2,5-Dihydroxyterephthalates, 2,5-Dichloro-1,4-benzoquinone-3,6-dicarboxylates, and Polymorphic 2,5-Dichloro-3,6-dihydroxyterephthalates

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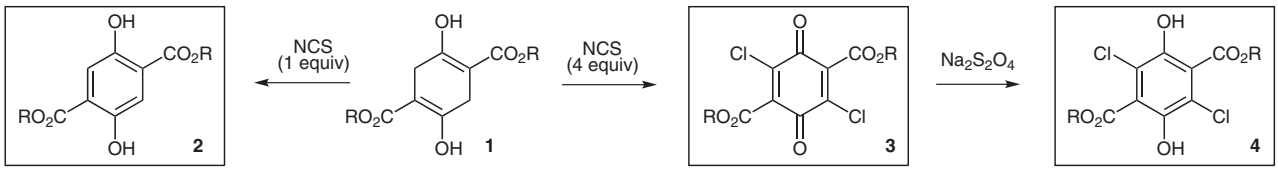
Abstract: Reaction of 2,5-dihydroxycyclohexa-1,4-diene-1,4-dicarboxylates with one equivalent of *N*-chlorosuccinimide cleanly gives 2,5-dihydroxyterephthalates; reaction with four equivalents of *N*-chlorosuccinimide gives 2,5-dichloro-1,4-benzoquinone-3,6-dicarboxylates instead. The latter compounds react with sodium dithionite to give 2,5-dichloro-3,6-dihydroxyterephthalates, which will find use in the study of polymorphic phase changes.

Key words: arenes, halogenation, hydroquinones, polymorphism, quinones



Scheme 1

Introduction

For synthesizing highly substituted benzene derivatives, cycloaddition or condensation approaches from aliphatic precursors are often more efficient than stepwise aromatic substitutions.[2] A good example is the synthetic sequence starting from succinic esters via (a) Claisen condensation to succinylsuccinates **1**,[3] (b) halogenation of **1** to 2,5-dihydroxyterephthalates **2**[4] or dichlorobenzoquinones **3**,[5–7] and (c) reduction of **3** to 2,5-dichloro-3,6-dihydroxyterephthalates **4** (Scheme 1).[5] The latter compounds show 'chromoisomeric' behavior due to polymorphism,[5,8] and methyl ester **4a** is a regular subject in spectroscopic,[9] crystallographic,[10] or theoretical[11] studies of polymorphic phase changes, because of its reliable and reproducible generation of a colorless and two yellow polymorphs.[8,10] The 2,5-dichloro-1,4-benzoquinone-3,6-carboxylates **3** are important intermediates in the synthesis of pigments and colorants themselves,[7] or serve as developers in pressure, heat, or light-sensitive colorants for applications in blue-print paper[12a] or DVD data storage media.[12b] The direct conversion of **1** into **3** is reported in the literature[5,6,9b,c] and patents,[7] but this reaction using chlorine gas is dangerous and capricious in terms of the yields (ca. 50%)[6,7,9b] and/or purity of products.[9b,c] In the course of a total synthesis project, we needed large amounts of **4** and have reinvestigated the classical route from **1** into **3** and into **4**.[5] These studies led us to find that by replacing chlorine gas with *N*-chlorosuccinimide and performing the reaction at higher temperatures (ca. 80 °C) in acetic acid, a clean conversion of **1** into **2** or **3** was achieved in a short reaction time. The products **2**–**4** are useful building blocks for a range of applications and **4a** is now an easily accessible demonstration and study object for solvatochromic, chromoisomeric, and polymorphic behaviors.

Scope and Limitations

While succinylsuccinates **1** can be obtained by a double Claisen condensation of dialkyl succinates,[3] the esters **1a**,**b** are now commercially available. They are readily transformed to higher esters by thermal transesterification.[13,14] We used 4-(dimethylamino)pyridine[15] rather than sodium alkoxide[14] as a catalyst.[13] The synthesis of benzyl ester **1c** and (1*R*)-menthyl ester **1d** exemplifies the procedure (Table 1).

