

Synthesis of the Geometric Isomers of the 1,2,4-trimethylcyclohexanes

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With 4 Figures

Summary

The four geometric isomers of the 1,2,4-trimethylcyclohexanes, **ctt**, **etc**, **ect** and **ccc** have been synthesized, characterized and their physical constants determined.

In the course of the work the stereospecificity of a catalytic reduction method of some olefins and the WOLFF-KISHNER reduction of some ketones were demonstrated.

Introduction

Cyclohexane and its polyalkyl derivatives are some of the many hydrocarbons that occur in petroleum and have long been recognized as important constituents of light naphtha.

There are six possible positional isomers of the trimethylcyclohexanes; 1,1,2; 1,1,3; 1,1,4; 1,2,3; 1,2,4; and 1,3,5.

Of the non-geminal isomers, synthesis and characterization have been completed satisfactorily only in the case of the 1,2,3-trimethylcyclohexanes which we have reported in a previous publication¹⁾ and as a continuation of this work, we have now prepared the geometric isomers of the 1,2,4-trimethylcyclohexanes.

BUSSERT²⁾ attempted to prepare the 1,2,4-trimethylcyclohexanes, but subsequent analysis of the products by gas liquid chromatography revealed that only one of them, the **ctt** isomer, was pure. The present work has proved that the assignment of configuration was also wrong in two cases.

Results and Discussion

Isoprene and crotonaldehyde were condensed together in a DIELS-ALDER reaction to give a mixture of adducts which was reduced to a mixture of cyclo-olefins by a WOLFF-KISHNER reaction. GLC analysis of the cyclo-

¹⁾ B. H. MAHMOUD and K. W. GREENLEE, *J. Org. Chem.* **27**, 2369 (1962).

²⁾ J. F. BUSSETT, Ph. D. Dissertation, The Ohio State University (1954).

olefins revealed only two very close boiling components which were impossible to fractionate apart and on hydrogenation at room temperature over a platinum catalyst, analysis of the product showed the presence of all four possible cycloparaffinic isomers, Fig. 1, which were labelled cryptically I, II, III and IV.

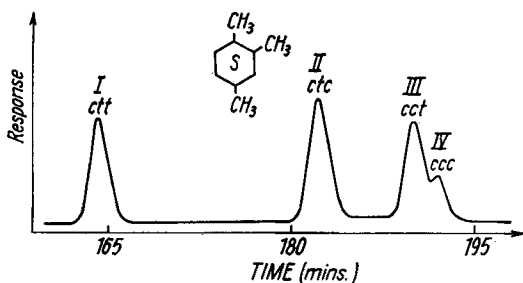


Fig. 1. Gas liquid chromatogram of a mixture of all four 1,2,4-Trimethylcyclohexanes

Only component I could be readily identified, its relative low boiling point fixing it as the ctt isomer. This hydrocarbon has been found³⁾ to be a component of petroleum and was later recognized⁴⁾ as such. In fact, this compound gas become available⁵⁾ as standard samples for the calibration of analytical equipment.

Separation of the cyclo-olefinic isomers failed however due to their close boiling points and the corresponding cycloparaffins could not be identified and a new approach to the problem was hence devised as outlined in Fig. 2.

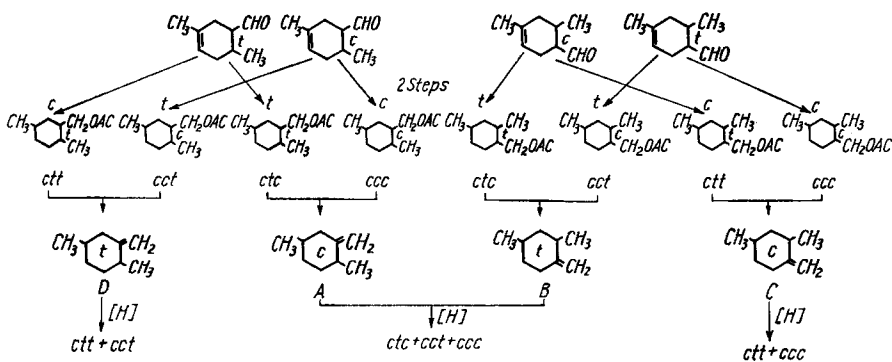


Fig. 2. Synthesis of the 1,2,4-Trimethylcyclohexanes

³⁾ I. WHITE and A. GLASGOW, J. Res. Nat. Bur. Stds. **22**, 137 (1939).

