

while similar treatment of the *cis*-decalone XVIIb led to the 2,2-*d*₂ analog XIXb of 100% purity.

trans-(XXa) and *cis*-(XXb)-5,5,6,6,7,7,8,8-*d*₈-9-Methyldecalone-1.—A sample (88 mg.) of the *d*₈- α -decalone VIII was transformed by the published procedure¹⁵ to the butylthiomethylene derivative, methylated, the blocking group removed and the *trans* and *cis* isomers separated by gas phase chromatography. Mass spectrometry showed the presence of 9% *d*₀, 40% *d*₈, 23% *d*₇, 11% *d*₆ and less than 4% each of *d*₀, *d*₁, *d*₂, *d*₃, *d*₄, and *d*₅ species.

trans-(XXIa) and *cis*-(XXIb)-4,4-*d*₂-9-Methyldecalone-1.—Methylation¹⁵ of XII and gas phase chromatographic separation gave the required ketones XXIa and XXIb, the composition of which was determined mass spectrometrically as: *d*₀ 13%, *d*₁ 38%, *d*₂ 35%, *d*₃ 14%.

trans-(XXIIa) and *cis*-(XXIIb)-3,3,10-*d*₃-9-Methyldecalone-1.—The identical procedure applied to XVI led to the ketones XXIIa and XXIIb of the isotope composition: *d*₃ 61%, *d*₂ 32% and *d*₁ 7%.

trans-(XXIVa) and *cis*-(XXIVb)-6,7-*d*₂-9-Methyldecalone-1.—The mixture (267 mg.) of *trans*-(XXIIIa) and *cis*-(XXIIIb) 9-methyl- Δ^8 -octalones⁸ was reduced with lithium aluminum hydride in ether solution (20 hr., room temperature), the resulting alcohol acetylated, reduced with N-trideuterio-*p*-toluenesulfonyl hydrazide (see preparation of VII), saponified, oxidized and the mixture (over-all yield, 93 mg.) of *trans*-(XXIVa) and *cis*-(XXIVb) isomers separated by gas phase chromatography on a Craig succinate column, the products consisting of 57% *d*₂, 33% *d*₁ and 27% *d*₀ species.

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, WASHINGTON UNIVERSITY, ST. LOUIS, MO.; POLYTECHNIC INSTITUTE OF BROOKLYN, BROOKLYN, N. Y.; STANFORD UNIVERSITY, STANFORD, CALIF.]

Absolute Configuration and Optical Rotatory Dispersion of 3-Methylcycloheptanone and 4-Methylcycloheptanone

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RECEIVED NOVEMBER 19, 1962

Ring enlargement of (+)-3-methylcyclohexanone, a compound of reliably established absolute configuration, is shown to yield (+)-3-methylcycloheptanone and (–)-4-methylcycloheptanone. The reassignment of the sign of rotation and the sign of the optical rotatory dispersion Cotton effect to the 3-methyl isomer eliminates the contradictions posed by the stereochemical outcome of the diazomethane ring enlargement of optically active 2-methylcyclohexanones and confirms the proposition that the diazoalkane-carbonyl reaction proceeds with retention of configuration.

A recent communication directed to the stereochemistry of the diazomethane ring enlargement of optically active 2-methylcyclohexanone⁴ required the conclusion, based on the data contained therein and on the existing data in the literature, that the diazoalkane-carbonyl reaction proceeds with inversion of configuration. On the basis of other facts concerning such reactions, however, this appeared to be inadmissible and to call for a reinvestigation of some of the earlier experiments. One of the several critical points in the argument focused on the previously reported synthesis of (–)-3-methylcycloheptanone by diazomethane ring enlargement of (+)-3-methylcyclohexanone,⁵ the absolute configuration of which had been established by methods generally accepted as reliable.⁶ The work reported in the present communication demonstrates that the product of ring enlargement of (+)-3-methylcyclohexanone is actually the (+)-rotating rather than the (–)-rotating 3-methylcycloheptanone, the earlier reported⁵ negative rotation (and negative Cotton effect) having been due to contamination with the strongly levorotatory 4-methylcycloheptanone which is also produced in the ring enlargement reaction. Thus the contradictions posed by the stereochemical outcome of the diazomethane ring enlargement of 2-methylcyclohexanone are resolved, and it is firmly established that the diazomethane-carbonyl reaction proceeds with retention of configuration.