The direct chlorination of **1** to **3** using chlorine sometimes gives products containing **2** and **4** as impurities.[9b,c] We now find that chlorination of **1** with *N*-chlorosuccinimide in acetic acid is high yielding, selective, and operationally simple. Addition of a single equivalent of *N*-chlorosuccinimide converts **1** into 2,5-dihydroxyterephthalates **2** in high yields (Table 2). This oxidation has previously been performed under less favorable conditions.[4]

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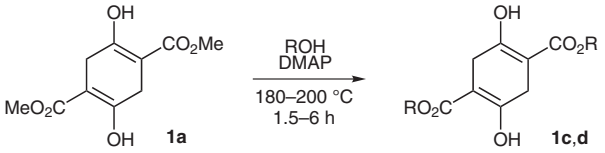
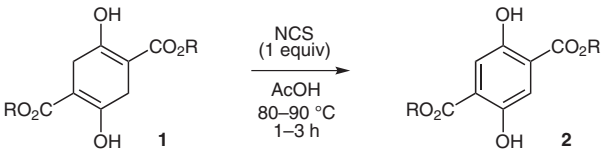
Table 1 Thermal Transesterification of Succinylsuccinates **1**



Entry	R	Solvent	Product	Yield (%)
1	Bn	*o*-xylene	**1c**	84
2	(1*R*)-menthyl	1,2-dichlorobenzene	**1d**	65

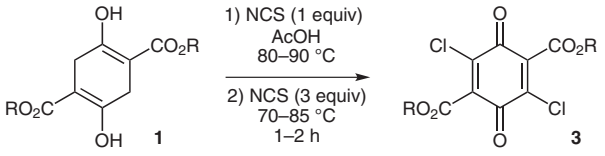
Table 2 2,5-Dihydroxyterephthalates **2** from Succinylsuccinates **1**



Entry	Substrate	R	Product	Yield (%)
1	**1a**	Me	**2a**	90
2	**1b**	Et	**2b**	85
3	**1c**	Bn	**2c**	77
4	**1d**	(1*R*)-menthyl	**2d**	87

If the first step *N*-chlorosuccinimide (**1** → **2**) is followed by addition of another three equivalents of *N*-chlorosuccinimide to the same pot, the reaction proceeds further to the 2,5-dichlorobenzoquinone esters **3** (Table 3). Notably, benzyl ester **1c** reacted without concomitant ring chlorination, and cleavage of the ester alkyl groups was not observed, even under harsh reaction conditions (HCl, 80 °C).

Table 3 2,5-Dichlorobenzoquinones **3** from Succinylsuccinates **1**

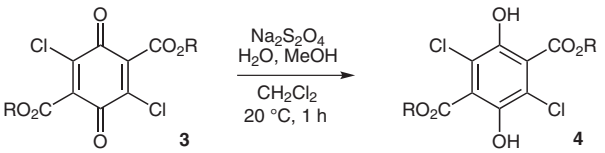


Entry	Substrate	R	Product	Yield (%)
1	**1a**	Me	**3a**	84
2	**1b**	Et	**3b**	84
3	**1c**	Bn	**3c**	78
4	**1d**	(1*R*)-menthyl	**3d**	63

Finally, hydroquinones **4** were conveniently obtained by reduction of 2,5-dihalobenzoquinones **3** with aqueous sodium dithionite (Table 4); this procedure[16] gave much cleaner products in comparison with those by the reduction with zinc in acetic acid.[5,9b,c]

Methyl 2,6-dichloro-3,6-dihydroxyterephthalate (**4a**), an important model compound in the study of polymorphism,[9–11] was thus readily obtained in 50-g batches. The chlorohydroquinones **4c**,**d** display similar solvatochromism as seen with **4a**,**b**.[5,8] From the colorless ethanol solution of **4d**, a stable colorless solvate **4d**·2 EtOH crystallized, whereas solvent-free yellow crystals separated from its greenish dichloromethane solutions.[17]

Table 4 Dithionite Reduction of Quinones **3** to Hydroquinones **4**



Entry	Substrate	R	Product	Yield (%)
1	**3a**	Me	**4a**	98
2	**3b**	Et	**4b**	95
3	**3c**	Bn	**4c**	90
4	**3d**	(1*R*)-menthyl	**4d**	98

Succinylsuccinates **1a** and **1b** were commercially available; **1b** was also synthesized from ethyl succinate.[3] Abbreviations: (1*R*)-menthyloxy = (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy. ^{1}H NMR spectra were recorded at 395 MHz in $CDCl_3$ and referenced to internal TMS. ^{13}C NMR spectra were recorded at 99 MHz in $CDCl_3$ and referenced to the solvent signal. Melting points are not corrected, unless noted. All compounds gave elemental analyses (C, H, N) within a ±0.3% range. *CAUTION*: In the syntheses of **2** and **3**, corrosive HCl vapors are released. We usually absorbed these by passing them *over* (not *directly into*) a stirred slurry of $Ca(OH)_2$ in H_2O.