⁴⁾ "Selected Values of Physical and Thermodynamic Properties of Hydrocarbons" A.P.I. Project 44, Carnegie Inst. of Technology, Pittsburgh, Penn.

⁵⁾ A.P.I. Sample Office, Carnegie Inst. of Technology, Pittsburgh, Penn.

The isoprene-crotonaldehyde mixture of adducts was hydrogenated over a 20% nickel-on-kieselguhr catalyst to give the corresponding saturated alcohols in 95–98% yield. The cyclic alcohols were acylated with acetic anhydride to give the corresponding mixture of acetates in 93% yield which were then purified and pyrolyzed at 525°C in a Vycor tube packed with

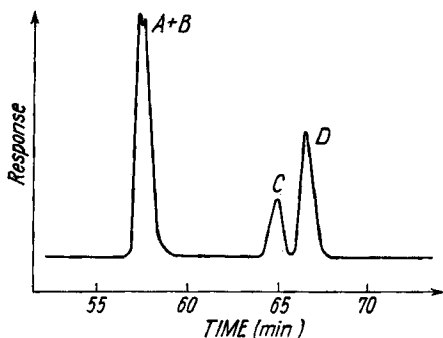


Fig. 3. Gas liquid chromatogram of the Dimethylmethylene-cyclohexanes related to 1,2,4-Trimethylcyclohexanes

glass helices to a mixture of dimethylmethylene-cyclohexane in a 75–80% yield. Chromatography revealed the presence of four components A, B, C and D (Fig. 3). Distillation of the olefinic mixture separated A and B as a close boiling mixture and C and D as pure compounds. Their properties are given in Tab. 1.

Table 1
Dimethylmethylene Cyclohexanes Related to the
1,2,4-Trimethylcyclohexanes

	A + B	C	D
Relative amount %	53	14	33
B.p./760 mm.	141.91	144.46	135.96
n_D^{20}	1.4497	1.4485	1.4497
Purity %	—	96	99

Hydrogenation of A + B cyclo-olefins over platinum oxide under mild conditions gave a mixture of three cycloparaffins II, III and IV in a 45:25:30 ratio, as determined by GLC, showing that A + B cyclo-olefins must be a mixture of *cis*-2,4-dimethylmethylene-cyclohexane and *trans*-2,5-dimethylmethylene cyclohexane since according to the scheme they are the only two olefins that do not yield *etc* cycloparaffins.

The *etc* cyclo paraffin (II) was separated by distillation while the *cct* and *ccc* isomers (III and IV) remained as a mixture.

Hydrogenation of cyclo-olefin C *cis*-2,4-dimethyl-methylenecyclohexane, gave two cycloparaffins in a 28:72 ratio corresponding to component I and IV that were separated and characterized, Table 2.

Table 2
1,2,4-Trimethylcyclohexanes

	(I) <i>ctt</i>	(II) <i>etc</i>	(III) <i>cct</i>	(IV) <i>ccc</i>
B.p./160 mm.	141.29	144.56	146.65	146.57
n_D^{20}	1.4274	1.4344	1.4345	1.4340
d_4^{20}	0.7743	0.7908	0.7908	0.7916
F.p. (m.p.), °C	-85.17	-85.53	-91.86	-77.45
F.p., 100%	0.0392	—	—	-78.31
A	-84.89	—	—	-77.45
Purity mole %	98.9	98+	99+	95.9

Cyclo-olefin D, *trans*-2,5-dimethyl methylene cyclohexane, on hydrogenation also gave two cycloparaffins in a 30:70 ratio corresponding to components I and III that were separated by distillation and characterized, Table 2.

This provided the final proof that II and the *etc* isomer, since it was the only one which, according to the scheme, cannot be paired with I (the *cct* isomer).

The remaining two cycloparaffins III and VI, thus had to be the *cct* and *ccc* isomers respectively and to differentiate between them, they were individually oxidized by aqueous permanganate solution to their corresponding dimethylcyclohexanones. Thus, C yielded *cis*-2,4-dimethylcyclohexanones and D yielded *trans*-2,5-dimethylcyclohexanone which are well known compounds⁶⁾ easily characterized by their semicarbazones. Both ketones were further reduced by a WOLFF-KISHNER reaction to give the corresponding dimethylcyclohexanes (Fig. 4).

