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**L-Ascorbic Acid in organic synthesis: DBU- catalysed one-pot synthesis of tetramic acid derivatives from 5,6-*O*-isopropylidene ascorbic acid[#]**

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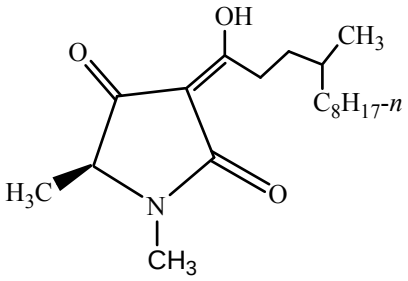
**Abstract**: Reaction of 5,6-*O*-isopropylidene-2,3-*bis*-*O*-alkyl ascorbic acid with different amines in the presence of DBU at ambient temperature resulted in the formation of 3,4-*bis*-*O*-alkyl-1-alkyl-5-(2-hydroxy ethyl)-5-hydroxy-1,5-dihydropyrrol-2-ones in moderate yields.

**Key Words:** Ascorbic Acid, Tetramic Acids**,** Addition reactions, Aminations, Eliminations.

Tetramic acid derivatives are the key structural core found in a variety of natural products including many antibiotics such as melophilin B, reutericyclin, tirandamycin, BU2313A, blasticidin A and vancoresmycin.[1-5] The wide spectrum of biological activities in this class of molecule include potent antiviral, antibiotic, and antifungal properties as well as cytotoxicities and antitumor action.[6,7,8] These compounds have also been designed as glycine site *N*-methyl-D-asparatate (NMDA) antagonists for the treatment of neurological disorders.[6] Only one of such prominent molecules is depicted in *Figure. 1*.




Melophilin B

**Figure 1**

Recently a number of solution and solid phase syntheses of tetramic acids have been reported. [9-13] Ascorbic acid has been used in organic synthesis for the preparation of many intermediates and biologically active molecules. Our interest in ascorbic acid chemistry arose from our quest for new drugs against tuberculosis. Thiolactomycins, thiotetronic acid derivatives, show antitubercular activity via mycobacterial FAS-II inhibition[14a, b] and many 5-hydroxymethyl tetronic acid analogs exhibit HIV protease inhibitory activity.[14c] We were interested in the synthesis of compounds where the ring oxygen of ascorbic acid is replaced with nitrogen and the resulting core, a tetramate, might serve as very good pharmacophore. Ascorbic acid as a synthon has been used in the synthesis of pyrano[3,4-*b*]indoles and a variety of other heterocycles by Preobrzhenskaya's group.[15] Very recently Dallacker's group[16] and Khan *et al*.[17] reported the reaction of liquid ammonia and amines with ascorbic acid derivatives to give lactams. Encouraged by their reports we decided to synthesise tetramic acid derivatives from suitably protected ascorbic acid.

The reaction of 2,3-*O*- *bis*-allyloxy-5,6-*O*-isopropylidene ascorbic acid **2a**, prepared by the slightly modified method reported earlier,[18] with butylamine in THF at 0 $^{o}$C to 40 $^{o}$C did not result in any product as evidenced by TLC. However, addition of DBU as catalyst led to the formation of many products (TLC) and compound **2a** was totally consumed within 10 h at ambient temperature. Column ($SiO_2$)