Dibenzyl 2,5-Dihydroxycyclohexa-1,4-diene-1,4-dicarboxylate (1c)

In a round-bottomed flask with mounted air-cooled condenser, **1a** (5.135 g, 22.5 mmol), BnOH (7.215 g, 66.7 mmol), and DMAP (60 mg) were stirred in *o*-xylene (10 mL) at 180 °C for 6 h. MeOH vapors were released. The mixture was cooled with vigorous stirring while EtOH (25 mL) was added. After standing at 0 °C and filtration, **1c** (7.159 g, 84%) was obtained as faint yellow crystals; mp 167–168 °C.

^{1}H NMR: δ = 3.24 (s, 4 H), 5.24 (s, 4 H), 7.3–7.5 (m, 10 H), 12.15 (s, 2 H).

^{13}C NMR: δ = 28.3, 66.2, 93.2, 128.3, 128.6, 128.9, 135.8, 169.3, 171.4.

Bis[(1*R*)-menthyl] 2,5-Dihydroxycyclohexa-1,4-diene-1,4-dicarboxylate (1d)

In a round flask with mounted, air-cooled condenser, **1a** (2.524 g, 11.06 mmol), (–)-(1*R*)-menthol (5.79 g, 37.05 mmol), and DMAP (0.102 g, 0.83 mmol) in 1,2-dichlorobenzene (5 mL) were heated to 180 °C for 30 min and to 200 °C for 1.5 h. Vapors of MeOH were released. After cooling, MeOH (30 mL) was added with vigorous stirring and the mixture cooled to 0 °C and filtered to give **1d** (3.408 g, 65%) as fine yellow needles; mp 146–148 °C.

^{1}H NMR: δ = 0.76 (d, *J* = 7.0 Hz, 6 H), 0.90 (d, *J* = 7.0 Hz, 6 H), 0.92 (d, *J* = 6.6 Hz, 6 H), 0.95–1.20 (m, 6 H), 1.39–1.60 (m, 4 H), 1.65–1.76 (m, 4 H), 1.85 (sept d, *J* = 7.0, 2.7 Hz, 2 H), 2.00–2.10 (m, 2 H), 3.18 (s, 4 H), 4.80 (td, *J* = 10.9, 4.4 Hz, 2 H), 12.35 (s, 2 H).

^{13}C NMR: δ = 16.0, 20.4, 21.7, 23.1, 26.1, 28.4, 31.1, 33.9, 40.8, 46.8, 74.7, 93.6, 168.8, 171.4.

Dimethyl 2,5-Dihydroxyterephthalate (2a)

To a stirred suspension of **1a** (50.02 g, 219.2 mmol) in AcOH (150 mL) at 80 °C, powdered NCS (30.1 g, 225 mmol) was added to give a dark yellow soln. After 1 h at 80 °C (product precipitates) and cooling to r.t. with stirring, the product was isolated by filtration and washed with AcOH (20 mL), *t*-BuOMe (50 mL), and H_2O (500 mL). Pre-drying in air and drying under high vacuum gave **2a** (44.503 g, 90%) as yellow crystals; mp 176–177 °C (Lit.[9b] 177–178 °C).

^{1}H NMR: δ = 3.98 (s, 6 H), 7.47 (s, 2 H), 10.06 (s, 2 H).

^{13}C NMR: δ = 52.6, 117.9, 118.5, 153.3, 169.9.

Diethyl 2,5-Dihydroxyterephthalate (2b)

To a soln of **1b** (12.218 g, 47.68 mmol) in AcOH (85 mL) at 60 °C, NCS (6.38 g, 47.8 mmol) was added in portions and the mixture was stirred at 80 °C for 2.5 h. After cooling to r.t., crystallization was induced by scratching the vessel walls. The crystal slurry was filtered and washed with chilled MeOH. Drying under high vacuum gave **2b** (10.282 g, 85%) as yellow crystals; mp 133–134 °C (Lit.[4a] 133–133.5 °C).

