Solid-Phase Synthesis of Substituted 4-Acyl-1,2,3,4-tetrahydroquinoxalin-2-ones

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Introduction

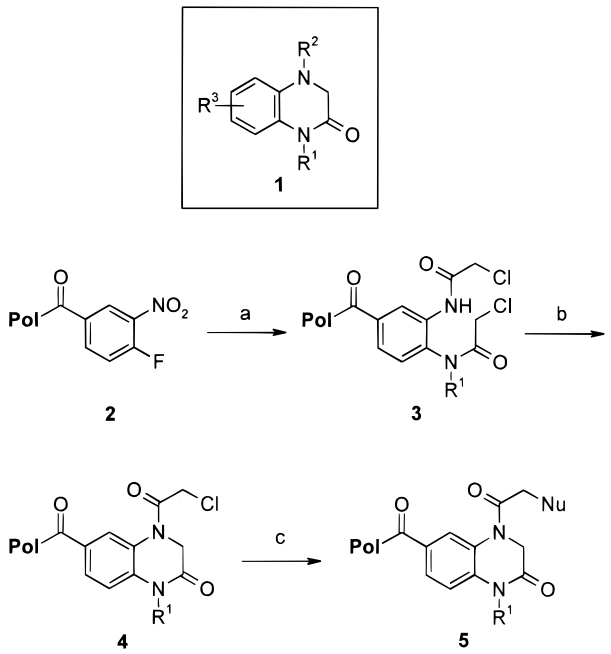
Synthetic sequences that enable the parallel automated synthesis of polysubstituted heterocycles have attracted considerable attention in recent years.[1−4] Robust syntheses of "drug-like" compounds permit the fast preparation of compound libraries suitable for lead discovery and optimization and are therefore of high interest for the pharmaceutical industry. Because compound libraries can generally not be purified before screening, crude products of high purity are a must for valuable new solid-phase protocols.

We report herein a new solid-phase synthesis of 1,2,3,4-tetrahydroquinoxalin-2-ones **1** that fulfills this requirement (Scheme 1). Quinoxalinones similar to **1** have previously been shown to interact with GABA and benzodiazepine receptors[5,6] and to inhibit aldose reductases[7] and might therefore be useful for the discovery of new CNS drugs or enzyme inhibitors. Quinoxalinones **1** have been prepared in solution[5] and on solid support[8,9] from α-amino acid esters and 2-fluoronitrobenzenes. Additional synthetic approaches, suitable for the preparation of quinoxalinones **1** in solution, include the base-induced cyclization of *N*-(chloroacetyl)-1,2-diaminobenzenes[6,10−12] and derivatization of the parent 1,2,3,4-tetrahydroquinoxalin-2-one.[7]

Results and Discussion

As part of a program directed toward the development of synthetic methodology for the automated production of drug-like compounds,[13−15] we attempted to realize on solid phase the tetrahydroquinoxalinone synthesis sketched in Scheme 1. This synthesis is related to a reported solution-phase procedure[11,12] in which *N*,*N*′-bis-(chloroacetyl)-1,2-diaminobenzenes were treated with amines and thereby converted into 4-(aminoacetyl)-1,2,3,4-tetrahydroquinoxalin-2-ones.

Scheme 1[a]



[a] Pol: polymeric support; a: (1) R^1NH_2, (2) $SnCl_2$, (3) chloroacetic anhydride; b: base; c: nucleophile Nu^-.

The starting material for our synthesis was 4-fluoro-3-nitrobenzoic acid esterified with (polystyrene-based) Wang resin[16−18] (**6**, Scheme 2). Aromatic nucleophilic substitution of fluoride in **6** with primary, aliphatic amines proceeded smoothly in DMSO at room temperature.[16,17] Reduction of the nitro group with tin(II) chloride in *N*-methyl-2-pyrrolidinone, followed by double acylation with an excess of chloroacetic anhydride in 1,2-dichloroethane led to the desired intermediates **7a**−**c**.[19]

The reaction of intermediates **7a**−**c** with different nucleophiles led to the expected quinoxalinones **5** only when the reaction conditions were sufficiently basic and weak nucleophiles were used. Thus, treatment of **7a** with piperidine at either room temperature or 80 °C led, after cleavage from the support, to pure quinoxalinone **8** (Scheme 2).

