Preparation and Stereochemistry of the Methyl 1,3-Dimethylcyclohexaneacetates and Related Compounds

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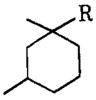
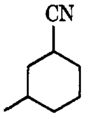
The two methyl 1,3-dimethylcyclohexaneacetates (**6e** and **7e**) have been prepared by Arndt–Eistert synthesis from the related cyclohexanecarboxylic acids **6b** and **7b**. Concomitant formation in this synthesis of the rearrangement products **11** and **12** from **6b** rigorously establishes the stereochemistry of these compounds. The assignment is in accord with data reported here from independent syntheses, nmr spectra, and vpc retention times. It leads to reversal of the assignment made earlier for **6b** and **7b** and methyl ketones **4**, and it suggests that the stereochemistry proposed for keto esters **19** and **20** may be in error.

In examining the steric course of certain photochemical reactions we required authentic samples of both diastereomers of 1,3-dimethylcyclohexaneacetic acid methyl ester (**1**). In this report we describe the preparation and rigorous assignment of stereochemistry for these esters, as well as for the related cyclohexanecarboxylic acids **2** and esters **3**. In the only pertinent earlier work[1] the stereochemistry of the methyl ketones **4** was deduced from their viscosities and from the failure of one isomer to yield a semicarbazone; each of these ketones was then degraded to the corresponding isomer of acid **2** by hypobromite oxidation. Our present assignments require reversal of these earlier conclusions.

The first line of evidence comes from alkylation of the lithium salt of 3-methylcyclohexanecarbonitrile (**5**)[2] with methyl iodide in dimethoxyethane. The 7:3 mixture of isomeric products formed in 89% yield was separated by preparative vapor phase chromatography (vpc), and each nitrile was fully characterized. Structures **6a** and **7a** can be assigned with reasonable confidence to the major and minor isomer, respectively, since alkylation of the *tert*-butyl-substituted nitrile **8** under these conditions yields a 71:29 mixture of **9** and **10**.[3] Nitriles **6a** and **7a** were then hydrolyzed in strong base to the corresponding crystalline carboxylic acids **6b**, mp 88.5–89.5°, and **7b**, mp 45–46°.



1, R = $CH_2CO_2CH_3$
2, R = CO_2H
3, R = CO_2CH_3
4, R = $COCH_3$



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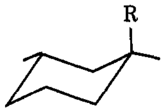

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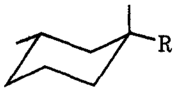

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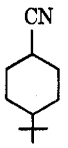
a, R = CN
b, R = CO_2H
c, R = CO_2CH_3
d, R = $COCHN_2$
e, R = $CH_2CO_2CH_3$

A most convincing confirmation of this stereochemical assignment comes from the Arndt–Eistert homologation of these acids **6b** and **7b**. Each was converted through the acyl chloride to the diazo ketone in the usual manner,[4] and these diazo ketones **6d** and **7d** were then treated[5] with silver benzoate and triethylamine in methanol. While **7d** gave the desired homologous ester **7e** without incident, the attempted Wolff rearrangement of **6d** gave some **6e** along with two ketones. On the basis of the spectroscopic properties detailed in the Experimental Section and the degradative correlation described below, we assign structures **11** and **12** to these substances. These are then carbon–hydrogen insertion products from so-called anomalous Wolff rearrangement, a process which has already received attention in closely related systems.[6] The structure of **11** was verified by a photochemical degradation.[7] Irradiation ($\lambda > 2800$ Å) of **11** in benzene led to α cleavage and subsequent hydrogen transfer, with formation of aldehyde **13** and ketene **14**. The latter reacted with methanol to give the corresponding ester, which was isolated and shown to be **6e** by comparison with a sample from the Arndt–Eistert synthesis. This correlation securely establishes the structure of ketone **11**. The formation of these insertion products **11** and **12** from **6d** rigorously defines, in turn, the stereochemistry in this series.