Ring enlargement of (+)-3-methylcyclohexanone was carried out by the *in situ* diazomethane method according to the procedure previously employed by Djerassi and Krakower,^{5,7} by the *ex situ* diazomethane

method,⁸ and by the Demjanow-Tiffeneau method⁹; in all cases the product consisted of approximately equal amounts of the 3- and 4-methylcycloheptanones. The two materials, however, are not easily separated, and it is this difficulty that obscured the earlier report⁵ concerning their optical rotations. By subjecting the crude mixture to distillation through a very efficient spinning band column at a very high reflux ratio or by passing the crude mixture through a sufficiently long and efficient vapor phase chromatographic (v.p.c.) column it is possible to obtain one fraction with $[\alpha] + 64^\circ$ and another fraction with $[\alpha] - 137^\circ$. Although resembling each other in boiling point, refractive index and nuclear magnetic resonance spectra (n.m.r.), the two fractions showed significant differences in detail in the infrared spectrum, in the mass spectrum, in v.p.c. behavior and especially in optical rotatory dispersion (R.D.) (Fig. 1). Furthermore, derivatives of the two fractions showed them to be quite different compounds. Identification of the (+)-fraction as (+)-3-methylcycloheptanone (strong positive Cotton effect) was based on a comparison with material previously obtained⁴ from the ring enlargement of 2-methylcyclohexanone; identification of the (–)-fraction as (–)-4-methylcycloheptanone (strong negative Cotton effect) was based on a comparison with material obtained from the ring enlargement of 4-methylcyclohexanone. Additional support for these structural assignments was adduced from the degradative reactions resulting in the conversion of the respective ketones to the corresponding dibasic acids followed by pyrolytic cyclization to a mixture of methylcyclohexanones which could be separated by v.p.c. As anticipated, application of this reaction sequence to (+)-3-methylcycloheptanone provided 2- and 3-methylcyclohexanone, while (–)-4-methylcycloheptanone afforded 3- and 4-methylcyclohexanone uncontaminated with 2-methylcyclohexanone.

(1) The work at Stanford University was supported by grant no. CRTY-5061 from the National Cancer Institute, U. S. Public Health Service.

(2) The work at the Polytechnic Institute of Brooklyn was supported by Chas. Pfizer, Co., Inc.

(3) The work at Washington University was supported by grant no. 628-A4 from the Petroleum Research Fund administered by the American Chemical Society and by grant no. G-21323 from the National Science Foundation.

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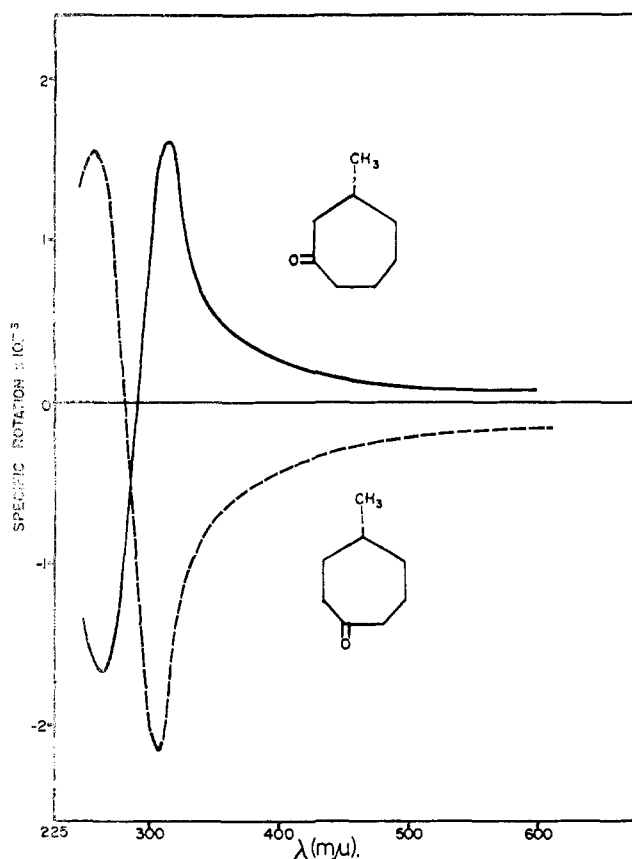


Fig. 1.—Optical rotatory dispersion (methanol solution) of (+)-3-methylcycloheptanone and (-)-4-methylcycloheptanone.

