 [M – MeOH], 293, 275; HRMS: $m/z$ calcd for $C_{22}H_{26}N_2O_4$: 382.18927. Found: $m/z$, 382.18957 [$M^+$]; Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 68.96; H, 6.81; N, 7.23. Found: C, 69.11; H, 6.81; N, 7.33.

*1*-n-*Butyl-2,3-dimethoxy-4-hydroxy-4-[1′-(2′-aminobutyl)ethyl]but-3-enimide* (**15a**). IR (neat): $\nu$ 3680 (broad OH), 3240 (NH), 1665 $cm^{-1}$ (C=O); $^1H$ NMR: $\delta$ 0.90 (6 H, t, $J$ 7.8, 2Me), 1.34 (4 H, quintet, $J$ 7.8, $-CH_2CH_2$), 1.43–1.63 (5 H, m, 5-H and chain H), 1.65–1.83 (1 H, m, 5-H), 1.97–2.14 (1 H, m, NH), 2.57–2.75 (2 H, m, $NCH_2$), 2.82–2.93 (1 H, m, NCH–), 3.07–3.22 (2 H, m, >NCH– and NCH), 3.22–3.38 (1 H, m, >NCH), 3.82 (3 H, s, OMe), 4.07 (3 H, s, OMe), 4.60 (1 H, bs, OH); $^{13}C$ NMR: $\delta$ 14.08 (high intensity), 20.48, 20.82, 31.11, 32.00, 33.57, 38.44, 44.64, 48.91, 59.56, 61.03, 86.59, 125.40, 154.39, 167.45; MS: $m/z$, 314 [$M^+$], 296 [$M-H_2O$], 253, 229, 168, 86 (100%); HRMS: $m/z$ calcd for $C_{16}H_{30}N_2O_4$: 314.2205. Found: $m/z$, 314.22343.

*1-Cyclohexyl-2,3-dimethoxy-4-hydroxy-4-[1′-(2′-aminocyclohexyl)ethyl]but-3-enimide* (**15c**). IR (neat): $\nu$ 3100–3540 (br, OH), 3240 (br, NH), 1665 $cm^{-1}$ (C=O); $^1H$ NMR: $\delta$ 1.0–1.40 (8 H, m, ring H), 1.50–2.05 (14 H, m, 5-H and ring H), 2.16–2.38 (1 H, broad m, OH), 2.38–2.54 (1 H, m, 6-H), 2.85–3.00 (1 H, m, 6-H), 3.04–3.25 (2 H, m, NCH<), 3.82 (3 H, s, OMe), 4.08 (3 H, s, OMe); $^{13}C$ NMR: $\delta$ 25.22, 26.41, 31.35, 33.10, 34.71, 40.30, 41.96, 42.20, 50.74, 52.59, 55.92, 57.64, 60.00, 61.95, 87.11, 125.13, 154.26, 166.72; MS: $m/z$, 366 [$M^+$], 348, 317, 269, 112 (100%); HRMS: $m/z$ calcd for $C_{20}H_{34}N_2O_4$: 366.25186. Found: $m/z$, 366.25304; Anal. Calcd for $C_{20}H_{34}N_2O_4$: C, 65.57; H, 9.29; N, 7.65. Found: C, 65.76; H, 9.22; N, 7.36.

*1*-n-*Butyl-3,4-dimethoxy-4-hydroxy-4-(hydroxyethyl)but-3-enimide* (**18a**). IR (neat): $\nu$ 3380 (broad, OH), 1680 $cm^{-1}$ (C=O); $^1H$ NMR: $\delta$ 0.90 (3 H, t, $J$ 6.8, Me), 1.20–1.40 (2 H, q, $J$ 6.8, $-CH_2-$), 1.42–1.73 (2 H, m, $-CH_2-$), 1.88–2.04 (1 H, dt, $J$ 15.6, 6.8, C-5), 2.15–2.30 (1 H, m, C-5), 2.88 (1 H, bs, OH), 3.04–3.20 (1 H, m, >NCH), 3.20–3.37 (1 H, m, >NCH), 3.56–3.65 (1 H, m, C-6), 3.65–3.83 (1 H, m, C-6), 3.78 (3 H, s, OMe), 4.05 (3 H, s, OMe), 4.63 (1 H, bs, OH); $^{13}C$ NMR: $\delta$ 14.06, 20.82, 31.94, 37.31, 38.41, 58.43, 59.51, 60.99, 86.31, 125.50, 153.46, 167.76; MS: $m/z$, 259 [$M^+$], 227, 214, 197, 198, 187, 157; Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.95; H, 8.07, N, 4.91. Found: C, 58.75; H, 8.07; N, 4.65.

