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New Pyridinylboronic Acid and New Heterobiaryls via Cross-Coupling Reactions of Pyridinylboronic Acids with Heteroaryl Halides

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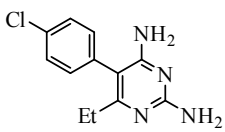
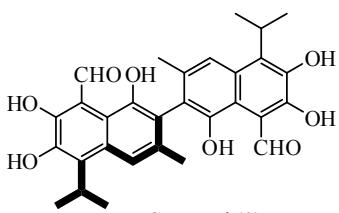
Introduction

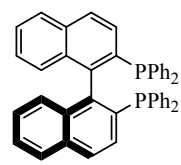
The biaryl framework is found in many medicinal molecules (**1**)[1], natural products (**2**)[2], ligands (**3**)[3] and advanced materials[4]. Kharasch, Negishi, Stille and Suzuki reactions are the four most commonly used catalytic methods[5] in biaryl synthesis. Palladium-catalyzed cross-coupling reaction between boronic acids [$Ar^1B(OH)_2$] and organic halides (Ar^2X) is called Suzuki reaction[6,7] and is a powerful method for the formation of carbon – carbon bonds.



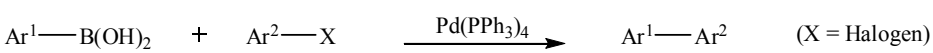
Antimalarial Pyrimethamine (**1**)



Gossypol (**2**)



Binap (**3**)



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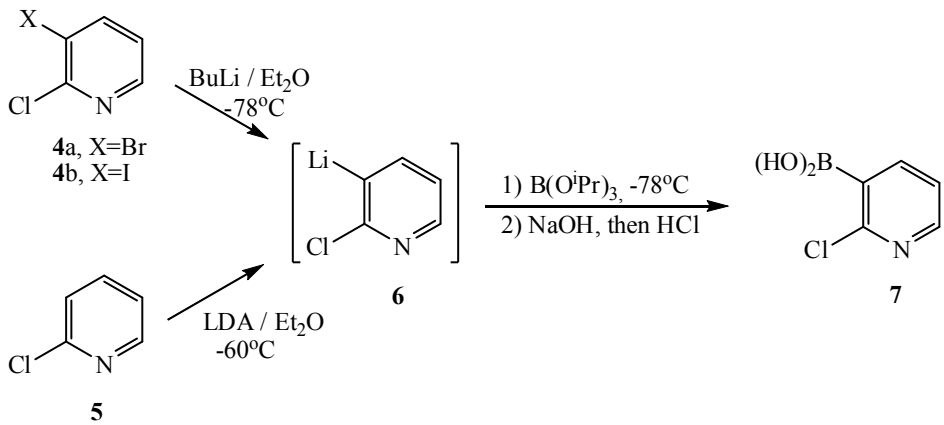
Arylboronic acids are important reagents for the synthesis of biaryls via a cross-coupling reaction with aryl halides especially catalyzed by palladium. In addition, arylboronic acids have significant medical roles[8-10]. Suzuki coupling reactions between heterocyclic halides and heterocyclic boronic acids are remarkably few in the literature. In the synthesis of 3- and 4-pyridinylboronic acids, authors use either directed *ortho*-metallation (DoM)[11-13] or metal-halogen exchange[14-16] processes in order to get desired compounds. For example Bouillon and co-workers[17] followed both of these procedures: Halogen-metal exchange reaction of **4** with n-butyl lithium afforded **6** and also *ortho*-metallation of **5** with LDA occured regioselectively and gave **6** and then quenched at low temperature by the addition of triisopropylborate to afford 2-chloro-3-pyridinylboronic acid (**7**) (Scheme 1). DoM protocol has also wide applications in aromatic and heteroaromatic natural product synthesis.[18]

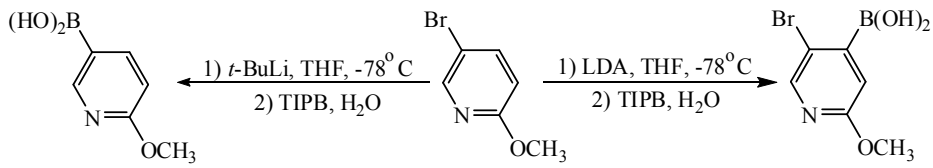


Scheme 1: The synthesis of 2-chloro-3-pyridinylboronic acid (**7**).