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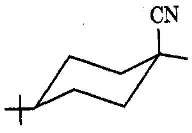

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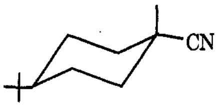

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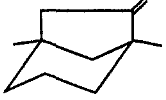

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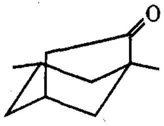

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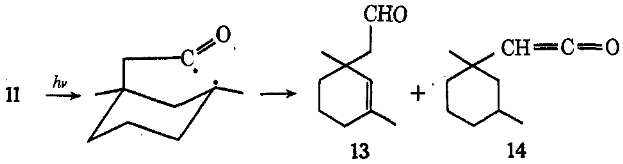

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[2] M. Mousseron and F. Winternitz, *Bull. Soc. Chim. Fr.*, 79 (1948), and references cited therein.

[3] H. O. House and T. M. Bare, *J. Org. Chem.*, **33**, 943 (1968).

[4] W. E. Bachmann and W. S. Struve, *Org. React.*, **1**, 38 (1942).

[5] M. S. Newman and P. F. Beal, III, *J. Amer. Chem. Soc.*, **72**, 5163 (1950).

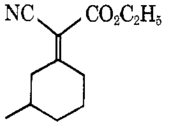
[6] E. Wenkert, B. L. Mylari, and L. L. Davis, *ibid.*, **90**, 3870 (1968); J. K. Chakravarty, S. S. Szinai, and A. Todd, *J. Chem. Soc. C*, 1303 (1970); R. C. Cambie and R. A. Franich, *Aust. J. Chem.*, **24**, 117 (1971); U. R. Ghatak and S. Chakrabarty, *J. Amer. Chem. Soc.*, **94**, 4757 (1972).

[7] S. Wolff, W. L. Schreiber, A. B. Smith, III, and W. C. Agosta, *J. Amer. Chem. Soc.*, **94**, 7797 (1972).

We have also independently prepared **6e** from 3-methylcyclohexanone by a sequence previously used with cyclohexanone[8] and 4,4-dimethylcyclohexanone.[7] Knoevenagel reaction between the ketone and cyanoacetic ester furnished **15** (geometry undetermined), which underwent stereoselective addition of methylmagnesium iodide in the presence of copper(I) catalyst to yield **16**. This was converted to **6e** through saponification and decarboxylation, followed by esterification with diazomethane. The exclusive equatorial 1,4 addition to **15** observed here is analogous to the stereoselective conversion of **17** under similar conditions (or using lithium dimethylcuprate) into **18**.[9]

These stereochemical deductions are all in complete accord with evidence from nmr spectra and vpc retention times. In the 220-MHz spectra of both acid **6b** and the derived methyl ester **6c** the resonance of two of the ring protons is shifted downfield and appears at δ 2.25 ppm (broad, 2 H). We ascribe this signal to the two protons in an axial 1,3 relation to, and somewhat deshielded by, the carbonyl group of these compounds. No such shifted signal appears for **7b** and **7c**, in which the carbonyl group is preferentially equatorial. Also the equatorial methyl substituent at C-1 in **6b**, **6c**, and **6e** is characterized by the expected[10] small upfield shift (Δ 0.02–0.06 ppm) of resonance relative to the axial methyl of **7b**, **7c**, and **7e**, respectively. In similar fashion the signal for the equatorial methylene substituent at C-1 in **7e** appears upfield (Δ 0.15 ppm) from its axial counterpart in **6e**. Previous observations[11] suggest that axial carboalkoxycyclohexanes should have shorter vpc retention times than their equatorial epimers. This relationship holds here for **6c** and **7c**, as well as for the homologous esters **6e** and **7e**.

One final matter deserves attention. A tentative stereochemical assignment has been made[12] for keto esters **19** and **20** on the basis of the data reproduced in Table I. In view of our present results and earlier work cited above it appears that isomer A should be considered to be **19**, and isomer B, **20**. This is the reverse of the original conclusion.