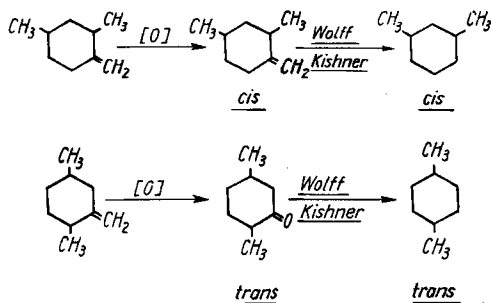


Fig. 4. Oxidation and reduction reactions to the Dimethylcyclohexanes

⁶⁾ D. CAPON et al., Bull. Soc. chim. France 837 (1958).

This fixed the identity of the olefins, C being the *cis*-1,3-dimethylmethylene cyclohexane and D being the *trans*-1,4-dimethyl methylenecyclohexane. Therefore their hydrogenated products must be *ett* and *ccc* isomer from C, and *cct* and *ctt* isomers from D. As the boiling point difference between these pairs was large enough, physical separation by distillation was possible and the physical constants of the four individual geometric isomers of the 1,2,4-trimethyl cyclohexanes were measured (Table 2).

Experimental

Analysis: The Gas-Liquid Chromatographic studies cited in this paper were all done on a Barber Colman IDS Model 20 gas chromatograph with capillary columns.

Cryoscopic determinations of purity were made by a somewhat simplified version of the method of ROSSINI et al.⁷⁾ The "true freezing points" (t_1) were determined geometrically from the freezing point curves and the cryoscopic constants ($A = \text{mole fraction/degree}$) were determined from the freezing point lowering caused by measured amounts of the added impurity. Purity (P) was then calculated from the equation:

$$\log P = 2 - A(t_1 - t)/2.303.$$

2,4- and 2,5-Dimethylcyclohexene-1-carboxaldehyde

In a typical run, 350 g. (5 moles) of freshly distilled crotonaldehyde, 352 grams (5.15 moles) of freshly distilled isoprene and one gram of hydroquinone were charged to a 3-litre steel bomb. The bomb was pressurized to 500 p.s.i.g. with nitrogen and heated to 180° with shaking. An exothermal reaction set in at 180°C raising the temperature to 250–275° for 10 minutes before dropping again to 180°. The bomb was left for 20 minutes at this temperature, then chilled and vented to the atmosphere. Unreacted isoprene and crotonaldehyde were stripped off and the residue was fractionally distilled at 10–15 plates efficiency at reduced pressure to give 510 g. (3.7 moles) of good adduct b.p. 92–95°/30 mm., n_D^{25} 1.4688–1.4693 in 74% yield, together with 21% of isoprene dimer, b.p. 82–85°/30 mm., n_D^{30} 1.48702–1.4734. GLC analysis of the good adduct showed two peaks in an 86:14 ratio.

1,4,5-Trimethylcyclohexenes

The adduct, 690 g. (5 moles) was reduced via a modified WOLFF-KISHNER reaction. The reaction was carried out in a 5-litre, 3-neck flask equipped with an electric heating mantle, stirrer, dropping funnel and (initially) with a thermometer and reflux condenser. The stirrer was of the HERSHBERG type, mercury sealed, and driven by a powerful variable-speed motor. The reflux condenser was attached to the flask through a 35/25 spherical joint and could be replaced in a few seconds by a wide-bore (i. d. 25 mm.) delivery tube of inverted U shape leading to a condensing system. This system comprised of a 2-necked, 5-litre flask bathed by cold water, a multibulb reflux condenser mounted over the flask, and a Dry Ice-cooled trap connected at the top of the condenser. A bubbler was provided at the outlet of the trap to indicate when nitrogen was being evolved

⁷⁾ B. J. MAIR, A. R. GLASGOW and F. D. ROSSINI, *J. Res. Nat. Bur. Stds.* **26**, 591 (1941).

The vessel was charged with diethylene glycol (100 ml.) dihydrazine sulfate (5.0 moles) and commercial flake sodium hydroxide (10.0 moles). This mixture was heated and stirred until homogeneous; at 95–110°, the cyclic aldehyde 690 g. (5.0 moles) was added rapidly and the mixture was stirred under reflux for 2–3 hours. Then, additional sodium hydroxide (8.0 moles) and 10 ml. of n-octanol (anti-foam) were added, the condensing system was attached and the product was distilled from the reactor with vigorous stirring. Most of the product condensed in the receiver flask, along with about a half volume of water, but some was swept into the trap by the escaping nitrogen. During the period of most vigorous evolution, foaming occurred, some solids were deposited in the delivery tube which did not plug however due to its wide bore. In 2–3 hours, distillation and nearly stopped and temperature of the reaction mixture reached 190°. At this point, 200 ml. of water were added slowly and the formed steam flushed the last part of the product into the receiver.

