[Contribution from the Department of Chemistry, University of Cincinnati and the Department of Industrial Medicine, New York University]

The Stereochemistry of the Formation and Dehydrohalogenation of *cis*-2-Chlorocyclohexyl Phenyl Ketone[1]

ALVIN I. KOSAK[2] and HARRY M. LEYLAND

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cis-2-Chlorocyclohexyl phenyl ketone has been prepared by a stereospecific synthesis from cyclohexene. The chloroketone obtained by the addition of hydrogen chloride to 1-cyclohexenyl phenyl ketone is this same isomer. Treating *cis*-2-chlorocyclohexyl phenyl ketone with base, or heating it alone, produces 1-cyclohexenyl phenyl ketone.

The synthesis of α,β-unsaturated ketones by acylation of an olefin followed by elimination of hydrogen halide was first reported by Kondakow[3] in 1892, and has been investigated frequently since that time.[4]

If one assumes that acylation occurs *via* a *trans* addition to the double bond, heterolytic dehydrohalogenation of the intermediate haloketone derived from a cyclic olefin would be expected, on steric grounds, to give a β,γ-unsaturated ketone,[5] and the α,β-unsaturated isomer should be produced by a homolytic reaction. In almost all cases previously reported, the unsaturated ketone obtained was stated to be the conjugated isomer. Colonge and Mostafavi[4k] found that ethyl 2-chloro-1,2-dimethylpropyl ketone (obtained from the reaction of propionyl chloride with trimethylethylene) gave a mixture of ethyl 1,2-dimethyl-1- and -2-propenyl ketones upon treatment with N,N-dimethylaniline. Braude, *et al.*[4o] similarly obtained two unsaturated ketones from 1-methylcyclohexene. Deno and Chafetz[4q] found that 1-methyl-cyclohexene yielded only the β,γ-unsaturated ketone when treated with acetic anhydride and zinc chloride. In contrast with this, Royals and Hendry[4p] obtained the conjugated ketone from cyclohexene with these reagents; and Colonge and Duroux[4l] found but one isomer, the α,β, when they acylated 1-methylcyclohexene with propionyl chloride under Friedel-Crafts conditions and dehydrohalogenated the product. It seemed of interest to synthesize *cis*- and *trans*-β-haloketones and to determine the nature of the olefins obtained under controlled conditions.

Difficulty was encountered in obtaining *trans*-2-chlorocyclohexyl phenyl ketone uncontaminated by unsaturated ketone, employing the Friedel-Crafts type reaction. Application of Wieland and Bettag's[4f] potassium permanganate oxidation technique for removal of olefinic material was not successful in our hands, nor was fractional recrystallization of the chloroketone.

The *cis* isomer was synthesized by adding hypochlorous acid to cyclohexene to give the *trans* chlorohydrin II.[6] II was converted to *trans*-2-cyanocyclohexanol (III) by potassium cyanide,[7] and the latter yielded *cis*-2-chlorocyclohexyl cyanide (IV) upon treatment with thionyl chloride in pyridine.[8] Van Coillie[9] had reported the separation of the *cis* and *trans* isomers of IV from the reaction product of cyclohexanone cyanohydrin and thionyl chloride, and had made a structure assignment on the basis of molecular refractivities, densities, and refractive indices. The physical constants of IV are in agreement with those reported by Van Coillie for his *cis* isomer and his structure assignment is thus given synthetic confirmation.

cis-2-Chlorocyclohexyl phenyl ketone (V) resulted from the reaction of phenylmagnesium bromide with IV.

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(2) Inquiries should be addressed to this author at New York University Post-Graduate Medical School, 550 First Ave., New York 16.

(3) Kondakow, *Bull. soc. chim.*, **7**, 576 (1892).