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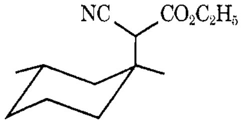

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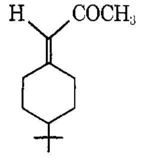

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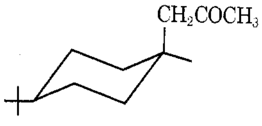

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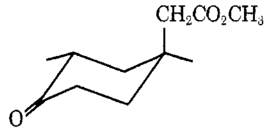

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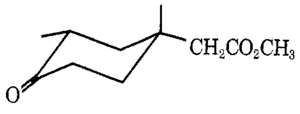

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TABLE I

NMR AND VPC DATA FOR 19 AND 20

Isomer	Chemical shift, δ: C-1 CH_3	Chemical shift, δ: C-1 CH_2	Vpc retention time, min
A	1.08	2.58	29.3
B	1.32	2.24	34.7

Experimental Section

Materials and Equipment.—All vpc was carried out using a Varian Aerograph Model 700 Autoprep or Model A-90-P3 with a 10 ft × 0.375 in. column prepared using 45–60 Chromosorb W in aluminum tubing and one of the following: A, 30% DEGS; B, 30% SE-30; C, 30% Carbowax 20M; D, 30% Carbowax 1500. Unless otherwise noted, the column oven was operated at 145–160°, and the helium carrier gas flow rate was 120–135 ml/min. Ir and nmr spectra were obtained for CCl_4 solutions, the former on a Perkin-Elmer Model 237B spectrophotometer and the latter on a Varian A-60 (60 MHz) or HR-220 (220 MHz)* spectrometer. Solutions were dried over $MgSO_4$ or Na_2SO_4; melting points are corrected; boiling points are uncorrected. Compounds purified by vpc were obtained as colorless oils. Photochemical experiments were carried out with a Hanovia Model L mercury lamp (no. 679A-36) in a quartz immersion well using Pyrex 7740 as filter.

***trans*- and *cis*-1,3-Dimethylcyclohexanecarbonitrile (6a and 7a).**—3-Methylcyclohexanecarbonitrile (**5**, 4.496 g, 36.5 mmol)[2] was alkylated according to the procedure of House.[3] Distillation afforded a mixture of isomers (4.458 g, 89%), which were separated on a preparative scale on column A to give first **6a** (70% of the mixture): ir 2890 (m), 2930 (s), 2876 (m), 2850 (m), 2230 (w), 1460 (s), 1375 (w), 1118 (w), 960 (w), 940 cm⁻¹ (w); nmr (60 MHz) δ 2.28–0.50 (br m), 1.32 (s, CH_3), 0.94 (d, CH_3).

Anal. Calcd for $C_9H_{15}N$: C, 78.77; H, 11.02; N, 10.21. Found: C, 78.42; H, 11.11; N, 10.12.

The second product was **7a** (30% of the mixture): ir 2930 (s), 2870 (m), 2235 (w), 1460 (s), 1450 (m), 1435 (m), 1375 cm⁻¹ (m); nmr (60 MHz) δ 2.30–0.78 (br m), 1.36 (s, CH_3), 0.94 (br d, CH_3).

Anal. Calcd for $C_9H_{15}N$: C, 78.77; H, 11.02; N, 10.21. Found: C, 78.85; H, 11.10; N, 10.22.

