Studies on dehydro-D-*erythro*-ascorbic acid 2-arylhydrazone 3-oximes: conversion into substituted triazoles and isoxazolones

Mohamed A. El Sekily*

Department of Chemistry, Faculty of Science, Alexandria University, Ibrahimia, PO Box 426, 21321 Alexandria, Egypt

D-*erythro*-2,3-Hexodiulosono-1,4-lactone 2-*o*-bromophenylhydrazone (**2**) was prepared from dehydro-isoascorbic acid. Reaction of **2** with NH_2OH gave the 2-hydrazone-3-oxime (**3**) which on boiling with Ac_2O, gave the triazole derivative **4**. The unacetylated triazole derivative **5** was obtained from **3** with Br_2–H_2O. Treatment of **4** or **5** with ammonia gave the triazole carboxamides **7** and **8** respectively. Vigorous acetylation of **7** and **8** with boiling Ac_2O gave tetraacetates, while Ac_2O/pyridine gave triacetates. Reaction of **3** with HBr–AcOH gave the 5-*O*-acetyl-6-bromo-6-deoxy derivative **14**, and a controlled reaction of **3** with NaOH, followed by neutralisation, gave the isoxazolone **16**.

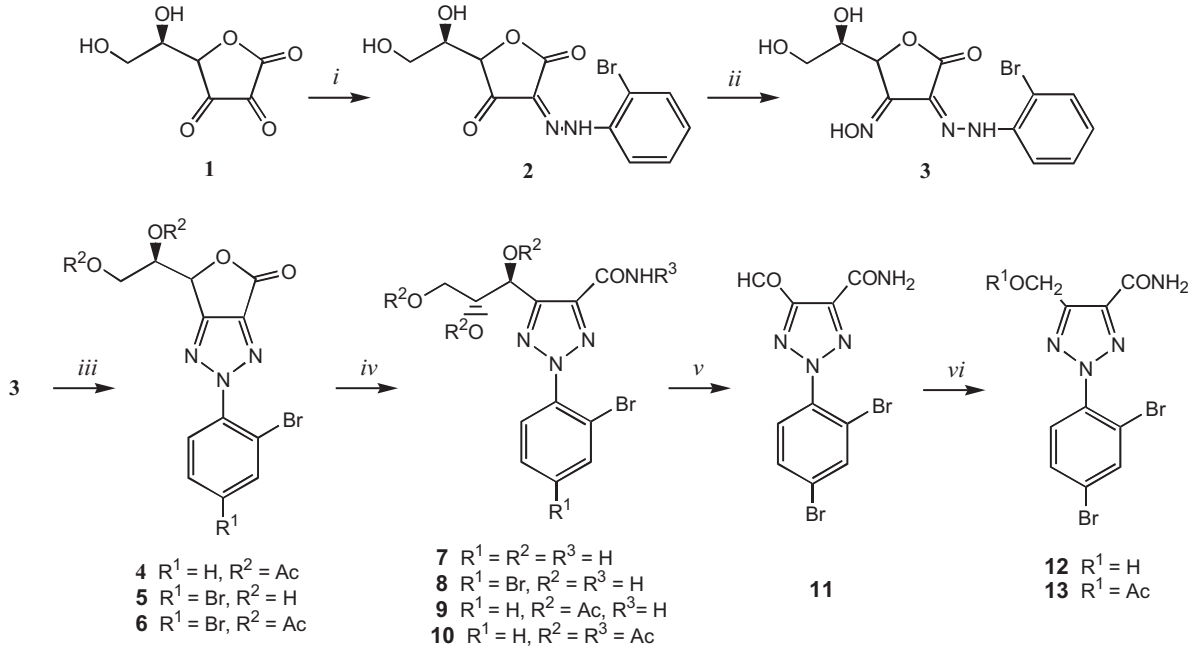
Keywords: dehydro-D-*erythro*-ascorbic acid 2-arylhydrazone 3-oximes, substituted triazoles, isoxazolones

The presence of three adjacent carbonyl groups (furantrione system) in dehydro-D-*erythro*-ascorbic acid explains the high chemical activity inherent in such a molecule. The mono- and bishydrazones of dehydro-L-*threo*- and dehydro-D-*erythro*-ascorbic acids could be excellent precursors for the synthesis of different heterocyclic compounds including quinoxalines, triazoles, pyrazolinediones, imidazoles and isoxazolines[1-7] which may show chemotherapeutic effects.