(4) (a) Blanc, *Bull. soc. chim.*, **19**, 699 (1898); (b) Krapivin, *Bull. soc. imp. Nat. Moscow*, 1 (1908); *Chem. Abstr.*, **5**, 1281 (1911); (c) Darzens, *Compt. rend.*, **150**, 707 (1910); (d) Darzens and Rost, *Compt. rend.*, **151**, 758 (1910); (e) Norris and Couch, *J. Am. Chem. Soc.*, **42**, 2239 (1920); (f) Wieland and Bettag, *Ber.*, **55**, 2246 (1922); (g) Schoeller and Zollner, *U. S. Patent* 1,737,203 (1929); (h) Ruzicka, Koolhaus, and Wind, *Helv. Chim. Acta*, **14**, 1151 (1931); (i) Frolich and Wiezevich, *U. S. Patent* 2,006,198 (1936); (j) Christ and Fuson, *J. Am. Chem. Soc.*, **59**, 893 (1937); (k) Colonge and Mostafavi, *Bull. soc. chim. France*, **6**, 335 (1939); (l) Colonge and Duroux, *Bull. soc. chim. France*, **7**, 459 (1940); (m) Nightingale, Milberger, and Tomisek, *J. Org. Chem.*, **13**, 357 (1948); (n) Catch, Elliot, Hey, and Jones, *J. Chem. Soc.*, 278 (1948); (o) Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J. Chem. Soc.*, 1890 (1949); (p) Royals and Hendry, *J. Org. Chem.*, **15**, 1147 (1950); (q) Deno and Chafetz, *J. Am. Chem. Soc.*, **74**, 3940 (1952); (r) Burton and Praill, *Chemistry & Industry*, 75 (1954).

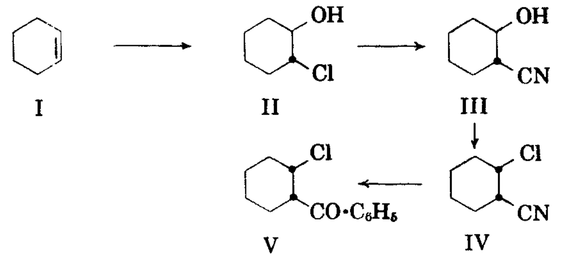
(5) Bartlett, in Gilman, *Organic Chemistry*, John Wiley and Sons, N. Y., 1953, Vol. III, pp. 51 ff.

(6) Bartlett, *J. Am. Chem. Soc.*, **57**, 224 (1935).

(7) Mousseron, Jullien, and Winternitz, *Bull. soc. chim.*, [5] **15**, 878 (1948).

(8) Lucas and Gould, *J. Am. Chem. Soc.*, **63**, 2541 (1941); Carroll, Kubler, Davis, and Whaley, *J. Am. Chem. Soc.*, **73**, 5382 (1951); Stevens and Grummitt, *J. Am. Chem. Soc.*, **74**, 4876 (1952).

(9) Van Coillie, *Bull. soc. chim. Belg.*, **42**, 419 (1933)

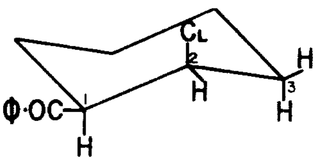


Isomerization of IV by the Grignard reagent is unlikely inasmuch as dehydrohalogenation of the chloronitrile would have been the preferred reaction had the organometallic compound functioned as a base.[10] The difference in melting point between V and the *trans* isomer[4f] (assuming that Wieland and Bettag had prepared the pure compound) also indicates that isomerization did not occur. We had earlier determined that hydrogen chloride adds stereospecifically to 1-cyclohexenyl phenyl ketone to give a single chloroketone in 87% yield; V proved to be identical with this compound, and this latter procedure constitutes the preferred synthesis. A possible explanation of this stereospecific control may lie in 1,4-addition of hydrogen chloride to the conjugated system to give an enol in which the chlorine is in the favored equatorial position, followed by preferential prototropic attack on the less hindered side of the enol double bond during the ketonization process as suggested by Zimmerman.[11] The geometry of the cyclohexylidene ring[12] is such that the *cis* axial hydrogens *alpha* to the double bond are displaced to a considerable extent outward from the ring and away from the double bond ring carbon as compared to cyclohexane which would favor such a concept. On the basis of current evidence we prefer this idea to an extension to this unsaturated ketone system of the suggestion of Vaughan, *et al.*[13] that hydrohalogenation of α,β-unsaturated systems (acids) proceeds by a *trans* addition to the carbon-carbon double bond, which proposal rests upon the assumption that protonation of the enol is equally probable from either side. It is of interest to note that Van Coillie[9] obtained only the *cis* chloronitrile upon adding hydrogen chloride to 1-cyanocyclohexene, another compound in which 1,4-addition can take place.[14]

