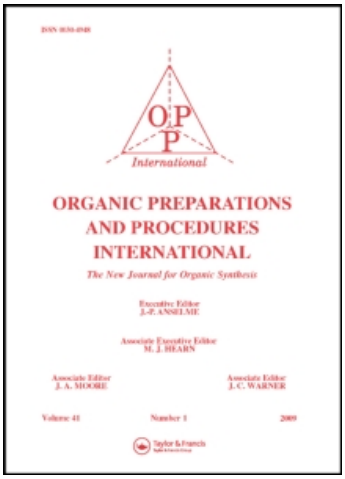

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8,12-SECOPROSTAGLANDINS. 8-AZADINOR ANALOGS

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8,12-SECOPROSTAGLANDINS. 8-AZADINOR ANALOGS

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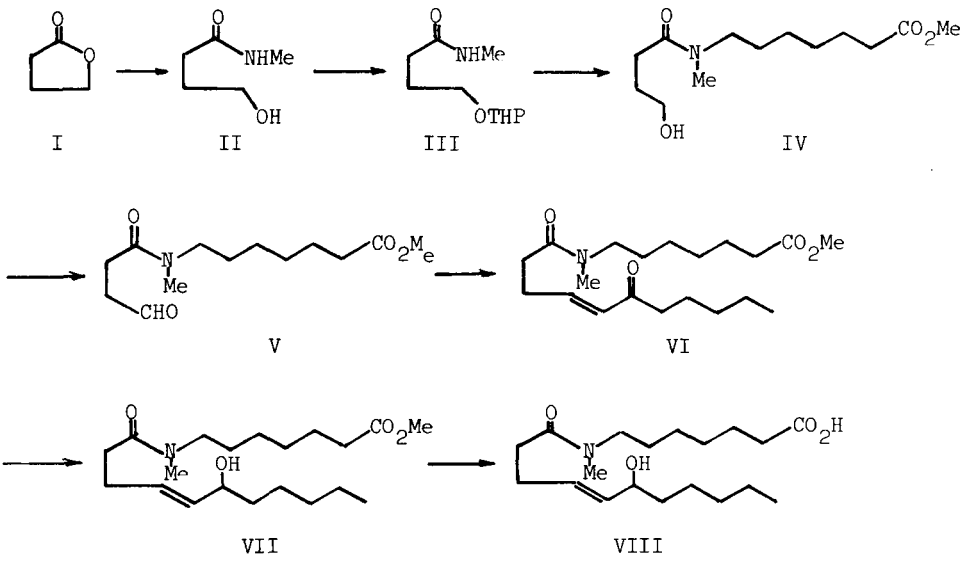
The synthesis of 8,12-secoprostaglandins,[1] 11,12-secoprostaglandins,[2] 9,11-secoprostaglandins[3] and the synthesis of eicosatrienoic acid[4] analogs have recently been reported. The secoprostaglandins have been shown to be physiologically active. In an effort to correlate structure-reactivity relationships in the hetero 8-aza-PGE series, we were interested in synthesizing the 8,12-seco-dinor analogs VIII and XIV to ascertain if such compounds might possess agonistic properties or alternatively act as prostaglandin antagonists.