The organic product from the receiver and trap were combined, washed three times with 5% sulfuric acid and dried by quick percolation through a 40–200 mesh activated silica gel. The resulting crude olefinic mixture, 590 g. (95% yield) was steam distilled and the product fractionated at about 50-plate efficiency. The purified product, b. p. 148.4–148.4 °C, n_D^{20} 1.4496, G.L.C. showed the presence of two close boiling components.

1, 2, 4-Trimethyleclohexanes

12.6 g. (0.1 mole) of the mixture of olefins was hydrogenated at room temperature with platinum on charcoal (0.2 g) in a 3-neck flask equipped with a fast stirrer and a condenser. After the theoretical uptake of hydrogen, the catalyst was filtered off and the material was treated exhaustively with potassium permanganate, steam distilled and dried. G.L.C. showed the presence of all four possible isomers, I, II, III and IV, Fig. 1. Only the first two isomers were fractionated apart the last two remaining as an inseparable mixture.

Component I (cet)

b.p. 141.29, n_D^{20} 1.4274, d_4^{20} 0.7743. .p., °C. — 85.17, F.p., 100% — 84.89, Purity, 99%.

Component II (cte)

b.p. 144.56, n_D^{20} 1.4344, d_4^{20} 0.7908, F.p. (M.p.) — 85.53, Purity, 98%.

Component III and IV (cet + cec)

b.p. 146.41–146.45, n_D^{20} 1.4342–1.4345.

2, 4- and 2, 5-Dimethyleclohexylmethanols

Isoprene-crotonaldehyde adduct 1382 g. (10 moles) was hydrogenated in a 3.5 litre rocking hydrogenator over 10% of its weight of 20% nickel in kieselguhr catalyst. The first absorption of hydrogen occurred at 110–125°, corresponding to saturation of the double bond. The temperature was then raised to 180–190° and hydrogenation of the aldehyde group started and was complete in about six hours. The crude alcohol was filtered and used in the next step without purification; it gave no qualitative test for unsaturation or for free aldehyde. Average yields were 95–98%.

2, 4- and 2, 5-Dimethyl-1-acetoxymethylclohexanes

A mixture of the crude alcohol, 2350 g. (17 moles) was added slowly to boiling acetic anhydride (16.5 moles) and 10 g. of a sulfonic acid type ion-exchange resin. Reflux occurred spontaneously during the addition and was maintained for 2 hours after the addition was

complete. The crude ester was then cooled, washed free of acetic acid and dried over anhydrous magnesium sulphate. Upon vacuum distillation the desired mixtures of acetates, b.p. 96–98°/12 mm., n_D^{20} 1.4473–1.4479, was obtained in 93% yield.

Anal. Calcd. for $C_{11}H_{20}O_2$: C 71.65; H 10.94;
 Found: C 71.74; H 10.85.

Pyrolysis of acetates and Purification of Olefins

The mixture of acetates was pyrolyzed at 525° in a 2.2 × 100 cm. electrically heated vertical Vycor tube packed with 1/4" glass helices. The feed was introduced at the top of the tube at a rate of 3 ml. per minute by a CORSON-CERVENY bellows pump, and the pyrolysate was condensed by a glass coil condenser. The pyrolysate was washed free of acetic acid and distilled to obtain 70–80% of olefinic product and 20–30% of unchanged ester which was recycled. By gas-liquid chromatography the product was found to contain 5% of low molecular weight "fragments" while the remainder was represented by four major peaks A, B, C and D in Fig. 3. A and B were only slightly separated under highly resolved conditions but appeared to be roughly equal. A + B, 53%; C 14%; D 33%.

Distillation of an 11.0 kilo lot of the olefinic mixture at about 120-plate efficiency separated "A + B" as a mixture, b.p. 141.91°, n_D^{20} 1.4497, pure "C", b.p. 144.46°, n_D^{20} 1.4485 and pure "D", b.p. 145.96, n_D^{20} 1.4497.

Anal. Calcd. for C_9H_{16} : C 87.03; H 12.97;
 Found for olefins "A + B": C 87.20; H 12.77;
 Found for olefin "C": C 86.92; H 13.07;
 Found for olefin "D": C 87.18; H 13.11;
 Infrared spectra, Plate No. III.