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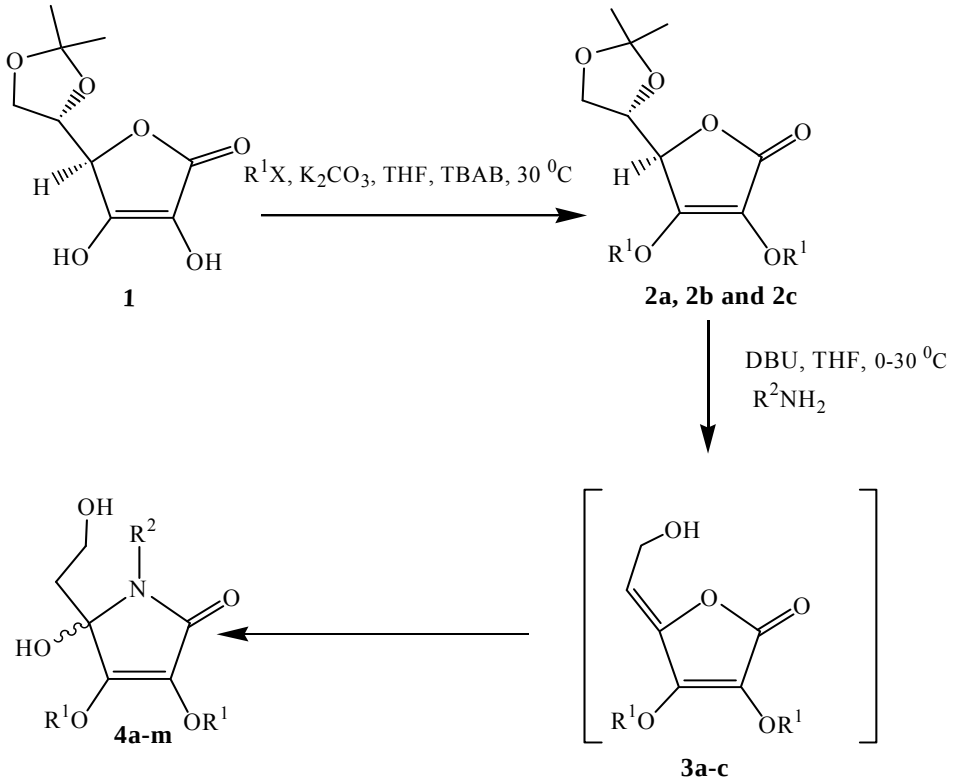
chromatography of the crude reaction mixture led to the isolation of only two compounds as major and minor products. Other compounds (in very minute amounts) could not be isolated in pure forms. The major compound isolated was found to be 3,4-*bis*-allyloxy-1-butyl-5-hydroxy-5-(2-hydroxyethyl)-1,5-dihydropyrrol-2-one **4b** in 50% yield. The structure was evidenced by its spectroscopic data and analysis.[19] The minor product was characterized as 3,4-*bis*-allyloxy-5-(2-hydroxyethylidene)-5*H*-furan-2-one **3a** in 10% yield. The *Z* geometry of the double bond in this compound was evidenced on the basis of its PMR spectrum. Its structure was also evidenced on the basis of spectroscopic data. A careful monitoring of the reaction with TLC showed that **3a** is formed first and with the passage of time it is converted into **4b**. We reacted **3a** under similar conditions with butylamine to give **4b** in good yield. Similarly, reaction of 2,3-allyloxy-5,6-*O*-isopropylidene ascorbic acid with other amines in the presence of DBU at ambient temperature led to the formation of the respective 1-alkyl tetramates (**4a**-**4h**) in good yields along with the 5-hydroxyethylidene product in minor amounts in a few cases (Table 1).

To see the effect 2,3-alkoxy substitutent in this reaction we have carried out the reaction of 2,3-*bis*–benzyloxy-5,6-*O*-isopropylidene ascorbic acid **2c** and 2,3- *bis*–methoxy-5,6-*O*-isopropylidene ascorbic acid **2b**, which were reacted with butylamine separately. The products obtained were the respective 1-alkyl tetramates **4j** and **4k** in moderate yields along with the intermediate ethylidene derivatives (**3b** and **3c**) in ≤ 15% yields. There was no major improvement in the yield of the isolated products in any case suggesting that 2,3-*O*-substitutents do not affect the course of the reaction. Dichloromethane, ethanol or chloroform were also used as solvents in this reaction but resulted in no improvements in the yields. 4-Dimethyl aminopyridine and triethylamine used as base did not lead to any reaction.




**Scheme 1**

Introduction of nitrogen atom in place of oxygen atom in the ring of ascorbic acid leading to formation of tetramates could be explained via the intermediates **3a-c** (*Fig. 2*). In fact the formation of these intermediates is evidenced by TLC, just after few minutes during the course of reaction and with the passage of time they are consumed to give respective products. A reaction mechanism proposed for this reaction most probably involves the abstraction of a proton from C-4 of ascorbic acid derivatives followed by β-elimination of acetone from 5,6-*O*-isopropylidene unit of **2** resulting in the unsaturated 5-ethylidene

derivatives **3a-c**. Such a rearrangement has also been reported by Poss[20] et. al. during reaction of 5,6-*O*-isopropylidene derivative with *t*-Bu*O*Li in Bu*O*H at ambient temperature. Once the unsaturated lactone **3** is formed it undergoes ring-opening reactions with amines to give the enol-keto amides. The latter undergoes intramolecular ring closure to give the lactams or teramates *Figure 2*.