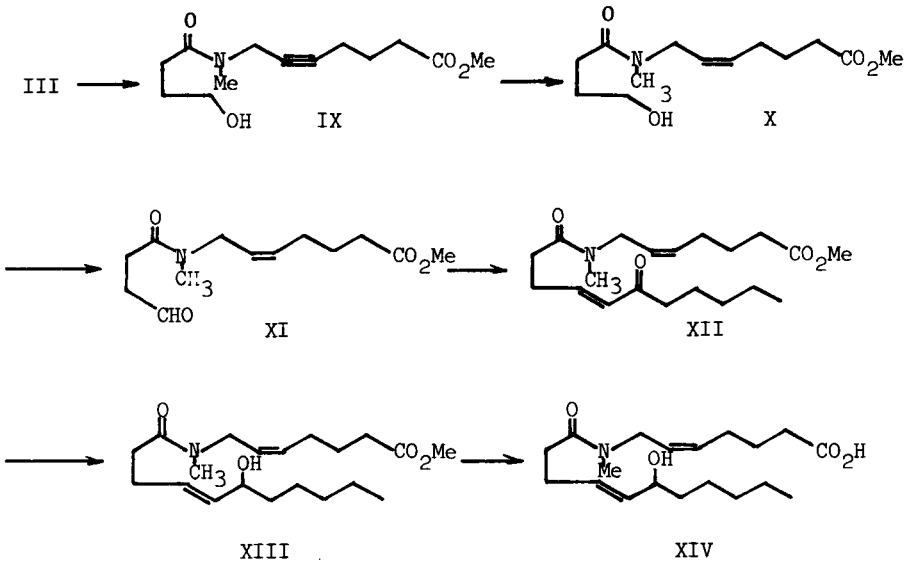
Reaction of γ-butyrolactone I (Scheme 1) with methylamine gas in THF at 0° afforded the lactam alcohol II. Treatment of II with dihydropyran in the presence of a catalytic amount of HCl gave the tetrahydropyranyl amide III. Alkylation of the sodium salt of III with methyl 7-bromoheptanoate and subsequent cleavage of the protecting group with methanol in the presence of a catalytic amount of p-toluenesulfonic acid yielded the hydroxy ester IV. Oxidation of IV with Collins reagent[5] at 0° and subsequent chromatography on silica gel afforded aldehyde V. Reaction of V with the lithium salt of dimethyl (2-oxoheptyl)phosphonate at 0° in THF gave enone VI and subsequent hydride reduction of VI with sodium borohydride at -23° yielded the ester alcohol VII. Hydrolysis of VII with an aqueous methanolic sodium hydroxide solution and subsequent acidification

afforded acid VIII.



Scheme 1

The synthesis of the seco-PGE_2 analog XIV is outlined in Scheme 2. Alkylation of the sodium salt of III with methyl 7-bromo-hept-5-ynoate in refluxing THF followed by removal of the tetrahydropyranyl protecting group with methanol in the presence of p-toluenesulfonic acid gave the alcohol ester IX. Catalytic reduction of IX with 5% $Pd-BaSO_4$ in methanol in the presence of quinoline yielded the cis-olefin X. Oxidation of X with Collins reagent[5] at 0° in CH_2Cl_2 followed by chromatography afforded aldehyde XI. Reaction of XI with the lithium salt of dimethyl (2-oxoheptyl)-phosphonate at 0° in THF gave enone XII. Reduction of XII with $NaBH_4$ in MeOH at -23° afforded the hydroxy ester XIII. Saponification of XIII followed by chromatography on silica gel yielded the hydroxy acid XIV. Compounds VIII and XIV were only weakly effective in inhibiting gastric acid secretion in the rat. The E_2 analog XIV was also shown to weakly relax human bronchial muscle in vitro.



Scheme 2

EXPERIMENTAL

N-Methyl-4-hydroxybutanamide (II).- A solution of γ-butyrolactone I (51 g, 0.593 mol) in 125 ml of dry THF under N_2 was cooled to 0° and gaseous CH_3NH_2, generated from a 40% aqueous CH_3NH_2 solution, was passed slowly into the reaction mixture. The reaction was monitored by tlc analysis and when the lactone was consumed, the solvent was removed in vacuo. The resulting residue was dissolved in chloroform and the organic solution was dried ($MgSO_4$), filtered and concentrated in vacuo. Distillation afforded 61 g (88%) of II; bp. 160-165°/0.6 mm; NMR($CDCl_3$): δ 1.54-2.15 (m, 2H), 2.37 (t, 2H), 2.75 and 2.84 (s, 3H, N-methyls), 3.40-3.90 (m, 2H), 5.16 (t, 1H), and 7.55-8.15 (s, br, 1H); IR (neat): 3360, 1650 and 1555 cm^{-1}.