Treatment of chloroacetamide **7a** with the strongly nucleophilic 2-mercaptobenzothiazole in the presence of diisopropylethylamine led *not* to quinoxalinone formation

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(1) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643−5678.
(2) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449−472.
(3) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Chem. Eur. J.* **1997**, *3*, 1917−1920.
(4) Gordon, E. M.; Gallop, M. A.; Patel, D. V. *Acc. Chem. Res.* **1996**, *29*, 144−154.
(5) TenBrink, R. E.; Im, W. B.; Sethy, V. H.; Tang, A. H.; Carter, D. B. *J. Med. Chem.* **1994**, *37*, 758−768.
(6) Mickelson, J. W.; Jacobsen, E. J.; Carter, D. B.; Im, H. K.; Im, W. B.; Schreur, P. J. K. D.; Sethy, V. H.; Tang, A. H.; McGee, J. E.; Petke, J. D. *J. Med. Chem.* **1996**, *39*, 4654−4666.
(7) Sarges, R.; Lyga, J. W. *J. Heterocycl. Chem.* **1988**, *25*, 1475−1479.
(8) Lee, J.; Murray, W. V.; Rivero, R. A. *J. Org. Chem.* **1997**, *62*, 3874−3879.
(9) Morales, G. A.; Corbett, J. W.; Degrado, W. F. *J. Org. Chem.* **1998**, *63*, 1172−1177.
(10) Thomaides, J.; Maslak, P.; Breslow, R. *J. Am. Chem. Soc.* **1988**, *110*, 3970−3979.
(11) Mikiciuk-Olasik, E.; Trzebinski, P.; Nowak, R.; Kotelko, B. *Acta Pol. Pharm.* **1994**, *51*, 231−233.
(12) Mikiciuk-Olasik, E.; Kajkowski, T.; Bartczak, T. J. *Pharmazie* **1993**, *48*, 523−525.
(13) Stephensen, H.; Zaragoza, F. *J. Org. Chem.* **1997**, *62*, 6096−6097.
(14) Zaragoza, F. *Tetrahedron Lett.* **1997**, *38*, 7291−7294.
(15) Zaragoza, F.; Petersen, S. V. *Tetrahedron* **1996**, *52*, 10823−10826.
(16) Lee, J.; Gauthier, D.; Rivero, R. A. *Tetrahedron Lett.* **1998**, *39*, 201−204.
(17) Wei, G. P.; Phillips, G. B. *Tetrahedron Lett.* **1998**, *39*, 179−182.
(18) Wijkmans, J. C. H. M.; Culshaw, A. J.; Baxter, A. D. *Mol. Diversity* **1998**, *3*, 117−120.
(19) The structural proposals for intermediates **7a** and **7b** are inferred from the structure of the final products **8a**, **8b**, **9**, **11**, and **12**.

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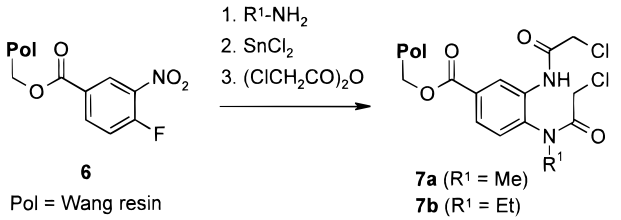
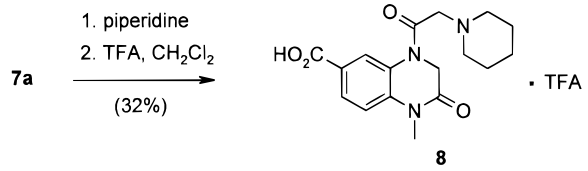
Scheme 2



6

Pol = Wang resin

7a (R^1 = Me)
7b (R^1 = Et)
7c (R^1 = 4-$ClC_6H_4CH_2$)