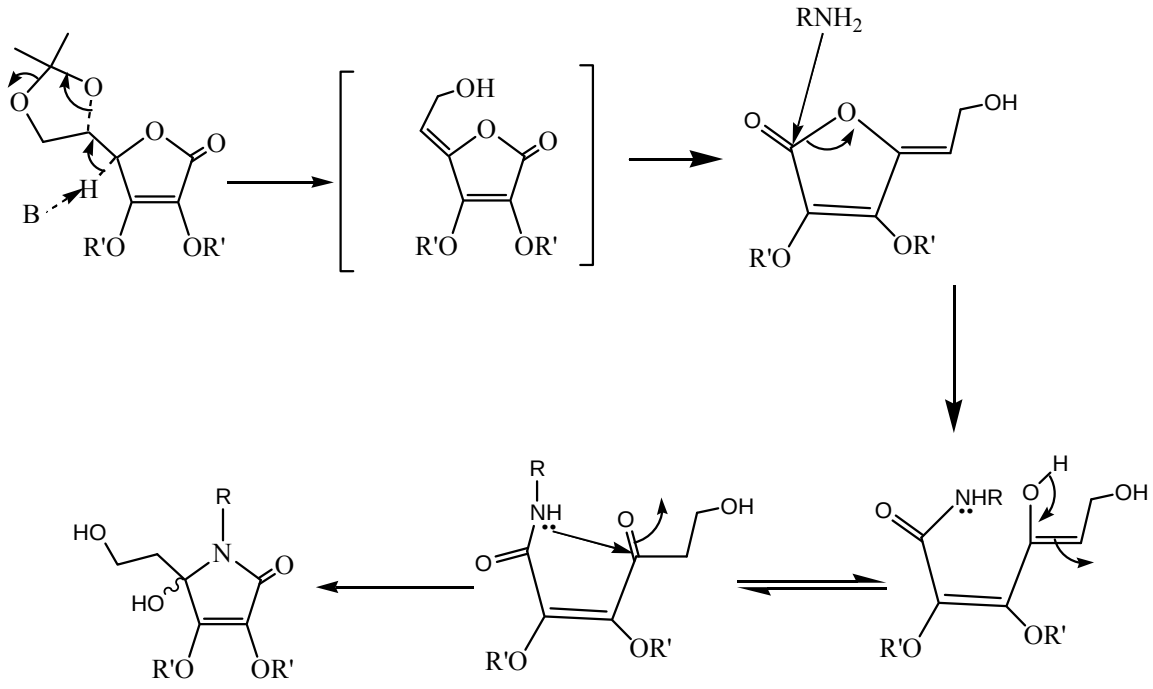



**Figure 2 Mechanism of Reaction**

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19 *General Procedure for the Synthesis of* **3a-c** *and* **4a-m***:* To a stirring solution of compound **2a** (1.7 g, 5.74 mmol) and *n*-propylamine (0.52 ml, 6.31 mmol) in THF (8 mL) at 0 ºC, DBU (50 mol %) was added and stirring continued for 10 min. at this temperature. Reaction mixture was further stirred at ambient temperature till the disappearance of **2a** (TLC). The solvent was evaporated and the residue was partitioned between ethyl acetate (5x20mL) and water (2x10mL). Ethyl acetate dried ($Na_2SO_4$) and evaporated under reduced pressure to get crude mass which was chromatographed over silica gel (240-400 mesh) using a gradient of hexane: EtOAc (4:1) as eluent to afford the intermediate 5-hydroxy-5-(2-hydroxyethylidene)-furanone **3a** followed by the required tetramic acid derivative **4a**. Similarly all other compounds were prepared. The spectroscopic and analytical data of few of the representative compounds are given here. Compound **3b**: MS (FAB) 187$(M+H)^+$ , IR (Neat) 3391, 1688 $cm^{-1}$, $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ = 1.39 (*bs*, 1H), 3.92 (*s,* 3H ), 4.16 ( *s*, 3H ), 4.41( (d, *J* = 7.0, 2H ), 5.50 ( *t*, *J* = 7.0 Hz, 1H ); $^{13}$C NMR (50 MHz, $CDCl_3$) 56.6, 59.9, 60.6, 108.1, 125.0, 142.3, 149.1, 164.7. **3c :** MS (FAB) 339 $(M+H)^+$; IR (Neat) 3389, 1676 $cm^{-1}$; $^1$NMR (200 MHz, $CDCl_3$) δ = 1.42 ( *bs*, 1H), 4.40 ( *d*, *J* = 7.0 Hz, 2H), 5.16 (s, 2H), 5.22 (*s*, 2H) 5.51 (*t*, *J* = 7.0 Hz, 1H ), 7.21- 7.37( *m*, 10H). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 56.9, 73.6, 74.4, 108.0, 124.1, 128.0 (integrating two carbons), 129.0 (integrating two carbons), 129.1 (integrating three carbons), 129.3 (integrating three carbons), 135.8, 136.1, 142.7, 148.7, 167.5. **4a**: MS (FAB): 298 $(M+H)^+$; IR (Neat): 3394, 1688 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 0.93 (*t*, *J* = 7.2Hz, 3H), 1.64-1.66 (*m*, 3H), 2.21-2.36 (*m*, 2H), 2.63-2.75 (*m,* 2H), 3.16-3.19 (*m*, 1H), 3.38-3.49 (*m*, 2H), 3.86-4.22 (*m*, 4H), 5.09-5.31 (*m*, 4H), 5.88-6.02 (*m*, 2H); $^{13}$C NMR (50 MHz, $CDCl_3$): 11.9, 22.5, 35.4, 36.5, 42.3, 66.2, 66.9, 82.6, 95.5, 104.7, 116.9, 119.0, 133.6, 135.5, 171.8 Anal. Calcd for $C_{15}H_{23}NO_5$ (%): C, 60.60; H, 7.74; N, 4.71. Found: C, 60.70; H, 7.62; N, 4.76. **4b**: MS (FAB) 312 $(M+H)^+$, IR (Neat) 3388, 1683 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 0.93 (*t*, *J* = 7.2Hz, 3H), 1.25-1.40 (*m*, 3H), 1.56-1.64 (*m*, 2H), 2.23-2.36 (*m,* 3H), 2.65-2.72 (*m,* 2H), 3.11-3.44 (*m*, 2H), 3.88-4.19 (*m*, 4H), 5.09-5.31 (*m*, 4H), 5.88-6.02 (*m*, 2H); $^{13}$C NMR (50 MHz, $CDCl_3$): 14.1, 20.7, 30.3, 35.3, 36.5, 40.4, 66.2, 66.9, 82.6, 95.2, 104.7, 116.9, 119.0, 133.6, 135.5 171.1: Anal. Calcd for $C_{16}H_{25}NO_5$ (%): C, 61.73; H, 8.03; N, 4.50. Found: C, 61.75; H, 8.19; N, 4.32. **4d**: MS (FAB) 368 $(M+H)^+$; IR (Neat) 3372, 1714 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 0.87 (*t*, *J* = 6.8Hz, 3H), 1.27 (*m*, 8H), 1.65 ( *m*, 3H), 2.17-2.37 (*m,* 2H), 3.15-3.50 (*m,* 3H), 3.96-4.43 (*m*, 8H), 5.17-5.39 (*m*, 4H), 5.92-6.00 (*m*, 2H); $^{13}$C NMR (50 MHz, $CDCl_3$): 14.4, 22.9, 27.6, 29.4 (integrating two carbons), 29.5 (integrating two carbons), 32.1, 36.3, 40.7, 65.4, 67.2, 72.6, 77.6, 96.2, 104.4, 117.3, 119.0, 134.4, 170.4. . Anal. Calcd for $C_{20}H_{33}NO_5$ (%): C, 65.39; H, 8.99; N, 3.81. Found: C, 65.40; H, 8.74; N, 3.82. **4e**: MS (FAB): 424 $(M+H)^+$; IR (Neat): 3353, 1685 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 0.86 (*t*, *J* = 7.2Hz, 3H), 1.24 (*m*, 20H), 2.27-2.31 (*m*, 2H), 2.65-2.68 (*m*, 2H), 3.20- 3.41 ( *m*, 2H), 3.82 (*m*, 2H), 4.19-4.21 (*m*, 4H), 5.07-5.30 (*m*, 4H), 5.94-5.98 (*m*, 2H); $^{13}$C NMR (50 MHz, $CDCl_3$): 14.4, 23.0, 27.6, 29.4(integrating two carbons), 29.7(integrating three carbons), 29.8, 30.0, 32.2, 35.5, 36.6, 40.5, 66.3, 67.0, 82.4, 95.3, 104.9, 116.6, 118.9, 133.8, 135.7, 171.3. Anal. Calcd for $C_{20}H_{33}NO_5$ (%): C, 68.08; H, 9.69; N, 3.30. Found: C, 68.10; H, 9.60; N, 3.38. **4f**: MS (FAB): 346 $(M+H)^+$; IR (Neat): 3339, 1699 $cm^{-1}$ $^1$H NMR (200