***trans*-1,3-Dimethylcyclohexanecarboxylic Acid (6b).**—The major nitrile (250 mg), ethylene glycol (10 ml), potassium hydroxide (3 g), and water (2 ml) were heated at reflux for 3 days. The reaction mixture was cooled, poured into water, and extracted with ether. Acidification of the aqueous phase, extraction with ether, drying, and removal of solvent *in vacuo* gave 247 mg (87%) of crystalline material, mp 86–87.5°. Recrystallization from aqueous methanol gave material of mp 88.5–89.5°, unchanged on further recrystallization (lit.[1] mp 90°): ir 3450–2400 (br), 2950 (m), 2930 (s), 2870 (m), 2850 (m), 1700 (s), 1465 (m), 1450 (m), 1250 (m), 1230 (m), 1175 cm⁻¹ (m); nmr (220 MHz) δ 12.03 (br s, 1 H), 2.22–2.04 (m, 2 H), 1.72–1.30 (m, 4 H), 1.20 (s, 3 H), 1.05–0.64 (m, 3 H), 0.88 (d, $J = 7$ Hz, 3 H).

***cis*-1,3-Dimethylcyclohexanecarboxylic acid (7b)** was prepared in 92% yield from **7a** as described above for **6b**. The crude product was a slightly yellow oil which slowly crystallized, mp 40–42.5°. Recrystallization from aqueous methanol gave material of mp 45–46° (lit.[1] mp 44°): ir 3400–2400 (br), 2955 (m), 2935 (m), 2870 (m), 1700 (s), 1468 (m), 1295 (m), 1270 (m), 1168 cm⁻¹ (w); nmr (220 MHz) δ 11.54 (br s, 1 H), 2.00–1.20 (br m, 8 H), 1.22 (s, 3 H), 0.95–0.73 (m, with d at 0.89, $J = 7$ Hz, 4 H).

Arndt–Eistert Synthesis with 6b.—A mixture of the acid (2.73 g, 0.0175 mol) and thionyl chloride (10 ml) was stirred at room temperature overnight. After heating to reflux for 1 hr, bulb-to-bulb distillation gave 2.95 g, bp 120° (14 mm), of acyl chloride. This was immediately taken up in ether and added to a large

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[8] W. Parker and R. A. Raphael, *J. Chem. Soc.*, 1723 (1955).

[9] H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).

[10] A. Segre and J. I. Musher, *J. Amer. Chem. Soc.*, **89**, 706 (1967); D. K. Dalling and D. M. Grant, *ibid.*, **89**, 6612 (1967).

[11] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley, New York, N. Y., 1965, pp 177–178, and references cited therein.

[12] W. F. Erman and T. W. Gibson, *Tetrahedron*, **25**, 2493 (1969).

excess of ethereal diazomethane (~0.06 mol). The mixture was left standing in an ice bath overnight. Removal of the ether afforded 3.14 g of a yellow oil; ir analysis indicated that the diazo ketone had been formed (2100 cm^{-1}), but that some acid chloride remained. Wolff rearrangement of this crude diazo ketone in methanol with silver benzoate catalysis[5] gave, after work-up and bulb-to-bulb distillation, 2.18 g of a colorless oil. Vpc analysis on column A indicated four components in the ratio 1.3:2.2:2.3:1. The first was **6c**, having a retention time identical with that of an authentic sample prepared from **6b** and diazomethane. The second component was identified as 1,5-dimethylbicyclo[3.2.1]-octan-6-one (**11**): ir 2955 (m), 2935 (m), 2875 (m), 2852 (m), 1745 (s), 1450 (m), 1398 (m), 1345 (m), 1250 (m), 1100 (m), 1082 (m), 950 cm^{-1} (w); nmr (220 MHz) δ 2.01 (dd, J = 18, 4 Hz, 1 H), 1.85 (d, J = 18 Hz, 1 H), 1.73–1.18 (br m, 8 H), 1.12 (s, 3 H), 0.95 (s, 3 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.79; H, 10.57.

The third component was identified as *trans*-1,3-dimethylcyclohexaneacetic acid methyl ester (**6e**): ir 2950 (m), 2925 (m), 2870 (m), 2845 (m), 1745 (s), 1450 (m), 1250 (m), 1195 (m), 1005 cm^{-1} (m); nmr (220 MHz) δ 3.57 (s, 3 H), 2.21 (s, 2 H), 1.74–0.65 (br m with s at 0.96 and d at 0.84, J = 7 Hz, 15 H).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.90. Found: C, 71.85; H, 11.13.