N-Methyl 4-[(tetrahydro-2H-pyran-2-yl)oxy]-butanamide (III).- To a solution of II (33.1 g, 0.283 mol) and dihydropyran (25.2 g, 0.30 mol) in 275 ml of CH_2Cl_2 was added 28 drops of conc. HCl. The reaction mixture was

stirred at room temperature for 3 hrs. The CH_2Cl_2 solution was extracted with two 300 ml portions of a 10% $NaHCO_3$ solution, two 300 ml portions of brine, dried ($MgSO_4$), concentrated in vacuo, and heated at approximately 75° at 0.05 mm for 2 hrs. giving 46.0 g (81%) of III. Distillation of III, bp. 160-162° (0.1 mm) showed some decomposition to the amide alcohol II via tlc, therefore a small sample of III was chromatographed on silica gel G to afford analytically pure III. NMR(CCl_4): δ 1.20-2.55 (m, 10H), 2.76 and 3.83 (s, 3H, N-methyls), 3.16-4.19 (m, 4H), 4.65 (s, br, 1H, OCHO) and 7.85-8.40 (s, br, 1H); IR (neat): 1650 and 1550 cm^{-1}.

Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96.

Found: C, 59.92; H, 9.81; N, 6.84.

Methyl 7-(N-methyl-4-hydroxybutanamido)heptanoate (IV).- A 50% suspension of sodium hydride in minearl oil (3.6 g, 0.075 mol) was suspended in 125 ml of dry THF under N_2. The tetrahydropyran III (15.1 g, 0.075 mol) in 200 ml of THF was added over a 15 min. period and the addition funnel was rinsed with an additional 15 ml of THF. The reaction mixture was stirred at room temperature for 10 min., heated at 55° for 2 hrs., and then cooled to room temperature. Methyl 7-bromoheptanoate (16.7 g, 0.075 mol) dissolved in 20 ml of THF was added over a 20 min. period. The addition funnel was rinsed with an additional 20 ml of THF and the reaction mixture was refluxed for three days. The reaction mixture was cooled to room temperature, concentrated in vacuo, poured into H_2O (200 ml) and extracted with two 300 ml portions of CH_2Cl_2. The organic solution was washed with 200 ml of water, dried ($MgSO_4$), filtered, and concentrated in vacuo. p-Toluenesulfonic acid (500 mg) was added to the tetrahydropyranyl ester (~ 25 g) in 150 ml of MeOH and the resulting reaction mixture was stirred at room temperature for 2.5 hrs. Solid $NaHCO_3$ (5 g) was added and stirring was continued for an additional 0.5 hr. The solids were filtered and the reaction mixture

was concentrated in vacuo. The residue was dissolved in 200 ml of CH_2Cl_2 and the organic solution was washed with 100 ml of a 10% $NaHCO_3$ solution, 100 ml of brine, dried ($MgSO_4$), filtered and concentrated in vacuo, giving an oil. The oil was chromatographed on silica gel G and elution with ether and methanol-ether solutions afforded 10.6 g (55%) of IV. NMR(CCl_4): δ 1.09-2.05 (m, 10H), 2.12-2.65 (m, 4H), 2.89 and 3.06 (s, 3H, N-methyls), 3.17-3.98 (m) and 3.65 (s)[8H]; IR (neat): 3445, 1750 and 1645 cm^{-1}.

Anal. Calcd for $C_{13}H_{25}NO_4$: C, 60.21; H, 9.72; N, 5.40.

Found: C, 60.57; H, 9.92; N, 5.46.

Methyl 7-(N-methyl-3-formylpropanamide)heptanoate (V).- The ester alcohol (IV) (6.0 g, 0.0232 mol) in 900 ml of CH_2Cl_2 was cooled to 0° under N_2. Collins reagent (42.0 g, 0.163 mol) in 400 ml of CH_2Cl_2 was added all at once and the reaction mixture was stirred at 0° for 1.5 hrs. Powdered sodium sulfate monohydrate (95 g) was added and stirring was continued for an additional 20 min. The reaction was decanted into a saparatory funnel and the reaction vessel was washed with two 400 ml portions of CH_2Cl_2. The organic solutions were combined and consecutively washed with 800 ml of a 10% HCl solution, 1 l. of H_2O, two 1 l. portions of a 10% $NaHCO_3$ solution, and 1 l. of brine. The CH_2Cl_2 solution was dried ($MgSO_4$), filtered, and concentrated in vacuo, giving an oil. The oil was chromatographed on silica gel G and elution with ether-hexane solutions and ether gave 2.6 g (44%) of V. NMR(CCl_4): δ 1.04-1.93 (m, 8H), 2.26 (t, 2H), 2.47-2.76 (m, 4H), 2.86 and 3.04 (s, 3H, N-methyls), 3.32 (t, 2H), 3.63 (s, 3H) and 9.92 (s, 1H); IR (neat): 1745 and 1650 cm^{-1}. The aldehyde was not characterized further but used directly in the Wadsworth-Emmons reaction.