In literature pyridinylboronic acids were synthesized at low yields that reflects the difficulty in their isolation because of the amphoteric nature of pyridinylboronic acids at a pH of 7. Polar and hydrophilic character of 3- and 4- pyridinylboronic acids makes their isolation difficult from aqueous media.[15,19] Acknowledgement of these isolation problems has led to improved procedures for their synthesis.

Materials and Methods

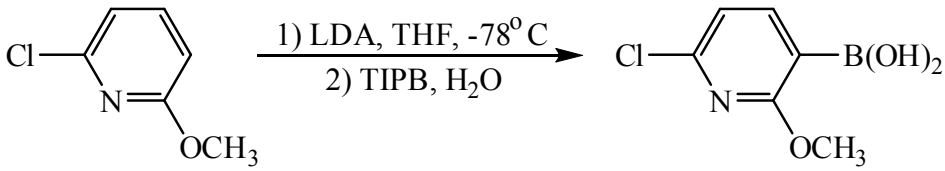
In our previous studies on biaryl systems,[20-22] we used directed ortho-metallation and metal-halogen exchange methods for lithiation reactions. This paper extends these studies in synthesizing a new pyridinylboronic acid and new heterobiaryls. In this context, it investigates lithiation ability of 2-methoxy-5-bromopyridine (**8**) and 2-chloro-6-methoxypyridine (**9**) for the synthesis of new heteroarylboronic acids. In the course of experimental work, 2-methoxy-5-bromopyridine (**8**) was lithiated at C (4) by reaction with LDA in THF at -78°C, and then treated with triisopropylborate (TIPB) to afford 5-bromo-2-methoxypyridin-4-ylboronic acid (**11**) (Scheme 2). Parry reported this synthesis before with



Scheme 2: Lithiation of 2-methoxy-5-bromopyridine (**8**) with LDA and *t*-BuLi, and then subsequent pyridinylboronic acid synthesis.

39% yield[23] but after all the careful handling and modifications done for better yield only 29% pure product was obtained. In this procedure, precipitation is a critical step and should be handled very carefully. Besides, chromatographic separation can not be applied for the purification of boronic acids and precipitation is only method for the isolation of the boronic acid as a pure product. The reaction of 2-methoxy-5-bromopyridine (**8**) with *tert*-butyllithium (t-BuLi) in THF at -78°C gave lithium-halogen exchange reaction and then treatment with triisopropylborate (TIPB) afforded 2-methoxypyridin-5-ylboronic acid (**10**) (Scheme 2). This is also a known boronic acid in literature and it was synthesized by using n-BuLi with 65% yield.[24] The strategy involving directed metallation was applied to 2-chloro-6-methoxypyridine (**9**) and *ortho*-metallation with respect to methoxide group occured and then treatment with triisopropylborate (TIPB) afforded 6-chloro-2-methoxypyridin-3-ylboronic acid (**12**) (Scheme 3). This is a new boronic acid and its cross-coupled products are

candidates as reagents for further coupling reactions since they have a chloro substituent (Entries 1-3 in Table 1). In addition, these heterobiaryls (**13**-**15**) are also valuable intermediates for the synthesis of conjugated oligoarylene systems as advanced materials.[25-27]



9 **12**

Scheme 3: The synthesis of 6-chloro-2-methoxypyridin-3-ylboronic acid (**12**).

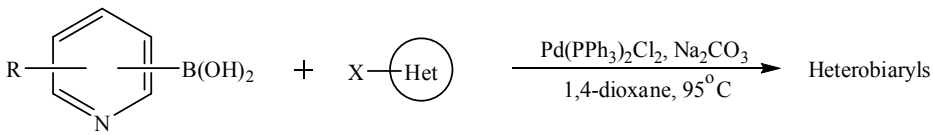
The synthesized heterobiaryl compounds may be a precursor of biologically active another compound or may have following activities. Bipyridines (**15**-**17**) synthesized here are similar compounds to some herbicides known as diquate[28] and paraquate[29]. Paraquat (*N*,*N*′-dimethyl-4,4'-bipyridinium dichloride) is one of the most widely used herbicide in the world and is also toxic to human beings and animals. Moreover, pyridyl pyrimidine (**13**-**14**) structure exists in some drugs. For example, imatinib[30] and nilotinib[31] are Bcr-Abl tyrosine kinase inhibitors used in the treatment of chronic myeloid leukemia. Pyridyl pyrimidine unit forms a part of the backbone of these drugs.