Oxidation of Olefin "C"

To an ice cooled solution of 50 g. (0.4 mole) of (XXVII) in 1.5 liters of water and 0.5 g. of sodium carbonate, a solution of 140 g. (0.88 mole) of potassium permanganate in 3.5 liters of water was added slowly with rapid stirring. The excess permanganate was destroyed with sodium bisulphite solution and on steam distilling a clear solution 35 g. (70%) of ketone was obtained, b.p. 176.5–177° (uncorr.), lit.⁴¹ 175–176°. The semicarbazone derivative had a m.p. 192–193°, lit.⁴¹ 193° and the oxime m.p. 97.5–98.0°, lit.⁴¹ 97–97.5°.

Anal. Calcd. for $C_9H_{17}N_3O$: C 58.98; H 9.35; N 22.93;
 Found: C 58.93; H 9.50; N 23.01.

Oxidation of Olefin "D"

Similarly 50 g. (0.4 mole) of XXVIII was oxidized to a ketone in 75% yield, b.p. 172–175°. The semicarbazone had a m.p. 174–175°, 175–176° and an oxime m.p. 110°, m.p. 110°.

Anal. Calcd. for $C_9H_{17}N_3O$: C 58.98; H 9.35; N 22.93;
 Found: C 58.90; H 9.55; N 23.04.

Reduction of *cis*-2,4-Dimethylcyclohexanone

The ketone was reduced to the corresponding dimethylcyclohexane was a WOLFF-KISHNER reaction previously described. The product obtained was distilled giving a 99+% pure hydrocarbon, b.p. 120.5°, n_D^{20} 1.4231. Its infrared spectra and other physical properties are identical to those for 1, *cis*-3-dimethylcyclohexane.

Reduction of *trans*-2,5-Dimethylcyclohexanone

The ketone was similarly reduced and the hydrocarbon obtained b.p. 119.5°, n_D^{20} 1.4209 was found to be 99+% pure and its infrared identical to that for 1, *trans*-4-dimethylcyclohexane.

Hydrogenation of Olefins "A + B"

The mixture of olefins, 1.5 litres, was hydrogenated over 120 g. of powdered Harshaw nickel at 90° until saturation. The catalyst was filtered off and the mixture of paraffins was fractionated at 60-plate efficiency to yield 3 components in a ratio of 45:25:30. G.L.C. showed the presence of three components II, III and IV in Fig. 1. The lower separable component had the following physical constants:

Component II (etc)

Cottrell b.p. °C./760 mm.	n_D^{20}	d_4^{20}	m.p.
144.56	1.4344	0.7908	-85.53

Anal. Calcd. for C_9H_{18} :	C 85.63; H 14.37;
Found:	C 85.60; H 14.29.

The two remaining higher boiling paraffins remained as a mixture, b.p. 146.40–146.46, n_D^{20} 1.4341–1.4345.

Hydrogenation of Olefin "C"

Hydrogenation of olefin "C" under the same conditions as before gave 2 cycloparaffins in the ratio of 28:72. G.L.C. showed that they corresponded to compounds I and IV. They were fractionated apart on a 50-plate efficiency column and had the following physical constants:

Component I (ctt)

Cottrell b.p. °C./760 mm.	n_D^{20}	d_4^{20}	F.p.	Purity %
141.29	1.4274	0,7743	-85.17	99

Component IV (ccc)

Cottrell b.p. °C./760 mm.	n_D^{20}	d_4^{20}	F.p.	Purity %
146.57	1.4340		-78.31	99+

Anal. Calcd. for C_9H_{18} :	C 85.63; H 14.37;
Found for I:	C 85.65; H 14.32;
Found for IV:	C 85.68; H 14.23.

Hydrogenation of Olefin "D"

Hydrogenation of olefin "D" under the same conditions as before gave 2 cycloparaffins in the ratio of 30:70. G.L.C. showed that they corresponded to compounds I and III. Fractionation afforded the components in high purity (99+), the lower boiling components being identical in physical properties to the previously described *ctt* isomer and the higher boiling component having the following physical properties.

Component III (*ctt*)

Cottell b.p. °C./760 mm.	n_D^{20}	d_4^{20}	M. p.
146.65	1.4345	0.7908	-91.86
Anal. Calcd. for C_9H_{18} :	C 85.63; H 14.37;		
Found for VI:	C 85.47; H 14.25.		

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