Synthesis and Herbicidal Activity of 2-Alkyl(aryl)-4-amino-3-[alkyl(alkoxy) carbonyl]-5-cyano-6-[(3-trifluoromethyl)phenoxy]-pyridines

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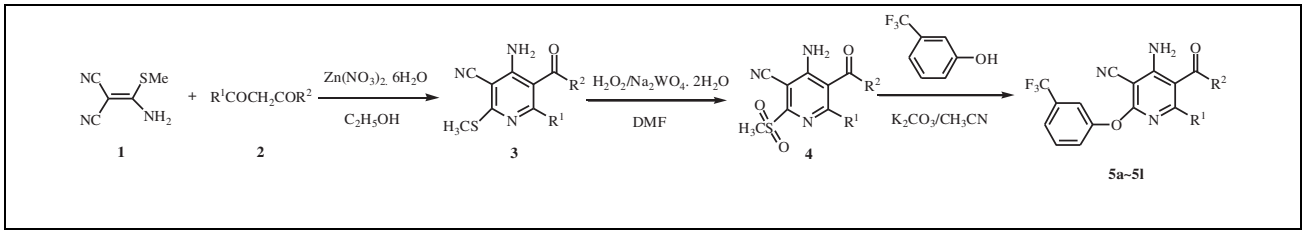

To find novel bleaching herbicide lead compounds, a series of novel 2-alkyl(aryl)-4-amino-3-[alkyl(alkoxy) carbonyl]-5-cyano-6-[(3-trifluoromethyl)phenoxy]-pyridines was designed and synthesized by the multistep reactions. *N*,*S*-acetal **1** reacted with **2** to obtain multisubstituted pyridines **3** in the presence of zinc nitrate as the catalyst. The target compounds **5a~5l** were formed by the oxidation of **3**, followed by the substitution with 3-(trifluoromethyl) phenol in the presence of potassium carbonate. Their structures were confirmed by IR, ^{1}H NMR, EI-MS, and elemental analyses. The preliminary bioassays indicated that some of them displayed moderate herbicidal activity against dicotyledonous weed *Brassica campestris L* at the concentration of 100 mg/L.

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INTRODUCTION

Compounds containing pyridine moiety exhibited a variety of biological activities and are widely used as insecticides, fungicides, and herbicides in modern plant protection [1–3]. Phytoene desaturase (PDS) is a key enzyme for photosynthetic apparatus of green plants. If PDS is inhibited by its inhibitors, a lack of carotenoid synthesis may lead to typical bleaching symptoms in plants, so the PDS inhibitors are developed as a kind of important bleaching herbicides in modern agriculture (Fig. 1). As for their structure–activity relationships, PDS inhibitors usually possess a central five-membered or six-membered heterocycle containing one or two substituted phenyl rings, in which a 3-(trifluoromethyl)phenyl group is a common structure in all inhibitors [4–6]. To find novel bleaching herbicide lead compounds, we designed and synthesized a series of novel multisubstituted pyridine derivatives containing of a 3-(trifluoromethyl)phenoxy group **5** by using commercially herbicides diflufenican and picolinafen as lead compounds. Herein, we would like to report the synthesis and herbicidal activities of the title compounds **5** in this paper (Scheme 1).

RESULTS AND DISCUSSION

N,*S*-acetal **1** reacted with β-diketone or β-keto ester **2** in the presence of zinc nitrate to obtain multisubstituted pyridine **3** in good to excellent yields, the oxidation of **3** with H_2O_2 in the presence of a catalytic amount of sodium tungstate to give pyridyl methylsulfone **4**, which reacted with 3-(trifluoromethyl)phenol in the presence of anhydrous potassium carbonate to give the target compounds **5** in 71–93% yields. Their structures were deduced from their spectral data (IR, ^{1}H NMR, and EI-MS) and elemental analyses, which were listed in the experimental part. For example, the IR spectra of **5b** revealed NH_2 at 3405 and 3332 cm^{-1}, the signal 2228 cm^{-1} is attributed to CN absorption, and 1660 and 1258 cm^{-1} are attributed to C═O and C-O-C absorption bands, respectively. In the ^{1}H NMR spectra of **5b**, the two methyl protons showed as two singlets at δ 2.50 and 2.58, respectively, whereas the amino protons displayed as a broad singlet at δ 6.78. However, in some cases, the amino protons could not be found in their ^{1}H NMR spectra; the aromatic protons of the target compounds **5** appeared in the chemical shift δ 7.1~8.2. The EI mass spectrum of **5b** shows strong molecular ion peak at *m*/*z* 335 with 100% abundance and anticipated fragmentation ion peaks.