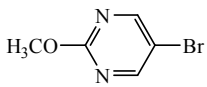
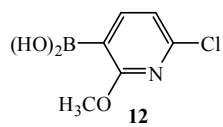
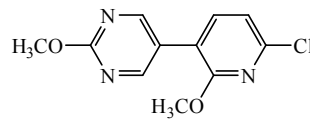
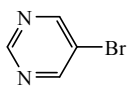
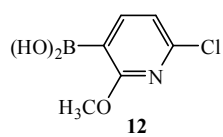
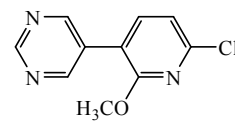
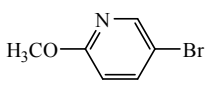
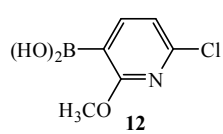
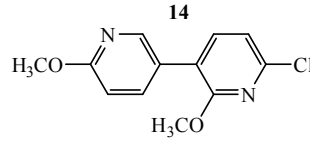
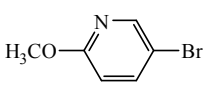
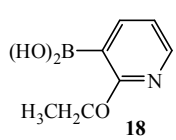
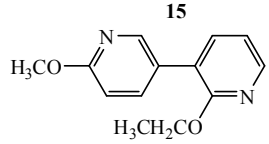
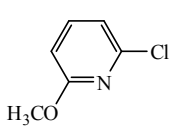
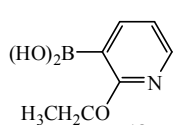
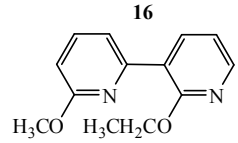
Experimental

All reagents were of commercial quality and reagent quality solvents were used without further purication. ^{1}H and ^{13}C NMR spectra were determined on a Bruker DPX 400 MHz FT spectrometer. Mass spectra were obtained on an Agilent 5973 Network Mass Selective Detector via HPP7-M Direct Insertion Probe. The purity of the compounds was assessed by thin layer chromatography on silica gel 60 F254. Column chromatography was conducted on silica gel 60 (mesh size 0.063-0.200 mm).

TABLE I

Suzuki–Miyaura coupling of haloheterocycles with boronic acids



Entry	Heteroarylhalide	Boronic acid	Product	Yield (%)
1		 **12**	 **13**	58
2		 **12**	 **14**	29
3		 **12**	 **15**	98
4		 **18**	 **16**	72
5		 **18**	 **17**	71

Methods Used for Pyridinylboronic acids:

*6-Chloro-2-methoxypyridin-3-ylboronic acid (**12**)*[21]: To a solution of 2-chloro-6-methoxypyridine (2.0 mL, 16.81 mmol) in anhydrous THF (40 mL) at -78°C was added lithium diisopropylamide (9.0 mL, 18.49 mmol, 2.0 M) dropwise during 0.5 hrs. The reaction was stirred for 2.0 h at -78°C, then triisopropylborate (4.7 mL, 20.17 mmol) was added dropwise

and left stirring overnight. The mixture was quenched with H_2O (40 mL). The organic solvent was evaporated in vacuo and the remaining aqueous layer, pH 9, was filtered. The filtrate was washed with diethyl ether (2×40 mL). The aqueous layer was then acidified to pH 4 (with 48% HBr) to give the product.