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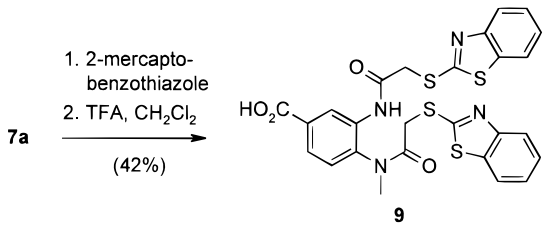
Scheme 3



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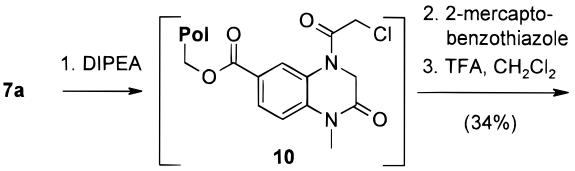

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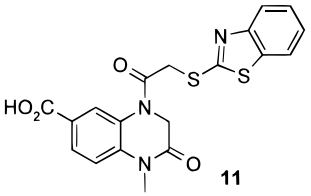


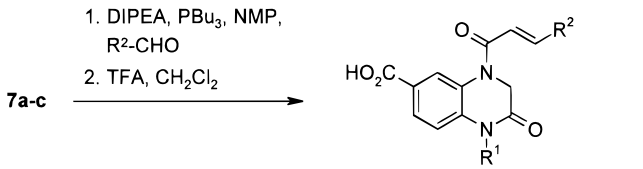
11

but to the product of 2-fold thioetherification **9** (Scheme 3). Occasionally, ring-opened products were also observed as byproducts (<20%) when amines were used as nucleophiles. This side reaction could be avoided by pretreatment of the intermediate bischloroacetamide **7a** with diisopropylethylamine (10% in *N*-methyl-2-pyrrolidinone, 5 h, 20 °C), followed by addition of the nucleophile. These reaction conditions led to the clean formation of thioether **11** (Scheme 3).

To our delight, the intermediate chloroacetamide **10** could also be easily converted to the corresponding phosphonium salt. Treatment of intermediate **10** with tributylphosphine led to clean P-alkylation. The resulting phosphonium salt was sufficiently acidic to enable one-pot ylide generation and Wittig olefination[20] of aromatic aldehydes to yield, after acidolytic cleavage from the support, the quinoxalinones **12**−**15** (Scheme 4).

Purities of crude products **8**, **11**, and **12**−**15**, as determined by evaporative light scattering (ELS), ranged

Scheme 4



12 (R^1 = Me; R^2 = 4-ClC_6H_4; 32%)
13 (R^1 = Et; R^2 = 2-naphthyl; 26%)
14 (R^1 = 4-$ClC_6H_4CH_2$; R^2 = 2-naphthyl; 43%)
15 (R^1 = 4-$ClC_6H_4CH_2$; R^2 = 4-ClC_6H_4; 36%)

from 80% to >90%. Although the weight of crude products (see Experimental Section) generally exceeded by far the theoretical yield (probably due to residual water and salts; compare, e.g., ref 21), the yields of recrystallized, analytically pure products were 30−40%, which we consider acceptable when considering the total number of synthetic steps.

In conclusion, we have found that resin-bound bischloroacetamides **7a**−**c** are easily accessible and suitable intermediates for the solid-phase preparation of differently substituted 1,2,3,4-tetrahydroquinoxalin-2-ones. Crude products of high purity are generally obtained, enabling their direct use in biological assays without any further purification. The synthesis reported herein can be realized at room temperature with standard equipment for solid-phase synthesis.

Experimental Section

Polystyrene (1% cross-linked) with Wang linker was purchased from Bachem and had a loading of 0.96 mmol g^{-1}. Yields of analytically pure products were calculated on the basis of this loading. All syntheses were conducted in fritted polypropylene reactors.