The fourth component was identified as *exo*-1,3-dimethylbicyclo[3.2.1]octan-7-one: ir 2955 (m), 2930 (m), 2870 (m), 1745 (s), 1450 (m), 1400 (m), 1370 (m), 1115 (m), 1032 (m) cm^{-1}; nmr (220 MHz) δ 2.47 (br s, 1 H), 2.15 (dd, J = 18, 7 Hz, 1 H), 2.00 (ddd, J = 18, 4, ~1 Hz, 1 H), 1.79–0.96 (br m, 7 H), 0.94 (s, 3 H), 0.89 (d, J = 6 Hz, 3 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.96; H, 10.50.

Arndt–Eistert Synthesis with 7b.—Similar treatment of acid **7b** (317 mg), but without distillation of the intermediate acid chloride, gave after work-up of the rearrangement product 314 mg, which was analyzed on column D. The major component (~95% of volatile material) was collected and identified as *cis*-1,3-dimethylcyclohexaneacetic acid methyl ester (**7e**): ir 2950 (m), 2930 (m), 2865 (m), 2845 (m), 1742 (s), 1450 (m), 1432 (m), 1427 (m), 1145 (m), 1130 (m), 1115 (m), 1000 cm^{-1} (w); nmr (220 MHz) δ 3.56 (s, 3 H), 2.06 (s, 2 H), 1.77–0.69 (br m with s at 0.98 and d at 0.85, J = 6 Hz, 15 H).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.86; H, 10.95.

***trans*-1,3-Dimethylcyclohexaneacetic Acid Methyl Ester from 3-Methylcyclohexanone.**—A mixture of 3-methylcyclohexanone (6.74 g, 0.06 mol), ethyl cyanoacetate (6.79 g, 0.06 mol), acetic acid (720 mg), ammonium acetate (480 mg), and benzene (21 ml) was heated at reflux for 4.5 hr with continuous removal of water with a Dean–Stark trap. The reaction mixture was cooled, poured into water, and extracted with ether; the combined organic phases were washed with saturated sodium bicarbonate and brine and dried. After removal of ether *in vacuo*, distillation afforded 8.79 g (71%) of a colorless oil considered to be **15**: bp 115–116° (0.5 mm); ir 2940 (m), 2225 (w), 1727 (s), 1602 (s), 1280 (m), 1255 (m), 1215 (s), 1198 (m), 1095 (m), 1038 (m), 945 (w), 850 cm^{-1} (w); the nmr spectrum indicated a mixture of isomers.

To a solution of methylmagnesium iodide [prepared from magnesium (558 mg, 0.023 g-atom) and iodomethane (3.12 g, 0.022 mol) in 15 ml of ether] was added a solution of tetrakisiodo(tri-*n*-butylphosphine)copper (394 mg, 0.001 mol) in 10 ml of ether and, immediately afterwards, a solution of the unsaturated cyano ester **15** (2.07 g, 0.01 mol) in 10 ml of ether at a rate that caused refluxing of the solvent. Immediately after completion of the addition, the reaction mixture was poured into saturated ammonium chloride. After extraction with ether, drying, and removal of solvent, 2.47 g of colorless oil was obtained. This material, considered to be **16**, was purified on column B (208°): ir 2930 (m), 2245 (w), 1747 (s), 1450 (m), 1235 (m), 1170 (m), 1023 cm^{-1} (m); nmr (60 MHz) δ 4.33 (q, J = 7 Hz, 2 H), 3.83 (s, 1 H), 2.25–0.55 [br m with t at 1.38, J = 7 Hz, s at 1.13, and d at 0.97 and d at 0.90 (due to diastereomers), 18 H].

