The Gas Chromatographic Separation and Characterization of δ-Cyclogeraniolene and α-Cyclogeraniolene Formed from Isophorone by Wolff-Kishner Reduction[1]

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Some isomers of cyclogeraniolene are known to serve as starting substances applicable[2-4] in the synthesis of ionone analogs. These isomers have been prepared by the cyclization of geraniolene[5,6] or by the dehydrative cyclization of 2, 6-dimethyl-5-hepten-2-ol[7,8] in the presence of various acidic catalysts; they have not, however, hitherto been separated in a pure state except in a single case in which δ- and ε-isomers,[8] i. e., 3, 5, 5- and 3, 3, 5-trimethylcyclohexene, were isolated in a reliable purity[9] from the dehydration products of dihydroisophorol.

A recent publication[10] describing how the modified Wolff-Kishner reduction of isophorone gave only the α-isomer, 2, 4, 4-trimethylcyclohexene, has prompted us to report on the isolation and characterization of δ- and α-isomers from the reaction products obtained during our independent studies.

We have found that the above reduction carried out at 160∼170°C produces, in a 55% yield, an inhomogeneous hydrocarbon along with a small amount of isophorone hydrazone and isophorone azine. The hydrocarbon mixture thus obtained gave, on gas chromatography, two large peaks which accounted for ca. 30 and 70% of the total. A very small peak at a much lower retention time was also detected thereby, but it has not yet been identified. The relative amounts of the two main components scarcely changed under the reaction conditions programmed from 140 to 200°C, while that of the minor component varied over a range of 0∼3%. The separation of these isomers was not sufficiently achieved even by careful distillation techniques, whereas the two principal components were completely isolated from the above mixture by preparative scale-gas chromatographic trapping.

The faster-eluted cyclogeraniolene gave, on ozonolysis, 2, 4, 4-trimethylhexanedioic acid, and the other major isomer yielded isogeronic acid in a high yield. Therefore, the former was considered to be δ-cyclogeraniolene and the latter to be α-cyclogeraniolene. The structural assignment was further confirmed by the NMR spectra, as will be described in the Experimental section.

The formation of the δ-isomer in the above reaction is not unexpected, as it has previously been recognized[11,12] that the Wolff-Kishner reduction of α, β-unsaturated carbonyl compounds in an alicyclic series gives essentially two olefinic isomers, of which one possesses the olefinic bond at the same position as before, while the other has a bond which has migrated to the site of the original carbonyl group.

We have found a linear relationship between the refractive indices and mole ratios for several mixtures of α- and δ-cyclogeraniolenes. The observed refractive values of both pure isomers (α, n_D^{25} 1.4433; δ, n_D^{25} 1.4383) were in good agreement with those estimated by graphical extrapolation. Alkonyi's "α-cyclogeraniolene,"[10] n_D^{25} 1.4408, is possibly inhomogeneous and is contaminated by an appreciable amount of δ-isomers and/or other substances.

Finally, isophorone azine,[10] which was obtained on the Wolff-Kishner reduction, as has been mentioned, was also formed when isophorone hydrazone was allowed to stand for a long period at room temperature.

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[1] Presented at the 6th Symposium on Perfumery, Terpene and Essential Oil Chemistry, Ina, August, 1962.

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[8] Cf. G. C. Oppenlander and A. R. Day, *J. Org. Chem.*, **21**, 961 (1956).

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Experimental[13]

The Wolff-Kishner Reduction of Isophorone. — A mixture of isophorone (69 g.), triethylene glycol (300 g.), 80% hydrazine hydrate (140 g.) and potassium hydroxide (93 g.) was heated at a bath temperature of 160~170°C for 2 hr. The reaction mixture was distilled at the same temperature to separate the product, which was obtained as an azeotropic mixture with a b. p. range of 123~135°C. The residue was again refluxed for 2 hr. and distilled. There was also obtained a pale yellow product boiling at 125~165°C. The combined distillates were then separated, and the water layer was extracted with ether. The extract and the organic layer were combined, washed with a saturated sodium chloride solution, dried over sodium sulfate and concentrated in vacuo. Distillation through a 20 cm. Vigreux column gave (1) a colorless liquid (39 g.) (b. p. 65~67°C/80 mmHg), (2) a pale yellow oil (8.5 g.) (b. p. 120~127°C/20 mmHg) and (3) a viscous yellow oil (8.3 g.) (b. p. 143~145°C/3 mmHg), which solidified immediately to give yellow prisms.