The reactions of dehydro-L-ascorbic acid bishydrazones differ from those of the sugar osazones (glycosulose 1,2-bishydrazones). The former readily undergo cyclisations involving either nucleophilic attack of the hydrazone nitrogen on the 1-carbonyl group, or attack of hydroxyl group on the hydrazone residue. Thus, for example, oxidation of dehydro-L-ascorbic acid bishydrazones yields bicyclic azo compounds,[8,9] whereas, the glycosulose osazones yield triazoles.[10]

In the present work, dehydro-D-*erythro*-ascorbic acid *o*-bromophenylhydrazone was prepared and converted into a number of triazole and isoxazoline derivatives. Thus, condensation (1 : 1 mol. ratio) of dehydro-D-*erythro*-ascorbic acid (**1**) and *o*-bromophenylhydrazine at room temperature afforded D-erythro-2,3-hexodiulosono-1,4-lactone 2-*o*-bromophenylhydrazone (**2**). The IR spectrum of **2** showed the lactone band at 1720 cm^{-1} and a carbonyl absorption (C-3) at 1680 cm^{-1}. On treatment of **2** with hydroxylamine, D-erythro-2,3-hexodiulosono-1,4-lactone 2-*o*-bromophenylhydrazone 3-oxime (**3**) was obtained.

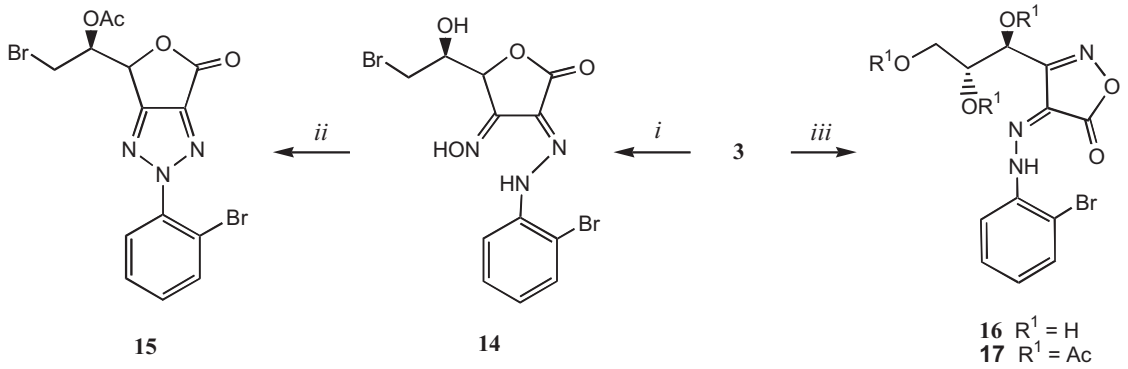
Treatment of **3** with acetic anhydride in pyridine resulted in acetylation of the hydroxyl groups on C-5 and C-6 and cyclisation with elimination of a molecule of water to form 2-*o*-bromophenyl-5-(2,3-di-*O*-acetyl-D-*erythro*-glycerol-1-yl)-1,2,3-triazole-4-carboxylic acid lactone (**4**), whose IR spectrum showed the lactone band at 1800 cm^{-1} and an ester band at 1740 cm^{-1}. The ^1H NMR spectrum of **4** showed two acetyl group signals at δ 2.03 and 2.09 in addition to the expected proton signals. Treatment of compound **3** with bromine-water induced cyclisation and bromination to give 2-(2,4-dibromophenyl)-5-(D-*erythro*-glycerol-1-yl)-1,2,3-triazole-4-carboxylic acid lactone (**5**), the IR spectrum of which showed hydroxyl absorption at 3450 cm^{-1} and



Reagents: *i:* 2-$BrC_6H_4NHNH_2/H^+$; *ii:* NH_2OH/H^+; *iii:* Ac_2O or Br_2/H_2O; *iv:* NH_3; *v:* $NaIO_4$; *vi:* $NaBH_4$

Scheme 1

* Correspondent. E-mail: prof_dr_m_a_elsekily@yahoo.com



15 **14** **16** R^1 = H; **17** R^1 = Ac

Reagents: *i:* HBr/AcOH; *ii:* Ac_2O/pyr; *iii:* (1) NaOH, (2) H^+

Scheme 2

the lactone band at 1800 cm^{-1}. Acetylation of compound **5** with acetic anhydride and pyridine afforded the di-*O*-acetyl derivative **6**.