Preparation of Intermediates 7a−c. Methylamine (for the preparation of **7a**, 0.3 mL of an 8 mol L^{-1} solution in ethanol), ethylamine (for the preparation of **7b**, 0.9 mL of a 12 mol L^{-1} solution in water), or 4-chlorobenzylamine (for the preparation of **7c**, 0.50 mL, 4.09 mmol) was added to a suspension of resin-bound 4-fluoro-3-nitrobenzoic acid **6** (0.30 g, 0.29 mmol) in DMSO (3.0 mL). The resulting mixture was shaken at room temperature for 16 h and filtered, and the resin was washed with *N*-methyl-2-pyrrolidinone. A solution of tin(II) chloride dihydrate (1.48 g, 6.56 mmol) in *N*-methyl-2-pyrrolidinone (4.0 mL) was added, and shaking was continued for 16 h. After filtration and washing with *N*-methyl-2-pyrrolidinone, a solution of chloroacetic anhydride (0.51 g, 2.98 mmol) in 1,2-dichloroethane (3.5 mL) and 4-(dimethylamino)pyridine (0.1 mL of a 1 mol L^{-1} solution in dimethylformamide) were added, and the resulting mixture was shaken for 24 h. Filtration and washing with dichloromethane yielded intermediates **7a**−**c**, which were used immediately after their preparation.

1-Methyl-2-oxo-4-(2-piperidinoacetyl)-1,2,3,4-tetrahydro-6-quinoxalinecarboxylic Acid Trifluoroacetate (8). Piperidine (0.30 mL, 3.03 mmol) was added to a suspension of resin **7a** (prepared from 0.10 g of **6**) in DMSO (3.0 mL). The resulting mixture was shaken at 80 °C for 14 h and filtered, and the resin was extensively washed with *N*-methyl-2-pyrrolidinone, dichloromethane, and methanol. Dichloromethane (1.5 mL) and trifluoroacetic acid (TFA, 1.5 mL) were added, and the mixture was shaken at room temperature for 0.5 h. Filtration and concentration of the filtrate yielded 64 mg of crude **8** as an oil, 87% pure by ELS. Addition of ethyl acetate (2.0 mL) to this oil led to crystallization. Filtration and drying under reduced pressure gave 14 mg (32%) of trifluoroacetate **8** as a colorless, microcrystalline hemihydrate: mp 232−234 °C; LCMS *m*/*z* 332 (MH^+);

(20) Blaskovich, M. A.; Kahn, M. *J. Org. Chem.* **1998**, *63*, 1119−1125.

(21) Stadlwieser, J.; Ellmerer-Müller, E. P.; Tako, A.; Maslouh, N.; Bannwarth, W. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1402−1404.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.20−1.90 (m, 6H), 2.85−3.10 (m, 2H), 3.25−3.70 (m, 5H), 4.32−4.64 (m, 4H), 7.35−7.49 (m, 1H), 7.80−8.42 (m, 2H), 9.55 (s, br, 1H), 13.08 (s, br, 1H). Anal. Calcd for $C_{17}H_{21}N_3O_4$ $C_2HF_3O_2$·0.5 H_2O (454.41): C, 50.22; H, 5.10; N, 9.25. Found: C, 50.44; H, 4.91; N, 9.10.

3-{[(1,3-Benzothiazol-2-ylsulfanyl)methyl]carboxamido}-4-[[(1,3-benzothiazol-2-ylsulfanyl)methyl](methyl)carboxamido]benzoic Acid (9). A solution of 2-mercaptobenzothiazole (0.64 g, 3.83 mmol) in dimethylformamide (4.0 mL) was added to resin **7a** (prepared from 0.20 g of **6**), followed by the addition of diisopropylethylamine (0.40 mL). The resulting mixture was shaken at room temperature for 21 h and filtered, and the resin was extensively washed with *N*-methyl-2-pyrrolidinone, dichloromethane, and methanol. Dichloromethane (2.0 mL) and TFA (2.0 mL) were added, and the mixture was shaken at room temperature for 0.5 h. Filtration and concentration of the filtrate yielded 174 mg of crude **9** as an oil, 99% pure by ELS. Recrystallization from aqueous ethanol yielded 50 mg (42%) of **9** as a colorless, microcrystalline hemihydrate: mp 165−168 °C; LCMS *m*/*z* 581 (MH^+); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.16 (s, 3H), 3.98 (d, J = 15 Hz, 1H), 4.24 (d, J = 15 Hz, 1H), 4.48 (d, J = 15 Hz, 1H), 4.54 (d, J = 15 Hz, 1H), 7.29−7.49 (m, 4H), 7.67−7.85 (m, 4H), 7.93−8.05 (m, 2H), 8.57 (s, br, 1H), 10.18 (s, 1H), 13.19 (s, br, 1H). Anal. Calcd for $C_{26}H_{20}N_4O_4S_4$·0.5 H_2O (589.74): C, 52.95; H, 3.59; N, 9.50. Found: C, 53.08; H, 3.61; N, 9.22.