*1-Benzyl-3,4-dimethoxy-4-hydroxy-4-(hydroxyethyl)but-3-enimide* (**18b**). $^1H$ NMR: $\delta$ 1.69–1.83 (1 H, m, C-5), 1.95–2.12 (1 H, m, C-5), 2.73 (1 H, bs, OH), 3.15–3.28 (1 H, m, C-6), 3.37–3.50 (1 H, m, C-6), 3.79 (3 H, s, OMe), 4.04 (3 H, s, OMe), 4.23 (1 H, d, $J$ 16, benzylic), 4.63 (1 H, d, $J$ 16, benzylic), 5.13 (1 H, bs, OH), 7.13–7.37 (5 H, m, Ph); $^{13}C$ NMR: $\delta$ 35.75, 37.54, 39.47, 41.45, 43.65, 55.97, 58.36, 60.05, 60.70, 62.36, 86.57, 125.30, 126.27, 127.17, 127.56, 128.87, 129.65, 130.07, 138.94, 154.44, 168.45; Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.43; H, 6.48; N, 4.78. Found: C, 60.81; H, 6.71; N, 4.39.

*1-Cyclohexyl-3,4-dimethoxy-4-hydroxy-4-(hydroxyethyl)but-3-enimide* (**18c**). $^1H$ NMR: $\delta$ 1.06–1.30 (4 H, m, ring, H), 1.45–1.80 (6 H, m, ring H), 1.82–1.95 (1 H, br, OH), 2.03–2.28 (3 H, m, C-5 and >NCH<), 3.14 (1 H, br t, $J$ 9, OH), 3.52–3.65 (1 H, m, C-6), 3.65–3.80 (1 H, m, C-6), 3.73 (3 H, s, OMe), 4.00 (3 H, s, OMe); $^{13}C$ NMR: $\delta$ 14.41, 21.30, 25.53, 26.65, 26.73, 30.99, 37.48, 52.05, 58.46, 59.33, 60.81, 61.06, 86.53, 125.68, 152.92, 167.06; MS: $m/z$, 285 [$M^+$], 253, 240, 187, 158, 98 (100%); Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.95; H, 8.07; N, 4.91. Found: C, 58.63; H, 8.07; N, 4.65.

*Crystal data of lactam* **15b**.—$C_{22}H_{26}N_2O_4$, $M = 382.45$, crystallises from ether solvent as colourless prisms; crystal dimensions $0.77 \times 0.32 \times 0.30$ mm. Triclinic, $a = 11.671(2)$, $b = 13.045(3)$, $c = 15.507(3)$ Å, $\alpha = 69.21(2)$, $\beta = 73.94(2)$, $\gamma = 70.390(10)°$, $U = 2045.6(7)$ $Å^3$, $Z = 4$, $D_{calc} = 1.242$ g/$cm^3$, space group $P\bar{1}$

($C_i^1$, no. 2), Mo $K_\alpha$ radiation ($\lambda = 0.71073$ Å), $\mu$(Mo $K_\alpha$) = 0.086 $mm^{-1}$, $F(000) = 816$.

Three-dimensional, room-temperature X-ray data were collected in the range $3.5 < 2\theta < 45°$ on a Siemens P4 diffractometer using the omega scan method. Of the 6191 reflections measured, all of which were corrected for Lorentz and polarisation effects but not for absorption, 4201 independent reflections exceeded the significance level $|F|/\sigma(|F|) > 4.0$ The structure was solved by direct methods and refined by full-matrix least-squares methods on $F^2$. Hydrogen atoms were included in calculated positions and refined in riding mode. Refinement converged at a final $R = 0.050$ ($wR_2 = 0.1474$ for all 5259 unique data, 522 parameters, mean and maximum $\delta/\sigma$ 0.000, 0.000), with allowance for the thermal anisotropy of all non-hydrogen atoms. Minimum and maximum final electron density were $-0.328$ and 0.407 e $A^{-3}$, respectively. A weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0806P)^2 + 1.2807P]$, where $P = (F_o^2 + 2F_c^2)/3$ was used in the latter stages of refinement. Complex scattering factors were taken from the program package SHELXL-93 [5], as implemented on a Viglen 486dx computer.

## 2. Supplementary material

Tables of atomic coordinates, bond lengths and bond angles for **15b** have been deposited with the Cambridge Crystallographic Data Centre. These tables may be obtained, upon request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

## Acknowledgements

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