Upon treatment of the triazole **4** or **5** with methanol and ammonia, deacetylation occurred with opening of the lactone ring to afford 2-*o*-bromophenyl-5-(D-*erythro*-glycerol-1-yl)-1,2,3-triazole-4-carboxamide (**7**) and the corresponding 2-(2,4-dibromophenyl) compound (**8**). The IR spectra of **7** and **8** showed amide bands at 1660 cm^{-1}. Mild acetylation of compound **7** with acetic anhydride and pyridine afforded the triacetate **9**, as 2-*o*-bromophenyl-5-(1,2,3-tri-*O*-acetyl-D-*erythro*-glycerol-1-yl)-1,2,3-triazole-4-carboxamide. The mass spectrum of **9** showed molecular ion peaks at *m/z* 482 and 484 and a series of ions from elimination processes involving the sugar moiety attached to the nitrogen heterocycle On the other hand, vigorous acetylation of compound **7** with boiling acetic anhydride afforded the tetraacetate **10**. The NMR spectrum of compound **10** showed three *O*-acetyl group signals at δ 2.02, 2.07 and 2.14 in addition to an *N*-acetyl signal at 2.62.

Periodate oxidation of compound **8** resulted in the consumption of two moles of the oxidant with the formation of 2-(2,4-dibromophenyl)-5-formyl-1,2,3-triazole-4-carboxamide (**11**). Reduction of compound **11** with sodium borohydride afforded 2-(2,4-dibromophenyl)-5-(hydroxy-methyl)-1,2,3-triazole-4-carboxamide (**12**). Acetylation of **12** with acetic anhydride and pyridine formed the 4-acetoxymethyl derivative **13**.

Treatment of compound **3** with hydrogen bromide-acetic acid gave 5-*O*-acetyl-6-bromo-6-deoxy-D-erythro-2,3-hexodiulosono-1,4-lactone-2-*o*-bromophenylhydrazone 3-oxime (**14**). Acetylation of **14** with acetic anhydride and pyridine, gave 5-(2-*O*-acetyl-3-bromo-3-deoxy-D-*erythro*-glycerol-1-yl)-2-*o*-bromophenyl-1,2,3-triazole-4-carboxylic acid lactone (**15**). On careful treatment of compound **3** with sodium hydroxide, followed by neutralisation, opening of the lactone ring occurred, followed by elimination of a molecule of water, affording 3-(D-*erythro*-glycerol-1-yl)-isoxazole-4,5-dione 4-*o*-bromophenylhydrazone (**16**). Acetylation of compound **16** with acetic anhydride in pyridine afforded 3-(tri-*O*-acetyl-D-*erythro*-glycerol-1-yl) derivative **17**, the IR spectrum of which showed the lactone carbonyl band at 1720 cm^{-1} and the ester band at 1740 cm^{-1}.

Experimental

Melting points were recorded on a Tottoli (Büchi) apparatus. IR (KBr) spectra were recorded on a 580B Perkin Elmer IR spectrometer. The ^1H NMR spectra were run on a Varian EM-399 MHz NMR spectrometer using TMS as standard. Chemical shifts (δ) are given in ppm.

D-erythro-2,3-Hexodiulosono-1,4-lactone 2-o-bromophenylhydrazone (**2**): A solution of D-*erythro*-2,3-hexodiulosono-1,4-lactone, obtained by oxidation of D-isoascorbic acid (17.6 g, 0.1 mol), in water (200 ml) was treated with *o*-bromophenylhydrazine hydrochloride (22.3 g, 0.1 mol) and sodium acetate (8.2 g, 0.1 mol) in ethanol (100 ml). The mixture was kept overnight at room temp., and the desired solid was filtered off, washed with water, ethanol and dried. It was crystallised from ethanol in yellow needles (6 g, 17%), m.p. 166–168°C; IR: ν_{max}/cm^{-1} 3450 (OH), 1720 (lactone C=O). and 1680 (C=O). Anal. Calc. for $C_{12}H_{11}BrN_2O_5$: C, 42.0; H, 3.20; Br, 23.32; N, 8.16. Found: C, 42.36; H, 3.45; Br, 23.0; N. 8.36%.