(E)-Methyl 7-(N-methyl-6-oxo-4-undecanamido)heptanoate (VI).- Dimethyl(2-

oxoheptyl)phosphonate (2.04 g, 0.0092 mol) in 20 ml of THF was cooled to 0° under N_2. A hexane solution of 2.4 M n-butyllithium (3.84 ml, 0.0092 mol) was added with a syringe and the reaction mixture was allowed to stir at 0° for 25 min. The aldehyde V (2.5 g, 0.0097 mol) in 15 ml of dry THF was added all at once and the funnel was rinsed with an additional 7.5 ml of THF. The resulting reaction mixture was stirred at 0° for 3.5 hrs, poured into 150 ml of ice-water and extracted with three 250 ml portions of CH_2Cl_2. The organic extracts were combined and washed with 150 ml of brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford an oil. The oil was chromatographed on silica gel G and eluted with ether-hexane solutions to yield 2.0 g (62%) of VI. NMR (CCl_4): δ 0.93 (t) and 1.10-1.96 (m) [17H], 2.04-2.76 (m, 8H), 2.90-3.03 (s, 3H, N-methyls), 3.34 (t, distorted, 2H), 3.66 (t, 3H), 6.08 (d, $J_{13,14}$ = 16.5 Hz) and 6.44-7.16 (m) [2H]; IR (neat): 1740 and 1650 (br) cm^{-1}.

Anal. Calcd for $C_{20}H_{35}NO_4$: C, 67.95; H, 9.98; N, 3.96.

Found: C, 68.07; H, 10.01; N, 4.05.

(E)-Methyl 7-(N-methyl-6-hydroxy-4-undecenamido)-heptanoate (VII).- Sodium borohydride (0.44 g, 0.0116 mol) was cooled to -23° under N_2. Enough absolute MeOH was added to give a clear MeOH-$NaBH_4$ solution. Enone VI (1.37 g, 0.0039 mol) in 15 ml of dry MeOH was added all at once and the reaction mixture was stirred at -23° for 5 hrs. The reaction mixture was poured into 200 ml of brine and extracted with three 200 ml portions of CH_2Cl_2. The combined organic solution was dried ($MgSO_4$), filtered, and concentrated in vacuo, giving an oil. The oil was chromatographed on silica gel G and eluted with ether-hexane solutions and ether yielded 1.1 g (80%) of VII. NMR (CCl_4): δ 0.93 (t, distorted) and 1.12-1.95 (m) [19H], 2.10-2.70 (m, 6H), 3.16-4.25 (m) and 3.71 (s) [10H], 2.93 and 3.05 (s), N-methyls) and 5.30-6.0 (m, 2H); IR (neat): 1745 and 1645 cm^{-1}.

Anal. Calcd for $C_{20}H_{37}NO_4$: C, 67.57; H, 10.49; N, 3.94.

Found: C, 67.28; H, 10.29; N, 3.90.

(E)-7 (N-Methyl-6-hydroxy-4-undecenamido)heptanoic acid (VIII).- A sodium hydroxide solution [NaOH (198 mg, 0.00494 mol) and 6 ml of H_2O] was added to the ester alcohol VII (1.17 g, 0.0033 mol) in 15 ml of MeOH and the resulting reaction mixture was stirred at room temperature for 27 hrs. The reaction mixture was poured into 50 ml of a 2.5% $NaHCO_3$ solution and extracted with two 100 ml portions of ether. The aqueous solution was acidified with concentrated HCl and extracted with two 75 ml portions of CH_2Cl_2. The combined organic solution was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford an oil. The oil was chromatographed on silica gel G and eluted with ether-hexane solutions and ether to afford 850 mg (76%) of VIII. NMR ($CDCl_3$): δ 0.89 (t, 3H); 1.02-2.0 (m, 18H]; 2.10-2.65 (m, 6H), 2.92 and 2.99 (s, N-methyls); 3.10-4.27 (m, 3H); 5.45-5.78 (m, 2H) and 6.33 (s, 2H). On addition of D_2O the peak at δ 6.33 disappeared.