*5-Bromo-2-methoxypyridin-4-ylboronic acid (**11**)*[23]: To a solution of 5-bromo-2-methoxypyridine (733 mg, 3.90 mmol) in anhydrous THF (10 mL) at -78°C was added LDA (2.0 M in heptane-THF-ethylbenzene, 6.9 mL, 13.8 mmol) dropwise. The reaction mixture was stirred for 1 h at -78°C, then TIPB (1.5 g, 7.8 mmol) was added dropwise. The mixture was stirred for 1 h at -78°C then quenched with H_2O (10 mL) and allowed to warm to room temperature overnight. The solvent was evaporated in vacuo and the aqueous layer was taken to pH 10 with 5% NaOH and was then washed with Et_2O. The aqueous layer was then acidified to pH 4 with 48% aq HBr to precipitate the product.

*2-Methoxypyridin-5-ylboronic acid (**10**):* To a solution of 5-bromo-2-methoxypyridine (1543 mg, 7.8 mmol) in anhydrous THF (20 mL) at -78°C was added *t*-BuLi (4.82 mL, 8.19 mmol, 1.7 M in pentane) dropwise. The reaction mixture was stirred for 1 h at -80°C then TIPB (3.8 mL, 16.13 mmol) was added dropwise. The mixture was allowed to warm to room temperature with stirring overnight. The solvent was evaporated in vacuo and the aqueous layer was taken to pH 10 with 1M NaOH and was then washed with Et_2O. The aqueous layer was then acidified to pH 4 with 48% HBr to precipitate the product.

General Procedure for the Cross-Coupling Reactions

The boronic acid (1.7 mmol) the arylhalide (1.5 mmol) and $Pd(PPh_3)_2Cl_2$ (5 mol% of boronic acid) were sequentially added to degassed 1,4-dioxane (10 mL) and the mixture was stirred at room temperature for 30 min. Degassed aqueous Na_2CO_3 solution (1M) was added and the reaction mixture was heated under nitrogen at reflux for 24 h. The solvent was removed *in vacuo* then ethyl acetate was added and the organic layer was washed with brine, separated, and dried over $MgSO_4$. The mixture was purified by chromatography on a silica gel column. Other products isolated were small amounts of the unreacted boronic acid and unreacted arylhalide which were usually the first materials to elute.

Results

6-Chloro-2-methoxypyridin-3-ylboronic acid (12): 2-Chloro-6-methoxypyridine (2.0 mL, 16.81 mmol) was used according to method to give product as a white solid (0.4 g, 13%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ_H 7.95 (2H, br s, 2×OH), 7.90 (1H, d, J=7.48 Hz, 4-CH), 7.03 (1H, d, J=7.48 Hz, 5-CH), 3.88 (3H, s, OCH_3). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ_C 166.06 (2-C), 148.58 (6-C), 147.38 (4-CH), 116.28 (5-CH), 115.02 (3-C), 53.78 (OCH_3). IR (KBr) ν_{max} (neat / cm^{-1}) 2995, 1770, 1759, 1375, 1246, 1057. MS (EI) m/z 187 (M^+, 100%), 117 (M^+-Cl-2×OH, 92%), 102, 84, 41.

*5-Bromo-2-methoxypyridin-4-ylboronic acid (**11**):* 5-Bromo-2-methoxypyridine (733 mg, 3.90 mmol) was used according to method to give product as a white solid (260 mg, 29%). ^{1}H-NMR ($(CD_3)_2CO$, 400 MHz) δ_H 8.19 (1H, s, 6-CH), 7.76 (2H, s, 2×OH), 6.86 (1H, s, 3-CH), 3.87 (3H, s, OCH_3). ^{13}C-NMR ($(CD_3)_2CO$, 100 MHz) δ_C 148.14 (6-C), 116.38 (3-C), 115.61 (5-C), 53.79 (OCH_3).

*2-Methoxypyridin-5-ylboronic acid (**10**):* 5-Bromo-2-methoxypyridine (1543 mg, 7.8 mmol) was used according to method to give product as a white solid (673 mg, 37%). ^{1}H-NMR ($(CD_3)_2CO$, 400 MHz) δ_H 8.63 (1H, s, 6-CH), 8.06 (1H, d, J=8.33, 4-CH), 7.19 (2H, s, 2×OH), 6.74 (1H, d, J=8.27, 3-CH), 3.92 (3H, s, OCH_3). ^{13}C-NMR ($(CD_3)_2CO$, 100 MHz) δ_C 166.53 (2-C), 154.41 (6-C), 145.03 (4-C), 110.64 (3-C), 53.38, (OCH_3).