Experimental¹⁰

Ring Enlargement of (+)-3-Methylcyclohexanone. (A) *Via Diazomethane in Situ*.—A 37-g. sample of 3-methylcyclohexanone with $[\alpha]^{25D} + 11.8^\circ$ (neat) was treated with 80 g. of *N*-nitroso-*N*-methyl-*p*-toluenesulfonamide according to published procedures.^{8,7} Steam distillation of the crude product yielded 13 g. of material which was fractionated by v.p.c. using a Wilkens Aerograph Autoprep model A-700 employing a 20 ft. \times 3/8 in. column packed with 30% phenyldiethanolamine succinate on 60–80 mesh Chromosorb P. In addition to starting material, two higher boiling fractions comprised of 3- and 4-methylcycloheptanone, respectively, were obtained. Alternatively, by distillation of the crude material through a spinning band column (Precision Distillation Apparatus Co, GE-125-2H) with better than 90 theoretical plate efficiency operating at a reflux ratio of greater than 1:1000 two higher boiling fractions were obtained which, on the basis of analytical v.p.c., were more than 95% pure. Redistillation of each fraction through the same column yielded materials of better than 99% purity.

(B) *Via Diazomethane ex Situ*.—A 77.2-g. sample of (+)-3-methylcyclohexanone with $[\alpha]^{25D} + 8.3^\circ$ in methanol was treated with 0.688 mole of diazomethane in 1620 ml. of ether-methanol (9:1). The reaction was carried out at room temperature for 1 week, after which time the solvent was removed by evaporation and the residue was distilled through a 90-cm. spiral column to yield 48 g. (55%) of product with b.p. 83–85.5° (19 mm.). Further purification could be effected by the methods indicated above.

(10) The infrared spectra were measured on Perkin-Elmer model 21 and model 421 spectrometers. The nuclear magnetic spectra were measured on a Varian model A-60 spectrometer. The optical rotatory dispersion measurements were made on a Japan Spectroscopic Co. (Jasco) automatically recording spectropolarimeter model ORD-2.

(C) *Via Demjanow-Tiffeneau Method*.⁹—A 9.5-g. sample of (+)-3-methylcyclohexanone was converted to the cyanohydrin by treatment for 1 hr. at 0° with liquid hydrogen cyanide (ca. 15 ml.) and a few drops of piperidine as catalyst. After neutralization of the base with Amberlite IR-120 followed by removal of the hydrogen cyanide, the residue was treated with 7 g. of lithium aluminum hydride in ether solution. The resulting amino alcohol was dissolved in 60 ml. of water containing 3 ml. of acetic acid, treated at 0° with 3 g. of sodium nitrite in 20 ml. of water, and the mixture allowed to stand for 4 hr. at 0° and 6 hr. at room temperature. The crude product was distilled through a Vigreux column to yield 5.9 g. (55%) of material with b.p. 86–100° (40 mm.). Purification by passage through a preparative v.p.c. column yielded 3-methylcycloheptanone as a lower-boiling fraction and the methylcycloheptanones as the two higher-boiling fractions.

(+)-3-Methylcycloheptanone possessed the following physical properties: b.p. 97.5–98° (40 mm.), $n^{25D} 1.4547$, $[\alpha]^{25D} + 64^\circ$ in methanol; $\lambda_{\text{max}}^{\text{liquid}}$ 5.92, 6.92, 7.13, 7.28, 7.44, 7.67, 7.82, 8.06, 8.87, 9.65, 10.02, 10.37, 11.58, 12.30 μ ; $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.97, 6.92 μ , R.D. (Fig. 1) in methanol (c 0.593): $[\alpha]_{589}^{25} + 70^\circ$, $[\alpha]_{311}^{25} + 1618^\circ$; $[\alpha]_{282}^{25} - 1686^\circ$; n.m.r. in CCl_4 : 7.68 (doublet), 8.0–8.8 (multiplet), 9.02 (doublet) τ ; mass spectrum: molecular ion at m/e 126 ($\text{C}_8\text{H}_{14}\text{O}$), no significant peaks at m/e 112, 140, 154 (*i.e.*, absence of higher or lower homologs), significant differences from the spectrum of 4-methylcycloheptanone at m/e 69, 70, 83, 97, 98.