Herbicidal activity. The preliminary herbicidal activities of compounds **5** were evaluated, against two representative targets, oil rape and barnyard grass, at concentrations of 100 and 10 mg/L, according to a literature method [7]. The results are listed in Table 1 and show that these compounds have moderate herbicidal activity against oil rape at the concentration of 100 mg/L. For example, compounds **5c** and **5j** possessed 80.9 and 81.7% inhibition against *Brassica campestris L* at the concentration of 100 mg/L. As for the preliminary structure–activity relationships, firstly, those compounds when R^2 is methoxy and R^1 is methyl or electron-donating substituents in aromatic ring (e.g., **5c** and **5j**) exhibited better activity than those when R^1 is electron-withdrawing ones in aromatic ring (e.g., **5g**, **5i**, **5k**,

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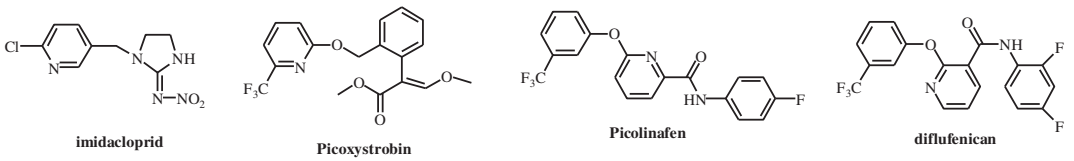
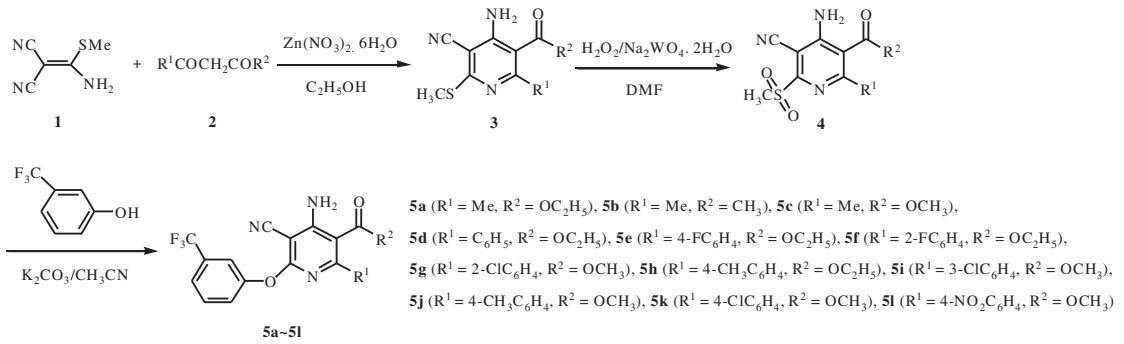


Figure 1. Some commercial pyridine pesticides and phytoene desaturase inhibitors.

Scheme 1. Synthetic route to compounds **5a~5l**.



and **5l**) did; secondly, those compounds when R^2 is methoxy displayed better activity than those when R^1 is ethoxy did. Further exploring of structure–activity relationships needs more experimental results to support. Further biological activity (*in vivo*) investigations are on the way.

In conclusion, a series of novel 2-alkyl (aryl)-4-amino-3-[alkyl(alkoxyl)carbonyl)]-5-cyano-6-[(3-trifluoromethyl) phenoxy]-pyridines was designed and synthesized by the multistep reactions. Their structures were confirmed by IR, ^{1}H NMR, EI-MS, and elemental analyses. The preliminary bioassays indicated that some of them displayed moderate herbicidal activity against dicotyledonous weed *B. campestris L* at the concentration of 100 mg/L.