D-erythro-2,3-Hexodiulosono-1,4-lactone2-o-bromophenyl-hydrazone 3-oxime (**3**): Hydrazone **2** (1 g) in ethanol (30 ml) was treated with hydroxylamine hydrochloride (2 g) and sodium acetate (2 g) in ethanol (30 ml), and the mixture was heated under reflux for 4 h, concentrated, and cooled to room temp. The solid product was filtered off, successively washed with water and ethanol, and dried. Compound **3** was recrystallised from ethanol in yellow needles (0.8 g, 75%), m.p. 237–239°C; IR: ν_{max}/cm^{-1} 3400 (OH) and 1730 (lactone C=O). Anal. Calc. for $C_{12}H_{12}BrN_3O_5$: C, 40.22; H, 3.35; N, 11.73. Found: C. 40.51; H, 3.62; N, 11.53%.

2-o-Bromophenyl-5-(D-erythro-2',3'-diacetoxy-1'-hydroxy-propyl)-1,2,3-triazole-4-carboxylic acid lactone (**4**): Compound **3** (0.1 g) in dry pyridine (5 ml) was treated with acetic anhydride (5 ml), kept overnight at room temp, and then poured onto crushed ice. The solid was filtered off, washed with water and dried (0.07 g, 65%). It was recrystallised from ethanol to give colourless needles, m.p. 115–116°C; IR: ν_{max}/cm^{-1} 1800 (lactone C=O) and 1740 (ester C=O). NMR: δ_H ($CDCl_3$) 2.03, 2.09 (2 s, 6H, 2 OAc), 4.3(m, 2H, CH_2), 5.52 (q, 1H, H-2), 5.80 (d, 1H, H-1), 7.0–8.06 (m, 4H, Ar–H). Anal. Calc. for $C_{16}H_{14}BrN_3O_6$: C, 45.28; H, 3.3; N, 9.9. Found: C, 45.62; H, 3.21; N, 9.6%.

2-(2,4-Dibromophenyl)-5-(D-erythro-1',2',3'-trihydroxypropyl)-1,2,3-triazole-4-carboxylic acid 4,1'-lactone (**5**): A suspension of **3** (1 g) in water (20 ml) was treated with bromine (2 g) and left overnight at room temp. with stirring. Excess of bromine was removed by passing a current of air and the solid was crystallised from ethanol as colourless needles(1 g, 80%), m.p. 188–190°C; IR: ν_{max}/cm^{-1} 3450 (OH), and 1800 (lactone C=O). Anal. Calc. for $C_{12}H_9Br_2N_3O_4$: C, 34.36; H, 2.14; N, 10.02. Found: C, 34.62; H, 2.5; N, 10.4%.

2-(2,4-Dibromophenyl)-5-(D-erythro-2',3'-diacetoxy-1'-hydroxypropyl)-1,2,3-triazole-4-carboxylic acid 4,1'-lactone (**6**): Acetylation of **5** as described for the synthesis of **4** provided **6** (0.1 g, 66%); m.p. 136–138°C; IR: ν_{max}/cm^{-1} 1790 (lactone C=O) and 1735 (ester C=O); NMR: δ_H ($CDCl_3$): 2.02 and 2.14 (2 s, 6H, 2OAc), 4.62 (m, 2H, CH_2). 5.60 (q, 1H, H-2), 5.94 (d, 1H, H-1) and 7.32–8.22 (m, 3H, Ar–H). Anal. Calc. for $C_{16}H_{13}Br_2N_3O_6$: C, 38.17; H, 2.56; N, 8.35. Found: C, 38.46; H, 2.84; N, 8.20%.

2-o-Bromophenyl-5-(D-erythro-1',2',3'-trihydroxypropyl)-1,2,3-triazole-4-carboxamide (**7**): A solution of **4** (0.1 g) in methanol (10 ml) was treated with conc. aqueous ammonia (10 ml), left overnight at room temp., and concentrated under reduced pressure. The separated solid (60 mg, 75%) was recrystallised from ethanol as colourless needles, m.p. 189–190°C; IR: ν_{max}/cm^{-1} 3400(OH), 3120 (NH) and 1660 (CO). Anal. Calc. for $C_{12}H_{13}BrN_4O_4$: C, 40.32; H, 3.64; N, 15.68. Found: C, 40.12; H, 3.40; N, 15.56%.