Anal. Calcd for $C_{19}H_{35}NO_4$: C, 66.83; H, 10.33; N, 4.10.

Found: C, 66.75; H, 10.35; N, 4.12.

Methyl 7-(N-methyl-4-hydroxybutanamido)hept-5-ynoate (IX).- The tetrahydropyranyl amide (III) (7.46 g, 0.0371 mol) in 20 ml THF was added dropwise over a 20 min. period under N_2 to a suspension of 50% NaH (1.78 g, 0.0371 mol) in 30 ml THF. The reaction mixture was stirred at room temperature for 20 min. and then heated at 60° for 45 min. The reaction was cooled to room temperature and a solution of methyl 7-bromohept-5-ynoate (8.5 g, 0.0371 mol) in 50 ml of THF was added and the reaction mixture was refluxed for three days. The solvent was removed in vacuo and the residue was poured into 200 ml of H_2O and extracted with three 250 ml portions of CH_2Cl_2. The organic solutions were combined, washed with 250 ml of 10% $NaHCO_3$, 150 ml of brine, dried (Na_2SO_4), filtered and concentrated in vacuo, to give

12.5 g of crude IX. p-Toluenesulfonic acid (300 mg) was added to crude IX (12.0 g) in 150 ml of MeOH and the reaction mixture was stirred at room temperature for 3.0 hrs. Solid $NaHCO_3$ (2.6 g) was added and stirring was continued for 0.5 hr. The reaction mixture was filtered and the solvent was removed in vacuo. The residue was dissolved in 150 ml of CH_2Cl_2 and extracted with a saturated $NaHCO_3$ solution (150 ml) and 100 ml of brine. The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to afford an oil. The oil was chromatographed on silica gel G and eluted with methanol-ether solutions to give 3.6 g (43%) of IX.

Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49.
Found: C, 61.01; H, 8.34; N, 5.29.

(Z)-Methyl 7-(N-methyl-4-hydroxybtanamido)hept-5-enoate (X).- To a solution of the alcohol IX (3.46 g, 0.0136 mol) in 40 ml of MeOH was added 5% Pd-$BaSO_4$ (220 mg) and quinoline (170 mg). The reaction mixture was reduced with H_2 at 1 atm. at room temperature. After one equivalent of H_2 was absorbed, the reaction was filtered through Celite and the residue was washed with 100 ml of MeOH. Removal of the solvent in vacuo afforded a yellow oil. The oil was dissolved in 300 ml of CH_2Cl_2 and the organic solution was washed with two 100 ml portions of 10% HCl, 100 ml of brine, dried ($MgSO_4$), filtered and concentrated in vacuo, giving 3.0 g (86%) of X. A small sample of X was chromatographed on silica gel G and elution with ether and methanol-ether solutions afforded an analytical sample of X. NMR ($CDCl_3$): δ 3.20 (s, OCH_3) and 5.10-5.77 (m, 2H); IR (neat: 3430 (br), 1740 and 1645 cm^{-1}.

Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44.
Found: C, 60.49; H, 8.87; N, 5.32.

(Z)-Methyl 7-(N-Methyl-3-formylpropanamido)hept-5-enoate (XI).- The ester alcohol (X) (2.7 g, 0.01 mol) in 600 ml CH_2Cl_2 was cooled to 0° under N_2.