*5-(6′-Chloro-2′-methoxypyridin-3′-yl)-2-methoxypyrimidine (**13**):* 6-Chloro- 2-methoxypyridin-3-ylboronic acid (100 mg, 0.534 mmol) and 5-bromo-2-methoxypyrimidine (89 mg, 0.471 mmol) was used according to the general method to afford the product as white solid (70 mg, 58%) ; R_f 0.33 (1:2 EtOAc-hexane). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ_H 8.62 (2H, s, 4,6-CH), 7.49 (1H, d, J=7.6 Hz, 4′-CH), 6.95 (1H, d, J=8.0 Hz, 5′-CH), 4.00 (3H, s, OCH_3), 3.95 (3H, s, OCH_3). ^{13}C-NMR ($CDCl_3$, CCl_4, 100 MHz) δ_C 164.91 (2-C), 160.23 (2′-C), 158.72 (4,6-CH), 148.34 (6′-C), 139.49 (4′-CH), 122.99 (3′-C), 116.96 (5′-CH), 116.25 (5-C), 54.94 (OCH_3), 54.39 (OCH_3).

*5-(6′-Chloro-2′-methoxypyridin-3′-yl)pyrimidine (**14**):* 6-Chloro-2-methoxypyridin-3-yl boronic acid (100 mg, 0.534 mmol) and

5-bromopyrimidine (75 mg, 0.471 mmol) was used according to the general method to afford the product as white solid (30 mg, 29%) ; R_f 0.16 (1:2 EtOAc-hexane). ^{1}H-NMR ($CDCl_3$, CCl_4, 400 MHz) δ_H 9.16 (1H, s, 2-C), 8.89 (2H, s, 4,6-CH), 7.61 (1H, d, J=7.6 Hz, 4′-CH), 7.06 (1H, d, J=8.0 Hz, 5′-CH), 4.03 (3H, s, OCH_3). ^{13}C-NMR ($CDCl_3$, CCl_4, 100 MHz) δ_C 160.32 (2′-C), 157.60 (2-CH), 156.22 (4,6-CH), 149.29 (6′-C), 140.04 (4′-CH), 129.51 (5-C), 117.11 (5′-CH), 116.03 (3′-C), 54.50 (OCH_3).

*4-(6-Chloro-2-methoxypyridin-3-yl)-6-iodopyrimidine (**15**):* 6-Chloro-2-methoxypyridin-3-ylboronic acid (100 mg, 0.534 mmol) and 4,6-diiodopyrimidine (156 mg, 0.471 mmol) was used according to the general method to afford the product as yellow solid (20 mg, 12%) ; R_f 0.50 (2:1 MeOH-hexane). ^{1}H-NMR (DMSO-d_6, $CDCl_3$, CCl_4, 400 MHz) δ_H 8.44, (1H, d, J=8.0 Hz, 4-CH), 8.25 (1H, s, 2-CH), 7.24 (1H, d, J=8.0 Hz, 5-CH), 6.89 (1H, s, 5-CH), 4.00 (3H, s, OCH_3).

*2-Ethoxy-6'-methoxy-3,3'-bipyridine (**16**):* 2-Ethoxypyridin-3-yl-boronic acid (150 mg, 0.901 mmol) and 5-bromo-2-methoxypyridine (150 mg, 0.795 mmol) was used according to the general method to afford the product as yellow oil (150 mg, 72%) ; R_f 0.23 ($CHCl_3$ only). ^{1}H-NMR ($CDCl_3$, CCl_4, 400 MHz) δ_H 8.30, (1H, s, 2′-CH), 8.08 (1H, d, 4-CH), 7.77 (1H, d, J=8.64 Hz, 4′-CH), 7.52 (1H, d, J=7.32 Hz, 6-CH), 6.88 (1H, dd, J=7.32 & 4.92, 5-CH), 6.74 (1H, d, J=8.60, 5′-CH), 4.41 (2H, q, J=7.04, OCH_2), 3.94 (3H, s, OCH_3), 1.37 (3H, t, J=7.04, CH_3). ^{13}C-NMR ($CDCl_3$, CCl_4, 100 MHz) δ_C 163.25 (6′-C), 160.47 (2-C), 146.67 (6-C), 145.77 (2′-C), 139.11 (4′-C), 137.60 (4-C), 125.64 (3-C), 121.04 (3′-C), 116.74 (5-C), 110.07 (5′-C), 61.65 (OCH_2), 53.21 (OCH_3), 14.58 (CH_3).