^{1}H NMR: δ = 1.42 (t, *J* = 7.1 Hz, 6 H), 4.42 (q, *J* = 7.1 Hz, 4 H), 7.47 (s, 2 H), 10.13 (s, 2 H).

^{13}C NMR: δ = 14.0, 62.0, 117.7, 118.5, 152.9, 169.1.

Dibenzyl 2,5-Dihydroxyterephthalate (2c)

To a suspension of **1c** (801.8 mg, 2.11 mmol) in AcOH (10 mL) at 60 °C, NCS (296 mg, 2.21 mmol) was added and the mixture was stirred at 80 °C for 70 min. The mixture was then cooled to ca. 10 °C with stirring, filtered, and washed with AcOH (5 mL), H_2O (10 mL) and MeOH (5 mL) to give **2c** (610.2 mg, 77%) as yellow crystals; mp 149–151 °C.

^{1}H NMR: δ = 5.39 (s, 4 H), 7.35–7.48 (m, 10 H), 7.52 (s, 2 H), 10.07 (s, 2 H).

^{13}C NMR: δ = 67.5, 118.1, 118.7, 128.7, 129.0, 129.0, 135.1, 153.4, 169.3.

Bis[(1*R*)-menthyl] 2,5-Dihydroxyterephthalate (2d)

A suspension of **1d** (242 mg, 0.51 mmol) and NCS (71 mg, 0.53 mmol) in AcOH (2 mL) was stirred at 90 °C for 4 h. The mixture was cooled and a few drops of H_2O were added to give a crystal suspension, which was diluted with MeOH (2 mL) at r.t., filtered, and washed with MeOH–H_2O (1:1, 5 mL) and MeOH (3 mL) to give **2d** (210 mg, 87%) as yellow crystals; mp 146–147 °C.

^{1}H NMR: δ = 0.78 (d, *J* = 7.0 Hz, 6 H), 0.92 (d, *J* = 7.0 Hz, 6 H), 0.95 (d, *J* = 6.5 Hz, 6 H), 0.95–1.03 (m, 1 H), 1.06–1.21 (m, 4 H), 1.49–1.65 (m, 4 H), 1.70–1.80 (m, 4 H), 1.91 (sept d, *J* = 7.0, 2.5 Hz, 2 H), 2.07–2.16 (m, 2 H), 4.97 (td, *J* = 10.9, 4.4 Hz, 2 H), 7.49 (s, 2 H), 10.32 (s, 2 H).

^{13}C NMR: δ = 16.0, 20.4, 21.7, 23.2, 26.2, 31.2, 33.9, 40.4, 46.9, 76.3, 117.8, 118.9, 153.4, 169.2.

Dimethyl 2,5-Dichloro-3,6-dioxocyclohexa-1,4-diene-1,4-dicarboxylate (3a); Typical Procedure

Powdered NCS (26.0 g, 195 mmol) was added to a suspension of **1a** (40.003 g, 175.3 mmol) in AcOH (100 mL) at 70 °C, the mixture slowly heated to 90 °C and kept at that temperature for 40 min (substrates dissolve, HCl is released, and yellow crystals form). After cooling to 60 °C, more NCS (76.24 g, 571 mmol) was added in portions. The temperature was slowly raised to 80 °C and the reaction stirred for 1 h. The resulting yellow slurry was cooled to ca. 10 °C with stirring, filtered, and the solids washed with AcOH (3 × 30 mL) and H_2O (500 mL) to dissolve any succinimide. The product was pre-dried in air and further dried under high vacuum to give **3a** (43.303 g, 84%) as a yellow crystalline powder; mp 241–243 °C (dec) (Lit.[6b] 243–244 °C).

^{1}H NMR: δ = 3.99 (s, 6 H).

^{13}C NMR: δ = 53.6, 137.5, 140.7, 161.2, 174.1.