The semicarbazone of (+)-3-methylcycloheptanone was obtained as colorless crystals, m.p. 176°.

Anal. Calcd. for $\text{C}_9\text{H}_{17}\text{N}_3\text{O}$: C, 58.98; H, 9.35; N, 22.93. Found: C, 58.79; H, 9.65; N, 22.83.

The 2,4-dinitrophenylhydrazone of (+)-3-methylcycloheptanone was obtained as orange crystals, m.p. 126–127°.

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_4\text{O}_4$: C, 54.89; H, 5.92; N, 18.29. Found: C, 54.89; H, 6.15; N, 18.33.

(-)-4-Methylcycloheptanone possessed the following physical properties: b.p. 98.5–99° (40 mm.), $n^{25D} 1.4555$, $[\alpha]^{25D} - 137^\circ$ in methanol; $\lambda_{\text{max}}^{\text{liquid}}$ 5.92, 6.92, 7.13, 7.30, 7.52, 7.67, 7.77, 8.03, 8.64, 9.49, 9.77, 10.19, 10.48, 11.18, 11.60, 11.81, 12.33 μ ; $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.96, 6.92 μ ; R.D. (Fig. 1) in methanol (c 0.465): $[\alpha]_{589}^{25} - 147^\circ$, $[\alpha]_{307}^{25} - 2150^\circ$, $[\alpha]_{255}^{25} + 1549^\circ$; n.m.r. in CCl_4 : 7.67 (triplet), 8.0–8.8 (multiplet), 9.05 (doublet) τ ; mass spectrum: molecular ion at m/e 126 ($\text{C}_8\text{H}_{14}\text{O}$), no significant peaks at m/e 112, 140, 154.

The semicarbazone of (-)-4-methylcycloheptanone was obtained as colorless crystals, m.p. 179–179.5°.

Anal. Calcd. for $\text{C}_9\text{H}_{17}\text{N}_3\text{O}$: C, 58.98; H, 9.35; N, 22.93. Found: C, 58.51; H, 9.59; N, 22.82.

The 2,4-dinitrophenylhydrazone of (-)-4-methylcycloheptanone was obtained as yellow crystals, m.p. 138–139°.

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_4\text{O}_4$: C, 54.89; H, 5.92; N, 18.29. Found: C, 54.76; H, 5.88; N, 18.49.

dl-4-Methylcycloheptanone, prepared by diazomethane ring enlargement of 4-methylcyclohexanone, was obtained as a colorless liquid, b.p. 85° (20 mm.), $n^{25D} 1.4559$. The semicarbazone of *dl*-4-methylcycloheptanone was obtained as colorless crystals with m.p. 157.5–158°; the 2,4-dinitrophenylhydrazone of *dl*-4-methylcycloheptanone was obtained as yellow crystals, m.p. 141–142°.

Degradation of (+)-3-Methylcycloheptanone and (-)-4-Methylcycloheptanone.—A Baeyer-Villiger oxidation of each of the methylcycloheptanones was carried out according to the procedure described for the oxidation of cycloheptanone.¹¹ In each case the crude material was subjected to alkaline permanganate oxidation under standard conditions.¹² The resulting product was hydrolyzed with 10% aqueous sodium hydroxide containing a small amount of ethanol, and the acidic fraction was subsequently pyrolyzed at 300° in the presence of 5% by weight of barium hydroxide. The neutral portion of the distillate was subjected to v.p.c. analysis; the material derived from 3-methylcycloheptanone was shown to contain 2- and 3-methylcyclohexanone but no 4-methylcyclohexanone, while the material from 4-methylcycloheptanone was shown to contain 3- and 4-methylcyclohexanone but no 2-methylcyclohexanone.

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