Table 1

Herbicide activity of compounds **5a~5l** (growth inhibition rate %).

	B. campestris root test		*E. crus-galli* cup test	
Compound	10 μg/mL	100 μg/mL	10 μg/mL	100 μg/mL
5a	18.2	50.2	0	25.0
5b	18.2	50.2	0	30.0
5c	50.2	80.9	0	25.0
5d	25.5	63.9	0	0
5e	0	31.1	0	0
5f	18.6	52.5	0	0
5g	23.9	52.5	5.0	0
5h	0	10.2	0	0
5i	0	10.5	15.0	25
5j	45.5	81.7	10.0	0
5k	0	41.8	5.0	0
5l	0	41.8	5.0	25.0

EXPERIMENTAL

Melting points were determined with a WRS-1B digital melting point apparatus and are uncorrected. ^{1}H NMR spectra (Wuhan, China) were recorded with a Varian Mercury PLUS 600 (600 MHz) spectrometer (CA, USA) with TMS as the internal reference and $CDCl_3$ as the solvent, whereas mass spectra were measured on a Finnigan TraceMS 2000 spectrometer (CA, USA) at 70 eV by using EI method. IR spectra were measured by a Nicolet NEXUS470 spectrometer (ThermoNicoletCorporation, USA). Elemental analyses were performed with an Elementar Vario ELIII CHNSO elemental analyzer (Elementar cooperation, Germany). Compounds **1** and **2** can be prepared according to the reported methods [8,9], respectively. All of the solvents and materials were reagent grade and purified as required (Beijing, China).

Synthesis of 4-amino-3-(ethoxy carbonyl)-5-cyano-6-methylthio-2-phenyl-pyridine 3a [10]. **1** (3.47 g, 25 mmol), ethyl benzoyl acetate (4.8 g, 25 mmol), zinc nitrate hydrate (14.9 g, 50 mmol), and anhydrous ethanol (50 mL) were added to a 100-mL three-necked flask; the mixture was stirred under reflux for 12 h till the reaction was complete (monitored by TLC). The resulting mixture was cooled to room temperature and filtered by suction, and the crude product was recrystallized in ethanol to give **3a** as white solid in 87% yield, mp 135.8–137.2°C; other compounds **3** can be synthesized in the similar procedure, which can be used in the next reaction directly without further structure characterization.

Synthesis of 2-alkyl (aryl)-4-amino-3-(alkyl or alkoxycarbonyl)-5-cyano-6-methylsulfonyl-pyridines 4 [10]. **3** (10 mmol), sodium tungstate (2 mmol, 0.66 g), and DMF (20 mL) were added to a 100-mL three-necked flask; the mixture was stirred at 40–50°C, whereas the solution of 30% H_2O_2 (4.5 g, 40 mmol) in ethanol (5 mL) was added dropwise slowly; after the addition was complete, the mixture was stirred at 60°C for 3 h (monitored by TLC). After most of solvents were removed in vacuum, the residue was poured into water (100 mL), the solid formed was filtered by suction, and the

crude product was recrystallized using the mixture of DMF and H_2O (1:1) to give **4** as light yellow solids in 68–89% yields, which can be used in the next reaction directly without further structure characterization.

General procedure for the synthesis of 2-alkyl(aryl)-4-amino-3-[alkyl(alkoxy)carbonyl]-5-cyano-6-[(3-trifluoromethyl)phenoxy]-pyridines 5. **4** (3.0 mmol), 3-(trifluoromethyl)phenol (6.0 mmol, 0.97 g), anhydrous potassium carbonate (3 mmol, 0.41 g), and CH_3CN (20 mL) were added to a 50-mL three-necked flask, and the mixture was allowed to be stirred under reflux for 1–2 h (monitored by TLC). The workup involved stripping of the solvent followed by addition of water (30 mL) and extraction of the product mixture into chloroform (15 ml*3). After phase separation, washing with 5% aqueous NaOH and drying over anhydrous magnesium sulfate, filtration, and evaporation, the crude product was recrystallized using the mixture of CH_2Cl_2 and petroleum ether (1:1) or purified by flash column chromatography on silica gel (eluent: petroleum ether/acetone 6:1) to give **5** in 71–93% yields.