2-(2,4-Dibromophenyl)-5-(D-erythro-1',2',3'-trihydroxypropyl)-1,2,3-triazole-4-carboxamide (**8**): Amide **8** (70 mg, 85%) was obtained from **5** as described in the synthesis of **7**, m.p. 174–175°C;

IR: ν_{max}/cm^{-1} 3380 (OH), 3120 (NH) and 1680 (CO). Anal. Calc. for $C_{12}H_{12}Br_2N_4O_4$: C, 33.03; H, 2.75; N, 12.84. Found: C, 33.40; H, 3.02; N, 13.1%.

2-o-Bromophenyl-5-(1',2',3'-triacetoxypropyl)-1,2,3-triazole-4-carboxamide (**9**): Amide **7** (0.1 g) in dry pyridine (5 ml) was treated with acetic anhydride (5 ml), kept overnight at room temp., and then poured onto crushed ice. The solid was filtered off, washed with water, ethanol and dried. It was recrystallised from ethanol giving colourless needles (60 mg, 48%), m.p. 156–158°C; IR: ν_{max}/cm^{-1} 1740 (ester C=O), 3160 (NH) and 1660 (CO); NMR: δ_H ($CDCl_3$) 2.02, 2.07 and 2.15 (3 s, 9H, 3OAc), 4.23 (m, 2H, CH_2), 5.81 (q, 1H, H-2), 5.85 (s, 2H, NH_2), 6.75 (d, 1H, $J_{1,2}$ = 6 Hz, H-1), 7.37–7.77 (m, 4H, Ar–H); MS: *m/z* 482, 484 (100), 441, 443 (14); 422, 424 (65); 384, 386 (60); 344, 346 (40); 222, 224 (20); 183, 185 (26), 155, 157 (61). Anal. Calc. for $C_{18}H_{19}BrN_4O_7$: C, 44.73; H, 3.93; N, 11.58. Found: C, 44.5; H, 3.72; N, 11.4%.

N-Acetyl-2-o-bromophenyl-5-(1',2',3'-triacetoxypropyl)-1,2,3-triazole-4-carboxamide (**10**): Compound **7** (0. 1 g) was suspended in acetic anhydride (5 ml) and boiled under reflux for 1 h. The mixture was then cooled and poured onto crushed ice, and the product was filtered off, washed with water, ethanol and dried (80 mg, 66%). It was recrystallised from ethanol in colourless needles, m.p. 134–135°C; IR: ν_{max}/cm^{-1} 1740 (ester C=O) and 1660 (amide C=O); NMR: δ_H ($CDCl_3$) 2.02, 2.07 and 2.14 (3 s, 9H, 3 OAc), 2.62 (s, 3H, NAc), 4.35 (m, 2H, CH_2), 5.82 (q, 1H, H-2), 6.74 (1H, $J_{1,2}$ = 6 Hz, H-1) and 7.22–8.0 (m, 4H, Ar–H). Anal. Calc. for $C_{20}H_{21}BrN_4O_8$: C, 45.71; H, 4.01; Br, 15.23; N, 10.66. Found: C, 45.8; H, 4.0; Br, 15.43; N, 10.0%.

2-(2,4-Dibromophenyl)-5-formyl-1,2,3-triazole-4-carboxamide (**11**): A suspension of **8** (0.1 g) in water (10 ml) was stirred for 6 h at room temp. with sodium metaperiodate (0.5 g) in water (10 ml). The resulting solid (50 mg, 58%) was recrystallised from ethanol as colourless prisms, m.p. 256–258°C; IR: ν_{max}/cm^{-1} 1690 (CH=O and amide C=O). Anal. Calc. for $C_{10}H_6Br_2N_4O_2$: C, 32.09; H, 1.60; N, 14.97. Found: C, 32.3; H, 2.0; N, 15.36%.