The ionic elimination of hydrogen chloride from V gave an unsaturated ketone, VI, melting at 31–32°. The assignment of the 1-cyclohexenyl phenyl ketone structure to VI was made on the basis of the absorption maximum at 245 mμ in the ultraviolet spectrum and the 6.12 μ band in the infrared spectrum, both of which are in agreement with a conjugated system, and the observation by Farkas and Stevens[15] that both 1- and 2-chlorocyclohexyl phenyl ketones yield the same unsaturated ketone on heating, and that this compound had the same melting point as VI. At no time during the elimination reaction was the concentration of the red-colored anion of 1-cyclohexenyl phenyl ketone high enough to be visible; this fact leads us to believe that a base-catalyzed rearrangement of initially formed β,γ-isomer was avoided.

Thermal dehydrohalogenation (120°) of V produced an unsaturated ketone whose melting point, and that of its semicarbazone, was identical with, and not depressed by, admixture with VI and its semicarbazone; the ultraviolet absorption spectrum was also identical with that of VI.

The *trans* ionic elimination of hydrogen chloride to yield VI is the expected observation. In order to have that orientation of the hydrogen and chlorine atoms wherein all four centers are coplanar and the projected valency angle between C-H and C-Cl is 180°,[16] it is necessary to picture V as being in the *axial* chlorine, *equatorial* benzoyl conformation (Va). Inasmuch as the benzoyl group is bulkier than the chlorine atom, it seems reasonable to assume that this structure is favored at equilibrium.



VA

We cannot say, without kinetic data, whether the thermal reaction can be acid-catalyzed or not. Were this so, the reaction could be visualized as proceeding through an enol intermediate and subsequent displacement of the axial chlorine.

As a by-product in the olefin acylation reaction there was sometimes obtained a small quantity (0–2%) of a chlorine-containing compound, $C_{13}H_{15}ClO$, melting at 113–114° which was thermally stable compared to V or its *trans* isomer, and which was undoubtedly 4-chlorocyclohexyl phenyl ketone.[15]

Attempts to prepare *trans*-2-cyano-1-chlorocyclohexane (as an intermediate for the synthesis of the *trans*-2-chloroketone) by the method of Van Coillie[9] were not successful.

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(10) Mousseron, Jullien, and Jacquier, *Bull. soc. chim. France*, [5] **15**, 79 (1948).

(11) Zimmerman, *J. Org. Chem.*, **20**, 549 (1955).

(12) Corey and Sneen, *J. Am. Chem. Soc.*, **77**, 2505 (1955).

(13) Vaughan, Craven, Little, and Schoenthaler, *J. Am. Chem. Soc.*, **77**, 1594 (1955).

(14) *Cf.* Cocker, Lapworth, and Peters, *J. Chem. Soc.*, 1382 (1931).

(15) Stevens and Farkas, *J. Am. Chem. Soc.*, **74**, 5352 (1952).

(16) Ingold, *Structure and Mechanism in Organic Chemistry*, Bell, London, 1953.

EXPERIMENTAL[17]

trans-2-Chlorocyclohexanol. Prepared by the method of Coleman and Johnstone[18]; b.p. 84–85°/16 mm.

trans-2-Cyanocyclohexanol. A 65% yield of material boiling at 145–147°/16 mm., m.p. 45–46°, was obtained by the procedure of Mousseron, *et al.*[7]

cis-2-Chlorocyclohexyl cyanide (IV). A solution of 25.5 g. (0.20 mole) of III in 33.8 g. (0.43 mole) of pyridine was added dropwise to 48.6 g. (0.41 mole) of thionyl chloride at such a rate as to maintain refluxing. After refluxing for an additional 2.5 hours, the cooled solution was poured into an ice-hydrochloric acid mixture. The resultant oil was dissolved in methylene chloride, washed with water, then several times with sodium bicarbonate solution, and again with water. The solvent was removed from the dried solution, and 18.0 g. (62% yield) of a product boiling at 123–126°/14 mm., n_D^{30} 1.4793, was collected. Redistillation gave 12.4 g. of IV boiling at 92–93°/2 mm., n_D^{30} 1.4792; lit.[9] b.p. 121°/12 mm., n_D^{30} 1.4797.