5a: colorless crystals, yield 76%, mp 135.4~136.3°C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 1.24 (t, J = 7.3 Hz, 3H, $CH_2\underline{CH_3}$), 2.52 (s, 3H, CH_3), 4.39 (q, J = 7.2 Hz, 2H, OCH_2), 7.37 (d, J = 6.6 Hz, 1H, ArH), 7.47 (s, 1H, ArH), 7.50–7.53 (m, 2H, ArH); IR (KBr) υ: 3411, 3365 (NH), 2984 (ArH), 2222 (CN), 1695 (C═O), 1620, 1568, 1536 (Ar), 1325 (C-F), 1274 (C-O-C) cm^{-1}; EI-MS (70 eV) *m/z* (%): 365 (M^+, 100), 319 (61), 293 (87.8), 186 (77.4), 145 (45.5), 95 (9.7). *Anal*. Calcd for $C_{17}H_{14}F_3N_3O_3$: C 55.89, H 3.86, N 11.50; found C 55.94, H 3.93, N 11.37.

5b: colorless solid, yield 85%, mp 135.8~137.6°C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 2.50 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 6.78 (s, 2H, NH_2), 7.37 (d, J = 7.2 Hz, 1H, ArH), 7.47 (s, 1H, ArH), 7.51–7.53 (m, 2H, ArH); IR (KBr) υ: 3405, 3332 (NH), 2990 (ArH), 2228 (CN), 1660 (C═O), 1569, 1453, 1427 (Ar), 1325 (C-F), 1258 (C-O-C) cm^{-1}; EI-MS (70 eV) *m/z* (%): 335 (M^+, 100), 320 (53.2), 292 (17.8), 186 (80.7), 145 (41.8), 95 (9.9). *Anal*. Calcd for $C_{16}H_{12}F_3N_3O_2$: C 57.32, H 3.61, N 12.53; found C 57.47, H 3.50, N 12.77.

5c: colorless crytals, yield 79%, mp 153.2~154.0°C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 2.51 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 7.37 (d, J = 7.2 Hz, 1H, ArH), 7.47 (s, 1H, ArH), 7.49–7.53 (m, 2H, ArH); IR (KBr) υ: 3408, 3343 (NH), 2995 (ArH), 2223 (CN), 1686 (C═O), 1575, 1451, 1442 (Ar), 1327 (C-F), 1271 (C-O-C) cm^{-1}. *Anal*. Calcd for $C_{16}H_{12}F_3N_3O_3$: C 54.71, H 3.44, N 11.96; found C 54.53, H 3.20, N 11.75.

5d: colorless solid, yield 87%, mp 159.3~161.1°C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 0.79 (t, J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$), 3.98 (q, J = 7.2 Hz, 2H, OCH_2), 6.58 (s, 2H, NH_2), 7.31–7.51 (m, 8H, ArH), 7.56 (s, 1H, ArH); IR (KBr) υ: 3418, 3337 (NH), 2992 (ArH), 2225 (CN), 1662 (C═O), 1571, 1458, 1423 (Ar), 1327 (C-F), 1255 (C-O-C) cm^{-1}; EI-MS (70 eV) *m/z* (%): 427 (M^+, 100), 398 (57.6), 381 (21.7), 248 (65.1), 145 (36.5), 128 (39.1), 104 (14.6), 77 (31.0). *Anal*. Calcd for $C_{22}H_{16}F_3N_3O_3$: C 61.83, H 3.77, N 9.83; found C 61.98, H 3.64, N 9.60.