2-(2,4-Dibromophenyl)-5-hydroxymethyl-1,2,3-triazole-4-carboxamide (**12**): Compound **11** (0.1 g) in methanol (10 ml) was stirred with sodium borohydride (1 g) in water (5 ml), added in small portions. The solution was acidified with AcOH (5 ml) and the separated solid (80 mg, 80%) was recrystallised from ethanol as colourless needles, m.p. 192–194°C; IR: ν_{max}/cm^{-1} 3400 (OH), 3160 (NH) and 1680 (C=O). Anal. Calc. for $C_{10}H_8Br_2N_4O_2$: C, 31.91; H, 2.12; N, 14.89. Found: C, 31.80; H, 2.10; N, 14.63%.

5-Acetoxymethyl-2-(2,4-dibromophenyl)-1,2,3-triazole-4-carboxamide (**13**): Acetylation of **12** as described in the synthesis of **9** gave compound **13** (70 mg, 63%); m.p. 212–214°C; IR: ν_{max}/cm^{-1} 1740 (ester C=O) and 1660 (amide C=O); NMR: δ_H ($CDCl_3$) 2.06 (s, 3H, OAc), 4.82 (s, 2H, CH_2); 7.15 (s, 2H, NH_2), 7.41–7.96 (m, 3H, Ar-H). Anal. Calc. for $C_{12}H_{10}Br_2N_4O_3$: C, 34.44; H, 2.39; N, 13.39. Found: C, 34.24; H, 2.5; N, 13.7%.

5-O-Acetyl-6-bromo-6-deoxy-D-erythro-2,3-hexodiulosono-1,4-lactone 2-o-bromophenylhydrazone 3-oxime (**14**): A suspension of 3 (1 g) in 30% HBr - AcOH (30 ml) was stirred for 24 h at room temp., and then poured onto crushed ice. The solid was filtered off, washed with water and ethanol and dried. It was recrystallised from ethanol as yellow needles (0.9 g, 69%), m.p. 206–207°C; IR: ν_{max}/cm^{-1} 1740 (lactone and ester C=O). Anal. Calc. for $C_{14}H_{13}Br_2N_3O_5$: C, 36.31; H, 2.83; N, 9.07. Found: C, 36.62; H, 2.60; N, 9.35%.

2-o-Bromophenyl-5-(D-erythro-2'-acetoxy-3'-bromo-1'-hydroxypropyl)-1,2,3-triazole-4-carboxylic acid 4,1'-lactone (**15**): Acetylation of **14** as described in the synthesis of **9** gave the acetoxy-lactone **15** (90 mg, 72%), mp 130-132°C; IR: ν_{max}/cm^{-1}1800 (lactone (C=O) and 1740 (ester C=O); NMR: δ_H ($CDCl_3$) 2.0 (s, 3H, OAc), 3.84 (m, 2H, CH_2), 5.96 (q, 1H, H-2), 6.42 (d, 1H, H-1) and 7.24–7.92 (m, 4H, Ar–H). Anal Calc. for $C_{14}H_{11}Br_2N_3O_4$: C, 37.75; H, 2.47; N, 9.44. Found: C, 37.9; H, 2.72; N, 9.74%.

3-(D-erythro-1',2',3'-Trihydroxypropyl)isoxazole-4,5-dione 4-o-bromophenylhydrazone (**16**): A suspension of 3 (0.1 g) in water (10 ml) was treated with 10% aqueous sodium hydroxide (10 ml), and the mixture was heated at 80°C, cooled, made neutral with AcOH, and kept overnight at room temp. The product was filtered off, washed with water and ethanol, and dried. It was recrystallised from ethanol giving yellow needles (60 mg, 60%), m.p. 152–153°C; IR: ν_{max}/cm^{-1} 3450 (OH) and 1720 (lactone C=O). Anal Calc. for $C_{12}H_{12}BrN_3O_5$: C, 40.22; H, 3.35; N, 11.73. Found: C, 40.50; H, 3.52; N, 11.50%.

3-(D-erythro-1',2',3'-Triacetoxypropyl)isoxazole-4,5-dione 4-o-bromophenylhydrazone (**17**): Acetylation of **16** as described in the synthesis of **9** yielded compound **17**, which was recrystallised from ethanol, giving orange needles (60 mg, 50%) mp 121–123°C; IR: ν_{max}/cm^{-1} 3120 (NH), 1740 (ester C=O) and 1720 (lactone C=O). Anal Calc. for $C_{18}H_{18}BrN_3O_8$: C, 44.62; H, 3.72; N, 8.67. Found: C, 44.94; H, 3.46; N, 8.50%.

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