The crude cyano ester **16** was hydrolyzed with potassium hydroxide (5.0 g) in ethylene glycol (15 ml) containing 3 ml of water for 15 hr. The reaction mixture was cooled, poured into water, and extracted with ether; the aqueous phase was acidified with concentrated hydrochloric acid and extracted with ether. The combined organic extracts were washed with brine, dried, and evaporated *in vacuo* to yield a pale yellow oil which was heated to 205° for 0.75 hr. The reaction mixture was cooled, diluted with ether, and extracted with 5% aqueous sodium carbonate; the basic extracts were acidified, extracted with ether, and dried over magnesium sulfate. The ethereal filtrate was treated with diazomethane. After removal of solvent *in vacuo*, the residue (1.395 g, 76% from **15**) was analyzed by vpc on column C. One component was detected; this had an identical ir spectrum and vpc retention time with those of **7e** prepared by Arndt–Eistert homologation of **7b**.

Photolysis of 1,5-Dimethylbicyclo[3.2.1]octan-6-one.—A solution of ketone **11** (60 mg) in benzene (50 ml) was irradiated through Pyrex. Ir spectroscopy was used to monitor the disappearance of starting material and appearance of a ketone band at 2108 cm^{-1}; essentially no ketone remained after 8.25 hr. The photolysate was allowed to stand overnight with 3.0 ml of absolute methanol. After removal of solvents by distillation, vpc analysis on column B indicated two major components. The first was presumed to be 1,3-dimethylcyclohex-2-eneacetaldehyde (~40%) from the following data: ir 2930 (m), 2875 (m), 2840 (w), 2730 (w), 1722 (s), 1450 (m), 1375 (m), 855 (w), 825 cm^{-1} (w); nmr (220 MHz) δ 9.72 (t, J = 3 Hz, 1 H), 5.24 (br s, 1 H), 2.20 (t, J = 3 Hz, 2 H), 1.93–1.81 (m, 2 H), 1.71–1.33 (m, 4 H), 1.63 (d, $J \cong 1$ Hz, 3 H), 1.07 (s, 3 H). The second component (~60%) was **6e**, having ir and nmr (220 MHz) spectra and vpc retention time identical with those of the independently synthesized material described above.

***trans*-1,3-Dimethylcyclohexanecarboxylic Acid Methyl Ester (6c).**—Acid **6b** was esterified with etheral diazomethane and the product was purified on column C: ir 2955 (s), 2940 (s), 2875 (m), 2845 (m), 1740 (s), 1455 (m), 1220 (m), 1200 (m), 1150 (s), 1125 cm^{-1} (m); nmr (220 MHz) δ 3.60 (s, 3 H), 2.17–2.02 (m, 2 H), 1.67–0.52 (br m with s at 1.09 and d at 0.86, J = 6 Hz, 13 H).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.53; H, 10.67.

***cis*-1,3-Dimethylcyclohexanecarboxylic Acid Methyl Ester (7c).**—This was prepared just as **6c** above: ir 2955 (s), 2860 (m), 1738 (s), 1462 (m), 1427 (m), 1245 (s), 1200 (m), 1110 cm^{-1} (s); nmr (220 MHz) δ 3.59 (s, 3 H), 1.72–1.12 (br m, 8 H), 1.17 (s, 3 H), 0.88 (d, J = 6 Hz, with m at ~0.85, 4 H).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.58; H, 10.72.

Registry No.—**5**, 38857-62-4; **6a**, 38864-01-6; **6b**, 38864-02-7; **6b** acid chloride, 38864-03-8; **6c**, 38864-04-9; **6d**, 38864-05-0; **6e**, 38864-06-1; **7a**, 38864-07-2; **7b**, 38864-08-3; **7c**, 38864-09-4; **7e**, 38864-10-7; **11**, 38857-63-5; **12**, 38857-64-6; **13**, 38857-65-7; **15**, 38857-66-8; **16**, 38857-67-9; 3-methylcyclohexanone, 591-24-2; ethyl cyanoacetate, 105-56-6.

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