Collins reagent (18.8 g, 0.07 mol) dissolved in 400 ml CH_2Cl_2 was added all at once and the reaction mixture was stirred at 0° for 1.5 hr. Powdered sodium sulfate monohydrate (46.3 g) was added and the reaction mixture was stirred for an additional 20 min. The reaction solution was decanted and the reaction vessel was washed with two 300 ml portions of CH_2Cl_2. The organic solutions were combined and consecutively washed with 800 ml of a 10% HCl solution, 1 l. of H_2O, two 1 l. portions of a 10% $NaHCO_3$ solution and 1 l. of brine. The CH_2Cl_2 solution was dried ($MgSO_4$), filtered, and concentrated in vacuo, giving an oil. Chromatography on silica gel G and elution with ether-hexane solutions and ether gave 1.4 g (52%) of aldehyde (XI). NMR (CCl_4): δ 3.73 (s, 3H) and 9.95 (s, 1H). The aldehyde was not characterized further, but used directly in the Wadsworth-Emmons reaction.

Methyl 7-(N-methyl-6-oxo-4E-undecenamido)hept-5Z-enoate (XII).- A hexane solution of 2.4 M n-butyllithium (2.27 ml, 0.00521 mol) was added with a syringe to dimethyl (2-oxoheptyl)phosphonate (1.16 g, 0.00521 mol) in 45 ml of THF under N_2 at 0°, and the reaction mixture was stirred at 0° for 10 min. The aldehyde (1.4 g, 0.0055 mol) in 20 ml of THF was added all at once and the reaction mixture was stirred at 0° for 4 hrs. The reaction mixture was poured into ice-cold brine (100 ml) and extracted with three 250 ml portions of CH_2Cl_2. The organic solutions were combined, washed with 100 ml of brine, dried ($MgSO_4$), filtered, and concentrated in vacuo, affording an oil. Chromatography on silica gel G and elution with ether hexane solutions and ether gave 1.2 g (66%) of XII.

Anal. Calcd for $C_{20}H_{33}NO_4$: C, 68.34; H, 9.46; N, 3.99.

Found: C, 68.18; H, 9.27; N, 3.84.

Methyl 7-(N-methyl-6-hydroxy-4E-undecenamido)hept-5Z-enoate (XIII).- Sodium borohydride (200 mg, 0.00526 mol) was cooled to -23° under N_2 and dry MeOH

was added to obtain a clear solution. Enone (XII) (850 mg, 0.00242 mol) in 10 ml of MeOH was added all at once and the reaction mixture was stirred at -23° for 4.5 hrs. The reaction mixture was diluted with 50 ml of brine and extracted with three 250 ml portions of CH_2Cl_2. The organic solutions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo, giving an oil. Chromatography on silica gel G and elution with ether-hexane solutions and ether afforded 780 mg (91%) of XIII. NMR ($CDCl_3$): δ 0.91 (t, distorted), 3.70 (s, OCH_3) and 5.16-5.92 (m, 4H); IR (neat): 3430, 1730 and 1635 cm^{-1}.

Anal. Calcd for $C_{20}H_{35}NO_4$: C, 67.95; H, 9.98; N, 3.96.
Found: C, 67.69; H, 9.84; N, 3.86.

7-(N-Methyl-6-hydroxy-4E-undecenamido)hept-5Z-enoic acid (XIV).- A solution of the ester alcohol (XIII) (550 mg, 0.00156 mol), MeOH (5 ml), H_2O (2 ml) and NaOH (80 mg, 0.002 mol) was stirred at room temperature overnight. The reaction mixture was diluted with H_2O, extracted with ether, acidified at 0° with conc. HCl and extracted with three 150 ml portions of CH_2Cl_2. The organic extracts were combined, dried ($MgSO_4$), filtered and concentration in vacuo, giving an oil. Chromatography on silica gel G and elution with ether-hexane solutions and ether gave 460 mg (87%) of XIV. NMR ($CDCl_3$): δ 0.86 (t, distorted, 3H), 2.91 and 2.94 (s, 3H, N-methyls, 5.10-5.98 (m, 4H) and 6.64 (s, 2H, OH and CO_2H); on addition of D_2O the peak at δ 6.55 disappeared; IR (neat): 3400 (br) 1725 and 1625 cm^{-1}.

Anal. Calcd for $C_{19}H_{33}NO_4$: C, 67.22; H, 9.80; N, 4.13.
Found: C, 67.00; H, 9.65; N, 4.01.

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† Undergraduate Research Participant.

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