Diethyl 2,5-Dichloro-3,6-dioxocyclohexa-1,4-diene-1,4-dicarboxylate (3b)

Following the typical procedure for **3a** using **1b** (22.40 g, 87.4 mmol) in AcOH (100 mL) with NCS (first 12.3 g, 92.1 mmol, then 37.0 g, 277 mmol). After the second addition, the mixture was stirred at 85 °C for 3 h. The mixture was cooled and filtered and the product was washed with AcOH (2 × 20 mL) and plenty of H_2O and dried under high vacuum to give **3b** (23.65 g, 84%) as yellow crystals; mp 197–199 °C (Lit.[5] 195 °C).

^{1}H NMR: δ = 1.40 (t, *J* = 7.1 Hz, 6 H), 4.47 (q, *J* = 7.1 Hz, 4 H).

^{13}C NMR: δ = 13.7, 63.3, 137.6, 140.3, 160.7, 174.3.

Dibenzyl 2,5-Dichloro-3,6-dioxocyclohexa-1,4-diene-1,4-dicarboxylate (3c)

A mixture of **1c** (3.068 g, 8.065 mmol) and NCS (1.08 g, 8.09 mmol) in AcOH (20 mL) was stirred at 90 °C for 70 min. More NCS (3.65 g, 27.3 mmol) was added and the mixture stirred at 90 °C for 2 h. The mixture was cooled to r.t. with stirring and the product was filtered and washed (MeOH) to give **3c** (2.794 g, 78%) as a yellow powder that was sensitive to light; mp 143–148 °C.

^{1}H NMR: δ = 5.40 (s, 4 H), 7.3–7.5 (m, 10 H).

^{13}C NMR: δ = 68.8, 128.9, 129.0, 129.2, 134.3, 137.3, 140.6, 160.6, 174.1.

Bis[(1*R*)-menthyl] 2,5-Dichloro-3,6-dioxocyclohexa-1,4-diene-1,4-dicarboxylate (3d)

A mixture of **1d** (2.00 g, 4.2 mmol) and NCS (0.598 g, 4.48 mmol) in AcOH (6 mL) was stirred at 90 °C for 2.5 h. More NCS (1.80 g, 13.5 mmol) was added and the mixture was stirred at 90 °C for 1.5 h. The mixture was cooled and the reaction was worked up with H_2O and *t*-BuOMe. The organic phase was washed with H_2O (3 ×), dried (Na_2SO_4), and evaporated. The product was recrystallized (hot MeCN, 15 mL) to give **3d** (1.257 g, 55%) as yellow needles; a second crop from the mother liquors (183 mg) raised the total yield to 63%; mp 182–183 °C.

^{1}H NMR: δ = 0.84 (d, *J* = 6.9 Hz, 6 H), 0.91 (d, *J* = 6.9 Hz, 6 H), 0.96 (d, *J* = 6.5 Hz, 6 H), ~0.8–0.9 (m, 2 H), 1.04–1.17 (m, 4 H), 1.40–1.60 (m, 4 H), 1.68–1.79 (m, 4 H), 1.98 (sept·d, *J* = 6.9, 2.7 Hz, 2 H), 2.15–2.23 (m, 2 H), 4.99 (td, *J* = 10.9, 4.4 Hz, 2 H).

^{13}C NMR: δ = 15.5, 20.3, 21.6, 22.8, 25.6, 31.2, 33.8, 40.2, 46.6, 78.3, 138.0, 139.6, 160.5, 174.6.

Dimethyl 2,5-Dichloro-3,6-dihydroxyterephthalate (4a)

In a 500-mL round-flask, **3a** (20.653 g, 70.47 mmol) was stirred at 0 °C in a mixture of CH_2Cl_2 (120 mL), MeOH (40 mL), H_2O (20 mL), and AcOH (1 mL). A soln of $Na_2S_2O_4$ (86% content; 21.0 g, 104 mmol) in H_2O (100 mL) was added dropwise over 10 min with vigorous stirring and the mixture was stirred at r.t. for 30 min. The heterogeneous (two-phase + solids) mixture was freed from CH_2Cl_2 and part of the MeOH on a rotatory evaporator at 40 °C (CAUTION: frothing), giving an aqueous suspension of the product, which was cooled to 0 °C, filtered, washed with ice H_2O (50 mL), and dried to give **4a** (20.360 g, 98%) as a yellow powder; mp 178–179 °C (Lit.[9b] 177–179 °C).