*2'-Ethoxy-6-methoxy-2,3'-bipyridine (**17**):* 2-Ethoxypyridin-3-yl-boronic acid (150 mg, 0.901 mmol) and 2-chloro-6-methoxypyridine (114 mg, 0.795 mmol) was used according to the general method to afford the product as yellow oil (130 mg, 71%) ; R_f 0.28 ($CHCl_3$ only). ^{1}H-NMR ($CDCl_3$, CCl_4, 400 MHz) δ_H 8.41 (1H, d, J=7.52, 4′-CH), 8.12 (1H, d, J=4.84, 6′-CH), 7.74 (1H, d, J=7.52, 5-CH), 7.55 (1H, dd, J=7.64 & 8.04, 4-CH), 6.95 (1H, dd, J=4.84 & 7.48, 5′-CH), 6.64 (1H, d, J=8.08, 3-CH), 4.48 (2H, q, J=7.08, OCH_2), 3.97 (3H, s, OCH_3), 1.44 (3H, t, J=7.08, CH_3). ^{13}C-NMR ($CDCl_3$, CCl_4, 100 MHz) δ_C 163.29 (2′-C), 160.86 (6-C), 150.71 (2-C), 146.50 (6′-C), 138.97 (4-C), 138.47 (4′-C), 122.17 (3′-C), 117.23 (5′-C), 116.84 (5-C), 109.42 (3-C), 61.78 (OCH_2), 52.87 (OCH_3), 14.75 (CH_3).

Conclusion

Lithiation ability of two compounds (**8** and **9**) was investigated in this study. Directed *ortho*-metallation reaction of 2-chloro-6-methoxypyridine (**9**) gave new boronic acid **12**. This new pyridinylboronic acid (6-chloro-2-methoxypyridin-3-ylboronic acid, **12**) was used as a coupling partner in Suzuki reaction for the preparation of new heterobiaryls (**13**-**15**). Substituted new bipyridines (**16**-**17**) were also formed via Suzuki coupling reaction by using 2-ethoxypyridin-3-ylboronic acid (**18**) as coupling reagent. The cross-coupled products (**13**-**15**) can be used as reagents for further coupling reactions since they possess a chloro substituent.

Summary

2-Chloro-6-methoxypyridine (**9**) was lithiated via directed *ortho*-metallation (DoM) reaction with LDA and then treatment with triisopropylborate (TIPB) afforded 6-chloro-2-methoxypyridin-3-ylboronic acid (**12**). Suzuki Cross-Coupling reaction of this new pyridinyl boronic acid (**12**) or 2-ethoxypyridin-3-ylboronic acid (**18**) with various heteroaryl halides gave five new heterobiarys (**13**-**17**). All synthesized compounds were characterized mainly by ^{1}H NMR and ^{13}C NMR spectral data.

Key Words: Heterobiaryl, cross-coupling, metallation, synthesis.

Özet

Yeni Piridinilboronik Asit ve Piridinilboronik Asitler ile Heteroaril Halojenürlerin Cross-Coupling Tepkimeleri ile Yeni Heterobiariller

2-Klor-6-metoksipiridin (**9**), LDA ile *orto*-metallasyon yönlendirme (DoM) tepkimesiyle lithiye edildi ve sonra triizopropilborat (TIPB) ile muamele edilerek 6-klor-2-metoksipiridin-3-ilboronik asit (**12**) oluşturuldu. Bu yeni piridinil boronik asit (**12**) veya 2-etoksipiridin-3-ilboronik asitin (**18**) birçok heteroaril halojenürle Suzuki Cross-Coupling tepkimesi sonucunda beş yeni heterobiaril (**13**-**17**) sentezlendi. Tüm sentezlenmiş

bileşiklerin yapıları başlıca ^{1}H NMR ve ^{13}C NMR spektral verilerle karakterize edildi.

Anahtar Kelimeler: Heterobiaril, cross-coupling, metallasyon, sentez.

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