5e: colorless solid, yield 91%, mp 131.5~132.3°C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 0.87 (t, J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$), 4.02 (q, J = 6.6 Hz, 2H, OCH_2), 7.01 (d, J = 8.4 Hz, 2H, ArH), 7.30 (dd, J = 4.8 Hz, J = 8.4 Hz, 2H, ArH), 7.40 (d, J = 6.6 Hz, 1H, ArH), 7.48–7.51 (m, 2H, ArH), 7.55 (s, 1H, ArH); IR (KBr) υ: 3410, 3334 (NH), 2985 (ArH), 2227 (CN), 1693 (C═O), 1625, 1572, 1546 (Ar), 1328 (C-F), 1275 (C-O-C) cm^{-1}. *Anal*. Calcd for $C_{22}H_{15}F_4N_3O_3$: C 59.33, H 3.39, N 9.43; found C 59.47, H 3.50, N 9.24.

5f: light yellow solid, yield 76%, mp 140.3~141.7°C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 0.75 (t, J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$), 3.96 (q, J = 6.6 Hz, 2H, OCH_2), 7.14 (d, J = 7.8 Hz, 1H, ArH), 7.24 (d, J = 7.2 Hz, 1H, ArH), 7.28 (d, J = 7.2 Hz, 1H, ArH), 7.33 (d, J = 7.8 Hz, 1H, ArH), 7.39 (d, J = 7.8 Hz, 1H, ArH), 7.42–7.48 (m, 2H, ArH), 7.51 (s, 1H, ArH); IR (KBr) υ: 3412, 3331 (NH), 2989 (ArH), 2228 (CN), 1693 (C═O), 1628, 1570, 1547 (Ar), 1327 (C-F), 1278 (C-O-C) cm^{-1}; EI-MS (70 eV) *m/z* (%): 426 (M-19, 100), 398 (82.3), 282 (14.6), 199 (9.7), 145 (21.0), 126 (14.6). *Anal*. Calcd for $C_{22}H_{15}F_4N_3O_3$: C 59.33, H 3.39, N 9.43; found C 59.12, H 3.45, N 9.47.

5g: colorless crystals, yield 86%, mp 169.5~170.5°C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 3.45 (s, 3H, OCH_3), 7.15 (d, J = 7.8 Hz, 1H, ArH), 7.22–7.28 (m, 2H, ArH), 7.34 (d, J = 7.2 Hz, 1H, ArH), 7.40 (d, J = 7.8 Hz, 1H, ArH), 7.43–7.48 (m, 2H, ArH), 7.51 (s, 1H, ArH); IR (KBr) υ: 3421, 3338 (NH), 2985 (ArH), 2225 (CN), 1691 (C═O), 1623, 1574, 1548 (Ar), 1321 (C-F), 1275 (C-O-C) cm−^{1}; EI-MS (70 eV) *m/z* (%): 447 (M, 0.51), 426 (5.9), 421 (100), 396 (8.1), 358 (4.2), 282 (7.8), 145 (18.8), 126 (9.5), 95 (5.2). *Anal*. Calcd for $C_{21}H_{13}ClF_3N_3O_3$: C 56.33, H 2.93, N 9.38; found C 56.49, H 3.13, N 9.10.

5h: colorless solid, yield 93%, mp 124.3~126.5°C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 0.84 (t, J = 7.8 Hz, 3H, $CH_2\underline{CH_3}$), 2.35 (s, 3H, CH_3), 4.01 (q, J = 7.2 Hz, 2H, OCH_2), 7.12 (d, J = 7.8 Hz, 2H, ArH), 7.22 (d, J = 7.8 Hz, 2H, ArH), 7.41 (d, J = 7.2 Hz, 1H, ArH), 7.48–7.50 (m, 2H, ArH), 7.57 (s, 1H, ArH); IR (KBr) υ: 3444, 3370 (NH), 2981 (ArH), 2219 (CN), 1692 (C═O), 1623, 1570, 1542 (Ar), 1328 (C-F), 1277 (C-O-C) cm^{-1}; EI-MS (70 eV) *m/z* (%): 441 (M, 100), 412 (59.7), 395 (17.2), 369 (70.3), 262 (53.4), 145 (24.5), 142 (30.6), 115 (12.1), 91 (11.6). *Anal*. Calcd for $C_{23}H_{18}F_3N_3O_3$: C 62.58, H 4.11, N 9.52; found C 62.39, H 4.20, N 9.36.