The low boiling fraction 1 was redistilled over sodium (1 g.) using a small Vigreux column to give a mobile liquid (38.2 g.) (b. p. 67.5~68°C/80 mmHg, n_D^{25} 1.4420), which on gas chromatography employing a 9 m., 30% PEG-6000-on-Celite DM-14A column at 128°C with a hydrogen flow rate of 35 ml./min. gave three peaks with the retention times of 18 min. 18 sec., 21 min. 18 sec. and 24 min. 42 sec. respectively. The second and third peak, accounting for 29 and 69% of the above fraction, are due to δ- and α-cyclogeraniolene respectively. The first peak, accounting for 2%, is due to the hydrocarbon, which has not yet been characterized. The relative amounts of this compound changed over a range of only 0~3% under several W.-K. reduction conditions (4~13 hr. at 140~200°C).

The distillation of fraction 2 gave a pale yellow oil (7.8 g.) which boiled at 125~127°C/21 mmHg and which solidified gradually when left standing. Crystallization from ether-petroleum ether (5 : 1) yielded isophorone hydrazone as colorless needles (m. p. 72~73°C), which was treated with the Brady reagent to give isophorone 2,4-dinitrophenylhydrazone as dark-red needles (m. p. 146~147°C) (Lit. m. p. 147~148°C[14]).

Isophorone hydrazone was unstable and, on exposure to air, yielded an orange-yellow tarry product with an isophorone-like odor from which isophorone azine, identified by the mixture melting point determination and by infrared comparison with an authentic sample, was obtained.

The yellow solid obtained from the high boiling fraction 3 was recrystallized from methanol to give isophorone azine in the form of yellow leaflets; m. p. 148.5~149°C (Lit. m. p. 147~148°C[10]). ν_{max}^{KBr} 3034, 1641 (C=N), 1580 (conju. C=C), 1381, 1362 (*gem*-dimethyl), 1121, 898 and 835 cm^{-1}.

Found: C, 79.54; H, 10.07; N, 9.91. Calcd. for $C_{18}H_{28}N_2$: C, 79.36; H, 10.36; N, 10.28%.

The treatment of this compound with the Brady reagent gave, in a quantitative yield, isophorone 2,4-dinitrophenylhydrazone; m. p. 146~147.5°C.

The Gas Chromatographic Separation of δ-Cyclogeraniolene and α-Cyclogeraniolene from the Hydrocarbon Mixture.—The hydrocarbon mixture (59 g., n_D^{25} 1.4419) consisting of 0.5% an unknown component, 28.5% δ-isomers and 71.0% α-isomers was injected in 6 ml. portions into a Beckmann "Megachrom" equipped with a 12 ft.×5/8 in.ϕ, Apiezon "J" on a firebrick column at 123°C with a 135°C pre-heated inlet and a nitrogen flow (inlet/outlet=15/1 (p. s. i.)). After the usual procedure, there were finally obtained three fractions: (1) 11.4 g. (retention time, 27 min. 48 sec.), (2) 34.0 g. (32 min. 32 sec.), and (3) 6.3 g. (the mixed hydrocarbon recovered). The distillation of fraction 1 through a 40 cm. Vigreux column over sodium (1 g.) gave δ-cyclogeraniolene (9.9 g.) as a colorless mobile liquid (b. p. 132.4~132.6°C/760 mmHg, n_D^{25} 1.4384, n_D^{15} 1.4428), which was gas chromatographed on a 2.5 m. column of 25% PEG-6000 substrate to show a single peak. (Lit. b. p. 133.58°C, n_D^{20} 1.4406[9]). ν_{max}^{film} 3014, 1653, 714, 672 (cis -CH=CH-), 1461 ($-CH_2$), 1398, 1387 and 1367 cm^{-1} (CH_3). NMR absorptions:[13] a multiplet in the 8.40~8.88 τ region (2H, CH_2 in the 4-position); an apparent triplet at 8.26 τ (2H, allylic CH_2 in the 6-position); a multiplet at 7.94 τ (1H, allylic CH in the 3-position); two peaks at 9.12 and 9.09 τ (6H, *gem*-dimethyl); a doublet at 9.04 τ (3H, CH_3 in the 3-position, J=5.01 c.p.s.), and an apparently unresolved doublet at 4.59 τ (2H, vinyl CH=CH, J=0.9 c.p.s., half-width=3.5 c.p.s.).