MHz, $CDCl_3$) $\delta$ 1.68 (brs, 1H), 2.00-2.16 (*m*, 2H), 3.45 (brs, 1H), 3.68- 4.00 (*m*, 2H), 4.18-4.39 (*m*, 4H), 4.53 (*d*, *J* = 15.2 Hz, 1H), 4.76 (*d*, *J* = 15.2 Hz, 1H), 5.17-5.41 (*m*, 4H), 5.94-6.02(*m*, 2H), 7.27-7.34 (m, 5H); $^{13}$C NMR (50 MHz, $CDCl_3$): 35.8, 43.3, 65.2, 67.1, 72.7, 82.6 96.0, 104.3, 117.2, 119.0, 127.7, 128.1(integrating two carbons), 128.7(integrating two carbons), 134.1, 134.2, 137.7, 170.8. Anal. Calcd for $C_{19}H_{23}NO_5$ (%): C, 66.08; H, 6.69; N, 4.05. Found: C, 66.10; H, 6.60; N, 4.18. **4j**: MS (FAB): 412 $(M+H)^+$; IR (Neat): 3748, 3389, 1676 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 0.93 ( *t*, J = 7.2 Hz, 3H), 1.25-1.39 (*m*, 2H), 1.57-1.64 ( *m*, 3H), 1.90-1.98 ( *m*, 1H ), 2.18-2.22 ( *m*, 1H ), 3.13- 3.18 (*m*, 2H ), 3.36-3.54 ( *m*, 3H), 5.06-5.28 ( *m*, 4H), 7.21-7.40 ( *m*, 10H).$^{13}$C NMR (50 MHz, $CDCl_3$): 14.2, 20.9, 32.0, 37.4, 38.5, 58.4, 73.4, 74.2, 86.5, 123.8, 128.0 (integrating two carbons), 128.7 (integrating two carbons), 128.9 (integrating four carbons) 129.5 (integrating two carbons), 136.6, 136.8, 153.1, 167.9. Anal. Calcd for $C_{24}H_{29}NO_5$ (%): C, 70.07; H, 7.05; N, 3.40. Found: C, 70.10; H, 7.15; N, 3.39. **4m**: MS (FAB) 294 $(M+H)^+$ ; IR (Neat) 3677, 3391, 1688 $cm^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.54 ( bs, 1H), 1.78-1.90( *m*, 1H) 2.05-2.17 ( *m*, 1H), 3.34-3.40 ( *m*, 1H), 3.54-3.60 ( *m*, 1H ), 3.88 ( *s*, 3H), 4.09 ( *s*, 3H), 4.16 ( bs, 1H), 4.37 ( d, *J* = 15.6 Hz, 1H), 4.64 ( d, *J* = 15.6 Hz, 1H), 7.26-7.34 ( *m,* 5H), $^{13}$C NMR (50 MHz, $CDCl_3$): 37.6, 41.6, 58.3, 59.6, 61.2, 86.6, 125.4, 127.6, 128.2, 128.4, 128.8, 128.9, 139.0 154.3, 168.3. Anal. Calcd for $C_{15}H_{19}NO_5$ (%): C, 61.43; H, 6.48; N, 4.77. Found: C, 61.41; H, 6.45; N, 4.75.

*Table 1*: Synthesis of 2,3-*O*-substituted-1-alkyltetramates (**4a-4m)**

| S.No | Entry | $R^1$ | $R^2$ | Reaction Time(h) | % yield* of (4a-m) | % yield* of (3a-c) |
|---|---|---|---|---|---|---|
| 1 | **4a** | $-CH_2CH=CH_2$ | *n*-propyl | 15 | 50 | 10 |
| 2 | **4b** | $-CH_2CH=CH_2$ | *n*-butyl | 16 | 50 | 10 |
| 3 | **4c** | $-CH_2CH=CH_2$ | *n*-hexyl | 14 | 60 | 8 |
| 4 | **4d** | $-CH_2CH=CH_2$ | *n*-octyl | 15 | 60 | 10 |
| 5 | **4e** | $-CH_2CH=CH_2$ | *n*-dodecyl | 10 | 55 | 10 |
| 6 | **4f** | $-CH_2CH=CH_2$ | benzyl | 8 | 60 | 15 |
| 7 | **4g** | $-CH_2CH=CH_2$ | piperidine | 15 | 45 | 10 |
| 8 | **4h** | $-CH_2CH=CH_2$ | adamantayl | 20 | 25 | 15 |
| 9 | **4i** | $-CH_2C_6H_5$ | *n*-propyl | 12 | 60 | 10 |
| 10 | **4j** | $-CH_2C_6H_5$ | *n*-butyl | 7 | 50 | 15 |
| 11 | **4k** | $-CH_3$ | *n*-butyl | 9 | 50 | 10 |
| 12 | **4l** | $-CH_3$ | *n*-octyl | 8 | 55 | 10 |
| 13 | **4m** | $-CH_3$ | benzyl | 8 | 35 | 15 |

* from chromatography