5i: colorless crystals, yield 89%, mp 116.4~117.6°C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 3.54 (s, 3H, OCH_3), 7.16 (d, J = 7.8 Hz, 1H, ArH), 7.25 (d, J = 7.8 Hz, 1H, ArH), 7.30 (s, 1H, ArH), 7.34 (d, J = 8.4 Hz, 1H, ArH), 7.40 (d, J = 6.6 Hz, 1H, ArH), 7.50–7.54 (m, 2H, ArH), 7.55 (s, 1H, ArH); IR (KBr) υ: 3443, 3364 (NH), 2985 (ArH), 2213 (CN), 1690 (C═O), 1625, 1568, 1546 (Ar), 1326 (C-F), 1272 (C-O-C) cm^{-1}. *Anal*. Calcd for $C_{21}H_{13}ClF_3N_3O_3$: C 56.33, H 2.93, N 9.38; found C 56.47, H 3.02, N 9.25.

5j: colorless solid, yield 85%, mp 139.5~141.3°C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 2.35 (s, 3H, CH_3), 3.54 (s, 3H, OCH_3), 6.45 (s, 2H, NH_2), 7.13 (d, J = 8.4 Hz, 2H, ArH), 7.22 (d, J = 7.8 Hz, 2H, ArH), 7.41 (d, J = 7.2 Hz, 1H, ArH), 7.48–7.51 (m, 2H, ArH), 7.57 (s, 1H, ArH); IR (KBr) υ: 3442, 3375 (NH), 2985 (ArH), 2216 (CN), 1690 (C═O), 1626, 1571, 1547 (Ar), 1325 (C-F), 1272 (C-O-C) cm^{-1}. *Anal*. Calcd for $C_{22}H_{16}F_3N_3O_3$: C 61.83, H 3.77, N 9.83; found C 61.63, H 3.84, N 9.61.

5k: colorless crystals, yield 87%, mp 142.5~142.8°C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 3.54 (s, 3H, OCH_3), 6.58 (s, 2H, NH_2), 7.24 (d, J = 8.4 Hz, 2H, ArH), 7.30 (d, J = 8.4 Hz, 2H, ArH), 7.39 (d, J = 6.0 Hz, 1H, ArH), 7.49–7.51 (m, 2H, ArH), 7.54 (s, 1H, ArH); IR (KBr) υ: 3445, 3366 (NH), 2982 (ArH), 2218 (CN), 1693 (C═O), 1621, 1567, 1544 (Ar), 1326 (C-F), 1270 (C-O-C) cm^{-1}. *Anal*. Calcd for $C_{21}H_{13}ClF_3N_3O_3$: C 56.33, H 2.93, N 9.38; found C 56.18, H 2.80, N 9.49.

5l: colorless crystals, yield 71%, mp 170.5~171.2°C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 3.52 (s, 3H, OCH_3), 7.39 (s, 1H, ArH), 7.43 (d, J = 8.4 Hz, 2H, ArH), 7.48–7.52 (m, 3H, ArH), 8.18 (d, J = 8.4 Hz, 2H, ArH); IR (KBr) υ: 3444, 3350 (NH), 2224 (CN), 1705 (C═O), 1633, 1570, 1522 (Ar), 1326 (C-F), 1280 (C-O-C) cm^{-1}; EI-MS (70 eV) *m/z* (%): 458 (M, 100), 432

(7.9), 411 (11.8), 357 (10.6), 293 (34), 282 (14.5), 247 (28.6), 219 (9.6), 195 (8.5), 153 (16.3), 145 (32), 138 (12.2), 77 (17.2). *Anal*. Calcd for $C_{21}H_{13}F_3N_4O_5$: C 55.03, H 2.86, N 12.22; found C 55.27, H 2.72, N 12.46.

Herbicidal activity testing. The herbicidal activity measurement method was adapted according to a literature method [7].

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