THE REACTION OF 2-CHLOROCYCLOHEXANONE WITH GRIGNARD REAGENTS AND THE REARRANGEMENT OF THE RESULTING CHLOROHYDRINS

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The reaction between a Grignard reagent and 2-chlorocyclohexanone (I), an important synthetic route to 2-alkyl- and 2-arylcyclohexanones (IV) (1–3), has been shown by Tiffeneau and Tchoubar (4) in the case of alkyl Grignard reagents to involve an initial addition of the reagent to the carbonyl group in I, and not a direct attack on the chlorine atom. The complex (II) so formed then on heating undergoes a rearrangement in which R migrates to the carbon originally carrying the chlorine atom, thus yielding the ketone IV (Chart I). This mechanism is supported by the following evidence.

CHART I
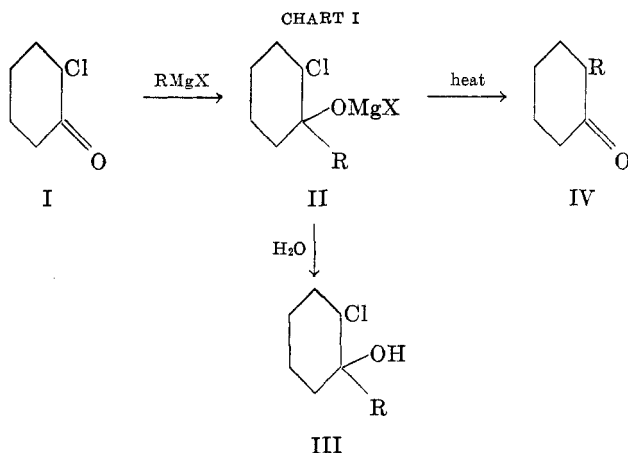
The experimental procedure for preparation of the ketones (IV) normally calls for heating of the Grignard reaction mixture with a moderately high-boiling solvent, e.g., benzene, toluene, or xylene, for periods of 8–16 hours. [A striking exception is found in the preparation of the p-anisyl homolog, for which no heating is necessary (2).] However, by carrying out the reaction in the cold, and hydrolysing the mixture directly without heating, the French workers were able to isolate, in high yields, the chlorohydrins (III, R = Me, Et), which could only have resulted from an addition of the Grignard reagent to the carbonyl group. Similar results were obtained simultaneously by Bartlett and Rosenwald (5) who were also able to show that even in 2-bromocyclohexanone, with a more reactive halogen atom, the preferred site of attack was still the carbonyl group. In further support of their mechanism, the French workers reported the formation of the ketone (VI), when 2-chloro-5-methylcyclohexanone (V) was substituted for I (Chart II).

In the aromatic series, evidence for this mechanism is scanty and inconclusive. The only claim of the isolation of an aromatic homolog of III has not been substantiated by experimental details (6), while another study using 2-chloro-4-methylcyclohexanone has proved equally inconclusive (7). Moreover, the method by which the chlorohydrins in the aliphatic series were obtained, when applied to the p-anisyl homolog, was found to give not the corresponding chlorohydrin, but the ketone (IV), the former having evidently suffered rearrangement before or during isolation. It would appear therefore that with certain aromatic groups at least, the chlorohydrins formed (or the magnesium complexes) undergo facile rearrangement, and cannot be isolated at all.

CHART II

V   VI
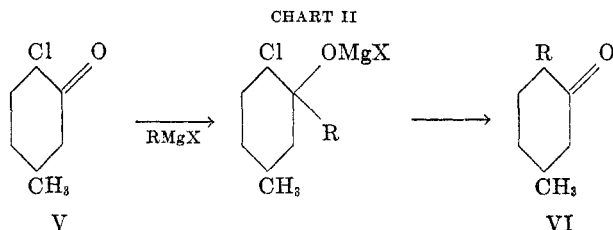
Since the methyl and ethyl groups on the one hand and the p-anisyl group on the other represent extremes in electron-releasing tendencies, it appeared of interest to ascertain whether a consistent relationship existed between such tendencies of the R group in III and the ease with which rearrangement takes place. The contrast in stability between the aliphatic and aromatic homologs then would be explicable in this light and, by the choice of appropriate aromatic groups of sufficiently low electronegativity, it should be possible to prepare chlorohydrins which are of sufficient stability to be isolated. This has proved to be the case. Furthermore, a study of such a relationship might yield results which have bearing on the mechanism of the rearrangement.

Three types of aromatic groups were chosen for investigation: (i) Groups of high electron-releasing capacities: p-phenetyl and p-tolyl; (ii) Groups of low electron-releasing capacities: p-chlorophenyl and m-chlorophenyl; and (iii) ortho-Substituted groups: o-anisyl, o-tolyl, and 1-naphthyl. In each case I (1 mole) was treated with the Grignard reagent (1.5 to 2 moles) at room temperature, the mixture then was decomposed with aqueous ammonium chloride, and the product was isolated by extraction and distillation. Groups of type (i) were found to yield the rearranged ketones only, as in the case of the p-anisyl group already reported (2), apart from some polymeric materials which were invariably formed in all such reactions. Groups of type (ii) by contrast furnished thermally stable chlorohydrins. Thus the chlorohydrin (III, R = p-chlorophenyl) was recovered unchanged after six hours' reflux in ethylbenzene (b.p. 139°), although heating in p-cymene (b.p. 175°) for the same time brought about decomposition into a variety of products. The chlorohydrin (III, R = m-chlorophenyl) was even more stable, being entirely unaffected by the latter treatment.