When thionyl chloride without pyridine was used, a 24% yield of IV was obtained along with 18% of 1-cyanocyclohexene, b.p. 90–92°/18 mm.

Reaction of thionyl chloride with cyclohexanone cyanohydrin. Seven 50-g. batches of cyclohexanone cyanohydrin were treated as directed by Van Coillie,[9] and together yielded 52 g. (7%) of IV; no *trans*-2-chlorocyclohexyl cyanide could be isolated.

cis-2-Chlorocyclohexyl phenyl ketone. (*a*). To a solution of 5.0 g. (35 mmoles) of IV in 35 ml. of anhydrous ether was added 40 ml. of an 0.875 *M* solution (35 mmoles) of phenylmagnesium bromide in ether dropwise over a 1.5 hour period at 0°. The product was poured into 250 ml. of ice-cold 4% sulfuric acid, the ether layer was removed, and the aqueous phase was extracted with 25 ml. of ether and then allowed to stand overnight at room temperature. Filtration gave 0.8 g. (14%) of V melting at 96–99°. Recrystallization from petroleum ether (60–90°) yielded colorless crystals, m.p. 100–101°, which did not show any melting point depression when mixed with a sample of V obtained as in (*b*).

(*b*). Anhydrous hydrogen chloride was passed into a solution of 42 g. of 1-cyclohexenyl phenyl ketone in 150 ml. of anhydrous ether until no more was taken up. The ether was removed under reduced pressure, and the residue was recrystallized several times from petroleum ether to give colorless V, m.p. 101.0–101.5°.

Anal. Calc'd for $C_{13}H_{15}ClO$: C, 70.1; H, 6.8. Found: C, 69.9; H, 6.9.

Ionic elimination. To a solution of 8.0 g. (36 mmoles) of V in 60 ml. of 95% ethanol was added, with shaking, 2.0 g. (36 mmoles) of potassium hydroxide. At the end of 10 minutes all of the potassium hydroxide had dissolved and the precipitation of potassium chloride had ceased. The solvent was removed from the filtered solution and distillation of the residue afforded 5.1 g. (76%) of colorless oil, b.p. 125–128°/0.7 mm., n_D^{25} 1.5652, which crystallized on standing, m.p. 31–32°; λ_{max} (alc.) 245 mμ, ϵ 10,900.

The *semicarbazone* of VI melted at 205–207°, λ_{max} (alc.) 264 mμ, ϵ 22,600; lit. m.p.[14] 209–211°. In one run, a semicarbazone of m.p. 185–187° was obtained by diluting an ethanolic solution of this compound with water. The ultraviolet and infrared (solution) absorption spectra of the two semicarbazones were identical, indicating that they were dimorphic forms of the same compound.

When VI was treated with alcoholic potassium hydroxide the solution immediately became red-colored; no coloration was observed during the elimination reaction described above.

Thermal elimination. Compound V (8 g., 36 mmoles) was heated at 120–125° under a vacuum until the evolution of hydrogen chloride had ceased (15 minutes), and the product then was distilled at 1.5 mm. to give 5.5 g. (83%) of colorless oil, b.p. 133–134°, n_D^{25} 1.5653, which soon crystallized and melted at 31–32°. A mixture m.p. with the material obtained in the ionic elimination was not depressed, and the ultraviolet and infrared absorption spectra of the two compounds were identical.

The semicarbazone melted at 205–207° and did not depress the semicarbazone of the unsaturated ketone in the ionic elimination.

Absorption spectra. The infrared measurements were made on a Baird Associates recording spectrophotometer through the courtesy of Dr. W. A. Patterson who also contributed to their interpretation. The ultraviolet data were obtained with a Beckman DU quartz spectrophotometer.

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CINCINNATI, OHIO
NEW YORK 16, NEW YORK

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[17] All m.p.'s are corrected; b.p.'s are uncorrected.

[18] Coleman and Johnstone, in *Org. Syntheses*, Coll. Vol. 1 (2nd ed.), 158 (1941).