^{1}H NMR (sat. soln): δ = 4.04 (s, 6 H), 9.28 (s, 2 H).

^{13}C NMR (sat. soln): δ = 53.3, 119.2, 119.6, 148.3, 167.4.

Diethyl 2,5-Dichloro-3,6-dihydroxyterephthalate (4b)

To a slurry of **3b** (321.5 mg, 1 mmol) in CH_2Cl_2 (5 mL) and AcOH (1 drop), a soln of $Na_2S_2O_4$ (86% content; 256 mg, 1.26 mmol) in H_2O (3 mL) was added and the two-phase mixture was stirred at r.t. for 2 h. *t*-BuOMe (20 mL) and H_2O were added and the organic phase was washed with sat. NaCl (2 ×). The soln was dried ($MgSO_4$), filtered, and evaporated to give a white solid from the yellow soln. Chromatography (silica gel, EtOAc–hexanes, 1:5 to 1:2) gave **4b** (306 mg, 95%) as mixed yellow and white (polymorphic) crystals; mp 123.7–124.0 °C (corr.) (Lit.[5] 123 °C). Note: Addition of MeOH or THF will speed up this biphasic reaction.

^{1}H NMR: δ = 1.45 (t, *J* = 7.2 Hz, 6 H), 4.50 (q, *J* = 7.2 Hz, 4 H), 9.34 (s, 2 H).

^{13}C NMR: δ = 14.0, 63.1, 119.2, 119.6, 148.3, 167.0.

Dibenzyl 2,5-Dichloro-3,6-dihydroxyterephthalate (4c)

A soln of **3c** (418.5 mg, 0.94 mmol) in CH_2Cl_2 (10 mL) and a soln of $Na_2S_2O_4$ (86%; 250 mg, 1.08 mmol) in H_2O (5 mL) were vigorously stirred while MeOH (10 mL) was slowly added, causing a color change from yellow to greenish yellow. After 10 min, the organic solvents (CH_2Cl_2, MeOH) were removed (by rotatory evaporation) and the resulting suspension was filtered. The yellow solid was washed with H_2O and dried in air to give **4c** (379.6 mg, 90%) as yellow crystalline leaflets; mp 113–114 °C.

^{1}H NMR: δ = 5.47 (s, 4 H), 7.34–7.51 (m, 10 H), 9.21 (s, 2 H).

^{13}C NMR: δ = 68.6, 119.4, 119.8, 128.8, 129.0, 129.0, 134.6, 148.6, 167.2.

Bis[(1*R*)-menthyl] 2,5-Dichloro-3,6-dihydroxyterephthalate (4d)

To a soln of **3d** (177.5 mg, 0.33 mmol) in THF (5 mL), a soln of $Na_2S_2O_4$ (90 mg, ca. 0.5 mmol) in H_2O (2 mL) was added dropwise. AcOH (2 drops) was added and the biphasic mixture was vigorously stirred for 10 min. The mixture was diluted with *t*-BuOMe (15 mL) and the organic phase was washed with aq NaCl (3 ×), dried (Na_2SO_4), and evaporated. The residue was purified by chromatography (silica gel, EtOAc–hexanes, 1:5). The collected product fractions were crystallized (hexanes, –20 °C) to give **4d** (173.9 mg, 98%) as a yellow solid; mp 130.2–130.6 °C (corr.). Note: Crystallization of **4d** from EtOH at 0 °C gave colorless crystals of a solvate [**4d**·2 EtOH].[17]

^{1}H NMR: δ = 0.81 (d, *J* = 6.9 Hz, 6 H), 0.91 (d, *J* = 7.0 Hz, 6 H), 0.86–1.00 (m, 2 H), 0.96 (d, *J* = 6.6 Hz, 6 H), 1.05–1.26 (m, 4 H), 1.50–1.62 (m, 4 H), 1.69–1.80 (m, 4 H), 2.01 (sept d, *J* = 7.0, 2.6 Hz, 2 H), 2.16–2.24 (m, 2 H), 5.07 (td, *J* = 10.9, 4.4 Hz, 2 H), 9.28 (s, 2 H).

^{13}C NMR: δ = 15.7, 20.4, 21.7, 22.9, 25.8, 31.3, 33.8, 40.3, 46.8, 77.9, 119.5, 119.8, 148.5, 167.0.

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