4-[2-(1,3-Benzothiazol-2-ylsulfanyl)acetyl]-1-methyl-2-oxo-1,2,3,4-tetrahydro-6-quinoxalinecarboxylic Acid (11). Diisopropylethylamine (0.40 mL) was added to a suspension of **7a** (prepared from 0.20 g of **6**) in *N*-methyl-2-pyrrolidinone (4.0 mL), and the mixture was shaken at room temperature for 5 h. The mixture was filtered, and a solution of 2-mercaptobenzothiazole (0.93 g, 5.56 mmol) in *N*-methyl-2-pyrrolidinone (4.0 mL) and then diisopropylethylamine (0.40 mL) were added to the resin. The resulting mixture was shaken at room temperature for 16 h and filtered, and the resin was extensively washed with *N*-methyl-2-pyrrolidinone, dichloromethane, and methanol. Dichloromethane (2.0 mL) and TFA (2.0 mL) were added, and the mixture was shaken at room temperature for 0.5 h. Filtration and concentration of the filtrate yielded 199 mg of crude **11** as an oil. Recrystallization from aqueous methanol yielded 29 mg (34%) of **11** as a light-brown, microcrystalline hemihydrate: mp 229−231 °C; LCMS *m*/*z* 414 (MH^+); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.37 (s, 3H), 4.54−4.68 (m, 4H), 7.31−7.49 (m, 3H), 7.68 (m, 1H), 7.90 (d, br, J = 8 Hz, 1H), 7.99 (d, J = 8 Hz, 1H), 8.27 (s, br, 1H). Anal. Calcd for $C_{19}H_{15}N_3O_4S_2$·0.5 H_2O (422.49): C, 54.02; H, 3.82; N, 9.95. Found: C, 53.82; H, 3.63; N, 9.76.

4-[3-(4-Chlorophenyl)-2-propenoyl]-1-methyl-2-oxo-1,2,3,4-tetrahydro-6-quinoxalinecarboxylic Acid (12). A solution of 4-chlorobenzaldehyde (0.59 g, 4.20 mmol) in *N*-methyl-2-pyrrolidinone (3.0 mL) was added to resin **7a** (prepared from 0.30 g of **6**), followed by the addition of diisopropylethylamine (0.50 mL) and tributylphosphine (0.75 mL, 3.05 mmol). The resulting mixture was shaken at room temperature for 24 h and filtered, and the resin was extensively washed with *N*-methyl-2-pyrrolidinone, dichloromethane, and methanol. Dichloromethane (2.5 mL) and TFA (2.5 mL) were added, and the mixture was shaken at room temperature for 0.5 h. Filtration and concentration of the filtrate yielded 198 mg of crude **12** as an oil, 100% pure by ELS, which crystallized upon addition of methanol (2 mL) and water (0.2 mL). Filtration and recrystallization from ethyl acetate/methanol yielded 37 mg (32%) of **12** as a colorless, crystalline monohydrate: mp 246−247 °C; LCMS *m*/*z* 371 (MH^+); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.33 (s), 4.61 (s, br, 2H), 7.05 (d, br, J = 15 Hz, 1H), 7.41 (d, J = 8 Hz, 1H), 7.48 (d, J = 8 Hz, 2H), 7.62−7.71 (m, 3H), 7.87−7.92 (m, 2H), 12.98 (s, br, 1H). Anal. Calcd for $C_{19}H_{15}ClN_2O_4$·H_2O (388.81): C, 58.69; H, 4.41; N, 7.20. Found: C, 58.66; H, 4.42; N, 7.10.