Found: C, 86.98; H, 12.92. Calcd. for C_9H_{16}: C, 87.02; H, 12.98%.

Fraction 2 was distilled through the same column to afford α-cyclogeraniolene (32.1 g.) as a colorless mobile liquid (b. p. 137~138°C/760 mmHg, n_D^{25} 1.4433), which was proven to be completely homogeneous by gas chromatographic analysis. (Lit. b. p. 103~105°C/200 mmHg;[7] b. p. 135°C, n_D^{25} 1.4408;[10] b. p. 54°C/40 mmHg[15]). ν_{max}^{film} 3042, 1679, 805 (>C=CH-), 1458 ($-CH_2$), 1381 and 1363 cm^{-1} ($-CH_3$). NMR absorptions:[13] a triplet at 8.64 τ (2H, CH_2 in the 5-position); a multiplet at 7.91 τ (4H, two allylic CH_2 in the 3- and 6-positions); two peaks at 9.03 and 8.97 τ (6H, *gem*-dimethyl); a singlet at 8.27 τ (3H, CH_3 in the 2-position), and a multiplet at 4.33 τ (1H, olefinic C-H).

Found: C, 87.05; H, 13.03. Calcd. for C_9H_{16}: C, 87.02; H, 12.98%.

The retention time ratios to cyclohexene as the standard of the two isomeric cyclogeraniolenes and related substances, when measured at 136°C by a 3 m., 30% PEG-6000-on-Celite DM-14B column with

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[13] All melting points were measured on a Kofler block and are uncorrected. The infrared spectra were recorded on a Nippon Bunkô, model IRS, recording spectrometer using sodium chloride optics, while the gas chromatographic analyses were performed with a Kotaki Super Fractioner, model GU-21. The NMR spectra were determined at 56.4 Mc./s. with a Varian V-4300C high resolution NMR spectrometer using a 20 vol. % solution in carbon tetrachloride and tetramethylsilane as the internal standard.

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a 25 ml./min. rate of hydrogen flow, are: the unknown hydrocarbon, 1.26; ε-cyclogeraniolene, 1.37; δ-cyclogeraniolene, 1.45, and α-cyclogeraniolene, 1.67.

2,4,4-Trimethylhexanedioic Acid.—Ozonized oxygen (c 17 g./m^3) was passed through a solution of δ-cyclogeraniolene (1.5 g.) in carbon tetrachloride (10 ml.) at a flow rate of 30 l./hr. over a period of 2.5 hr. The temperature was maintained at −10°C by cooling. Acetic acid (5 ml.) and 30% hydrogen peroxide (1.5 ml.) were added, and the resulting solution was allowed to stand overnight at room temperature. After the bulk of solvent had been removed in vacuo, the residue was treated as usual to give a colorless, viscous oil (0.65 g.) (b. p. 160~180°C/6 mmHg (bath temp.)), which solidified when stored for a week in a refrigerator. Crystallization afforded colorless prisms; m. p. 71°C (Lit. m. p. 69.7~70.0°C,[9] 72~73.5°C[16]). The dianilide crystallized from benzene in the form of colorless prisms; m.p. 165°C (Lit. m.p. 164~165°C,[16] 162.8~163.3°C[17]).

Isogeronic Acid.—α-Cyclogeraniolene (1.5 g.) in carbon tetrachloride (15 ml.) was ozonized, and the reaction mixture was treated in the manner described for δ-isomer. A colorless viscous oil (1.0 g., 67.0%) (b. p. 162~165°C/5 mmHg) was obtained.

Found: C, 62.32; H, 9.42. Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.36%.

The semicarbazone crystallized from methanol in the form of colorless prisms; m. p. 200~201°C (Lit. m. p. 197~198°C,[10] 198°C[18]).

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