1-Ethyl-4-[3-(2-naphthyl)-2-propenoyl]-2-oxo-1,2,3,4-tetrahydro-6-quinoxalinecarboxylic Acid (13). The preparation of compound **13** was analogous to the preparation of **12**. From 0.50 g of **6**, 261 mg of crude **13** was obtained, 100% pure by ELS. Precipitation from aqueous methanol yielded 53 mg (26%) of **13** as a yellow, microcrystalline hemihydrate: mp 233−235 °C (sublimes); LCMS *m*/*z* 401 (MH^+); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.21 (t, J = 7 Hz, 3H), 4.00 (q, J = 7 Hz, 2H), 4.63 (s, br, 2H), 7.17 (s, br, 1H), 7.48 (d, J = 8 Hz, 1H), 7.58 (m, 2H), 7.79 (s, br, 1H), 7.84 (d, J = 17 Hz, 1H), 7.90−8.01 (m, 5H), 8.19 (s, br, 1H), 13.00 (s, br, 1H). Anal. Calcd for $C_{24}H_{20}N_2O_4$·0.5 H_2O (409.45): C, 70.40; H, 5.17; N, 6.84. Found: C, 70.52; H, 5.16; N, 6.79.

1-(4-Chlorobenzyl)-4-[3-(2-naphthyl)-2-propenoyl]-2-oxo-1,2,3,4-tetrahydro-6-quinoxalinecarboxylic Acid (14). The preparation of compound **14** was analogous to the preparation of **12**. From 0.50 g of **6**, 328 mg of crude **14** was obtained, 95% pure by ELS. Precipitation from aqueous methanol yielded 108 mg (43%) of **14** as a tan, microcrystalline hemihydrate: mp > 250 °C; LCMS *m*/*z* 497 (MH^+); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.81 (s, br, 2H), 5.22 (s, 2H), 7.10−7.25 (m, 2H), 7.32 (d, J = 8 Hz, 2H), 7.41 (d, J = 8 Hz, 2H), 7.56 (m, 2H), 7.79 (d, br, J = 9 Hz, 1H), 7.88 (d, J = 17 Hz, 1H), 7.92 (m, 5H), 8.19 (s, br, 1H), 12.95 (s, br, 1H). Anal. Calcd for $C_{29}H_{21}ClN_2O_4$·0.5H_2O (505.96): C, 68.84; H, 4.38; N, 5.54. Found: C, 68.76; H, 4.33; N, 5.43.

1-(4-Chlorobenzyl)-4-[3-(4-chlorophenyl)-2-propenoyl]-2-oxo-1,2,3,4-tetrahydro-6-quinoxalinecarboxylic Acid (15). The preparation of compound **15** was analogous to the preparation of **12**. From 0.50 g of **6**, 410 mg of crude **15** was obtained, 91% pure by ELS. Recrystallization from aqueous methanol yielded 87 mg (36%) of **15** as a tan, microcrystalline hemihydrate: mp > 250 °C; LCMS *m*/*z* 481 (MH^+); ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.79 (s, br, 2H), 5.21 (s, 2H), 7.09 (s, br, 1H), 7.21 (d, J = 8 Hz, 1H), 7.31 (d, J = 8 Hz, 2H), 7.40 (d, J = 8 Hz, 2H), 7.48 (d, J = 8 Hz, 2H), 7.70 (m, 3H), 7.78 (d, J = 8 Hz, 1H), 7.90 (s, br, 1H), 13.00 (s, br, 1H). Anal. Calcd for $C_{25}H_{18}Cl_2N_2O_4$·0.5H_2O (490.35): C, 61.24; H, 3.91; N, 5.71. Found: C, 60.87; H, 3.75; N, 5.63.

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