This finding accords with the well known electronic effects of the m-chlorine ($-I$ only) and the p-chlorine ($-I > +M$) atoms.

The isolation of these chlorohydrins, as well as that of the o-anisyl and 1-naphthyl homologs to be reported below, furnishes the required evidence for the addition of aryl Grignard reagents to the carbonyl group. Moreover, the relationship thus far found between the electronegativity of R and the facility with which rearrangement takes place appears to favor the concept of a transient radical center or carbonium ion as in the case of the catalyzed rearrangement of pinacols. In the rearrangement of benzopinacols, the "migratory aptitudes" of various aromatic groups, which parallel the electron-donating capacities of such groups except when *ortho*-substituents are present, have been conveniently expressed in numbers by Bachmann and his co-workers (8). It is not surprising that Bachmann's values (in parentheses) show a correspondence with the tendencies with which the chlorohydrins rearrange: p-phenetyl (500), p-anisyl (500), p-tolyl (15) > p-chlorophenyl (0.7) > m-chlorophenyl (0.0).

The *ortho*-substituted aromatic groups in the benzopinacol rearrangement present anomalies, often ascribed to steric effects. For instance, symmetrical di-o-methoxy- and di-o-methylbenzopinacol have been found to be stable to conditions under which other pinacols rearrange (9), in spite of the high electronegativity associated with the o-anisyl and o-tolyl groups. It seemed worth while to investigate whether similar anomalies arise with such groups in the chlorohydrins being studied, since in these the presumed carbonium ion or radical center to which R migrates is linked to relatively small substituents (a methylene group and a hydrogen atom). The results obtained with groups of type (iii), in contrast to the other types studied, show marked departure from what might be expected by analogy with the benzopinacols. Thus, although both the o-anisyl and o-tolyl groups possess very low migratory capacities in the benzopinacols (8, 9), the former afforded a stable chlorohydrin (III), whereas the latter gave surprisingly the rearranged ketone (IV). As the methyl group is known to be more "bulky" than the methoxy group (*e.g.*, in the optically active biphenyls), this finding is not without interest. Another contrast is offered by the 1-naphthyl group, which though of a high migratory aptitude when present in a pinacol (10), gave rise to a stable chlorohydrin. Such anomalous results obviously cannot be explained on steric grounds alone.

In the course of the present study, evidence was also obtained which indicates that, while addition to the carbonyl group in I is the main reaction with both alkyl and aryl Grignard reagents, direct attack on the chlorine atom also occurs to an appreciable extent with the latter class of reagents. This is shown by the isolation of the carbinol (VII), in the o-anisyl series, in at least 6% yield. The presence of VII can only be accounted for by the addition of the Grignard reagent to the ketone (IV), which in turn must have been formed by a direct replacement of the chlorine atom in I. In the p-chlorophenyl series, IV was actually present in the reaction product albeit in traces, and its isolation was effected by the use of Girard reagent P. In the 1-naphthyl series, the yield of IV so obtained

(4.0 %) was actually higher than that reported by Orchin (2.6 %) using the conventional method of refluxing the reaction mixture in benzene for 16 hours (11). It appears likely that whatever ketone (IV) Orchin obtained was produced by the side reaction in question, and not by rearrangement of the magnesium complex of the chlorohydrin.
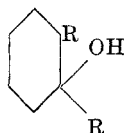
VII

EXPERIMENTAL

M.p. are uncorrected. Analyses by Drs. Weiler and Strauss, Oxford, England. All distillations of reaction products were carried out under an atmosphere of nitrogen.

2-Chlorocyclohexanone was prepared according to the method of Newman and Farbman (1). It was freshly distilled before use, b.p. 56–57°/1 mm. n_D^{24} 1.4796.

Reaction of 2-chlorocyclohexanone (I) *with p-phenetylmagnesium bromide.* A solution of I (13.0 g., 0.10 mole) in ether (25 cc.) was added during half an hour to a Grignard reagent prepared from *p*-bromophenetole (30.5 g., 0.15 mole) and magnesium (3.6 g., 0.15 mole) in ether (100 cc.) with stirring and external cooling (ice and water). Stirring was then continued at room temperature (28°) for two more hours. By the next day a reddish-brown layer had separated at the bottom of the flask, and the mixture was decomposed with a concentrated aqueous solution of ammonium chloride and extracted with ether. The ethereal extract was washed with ammonium chloride solution, and water, then dried over sodium sulphate and concentrated on the water-bath (temperature not exceeding 50°) to give a light brown liquid. Small aliquots taken from this gave the following tests: (i) it turned dark on adding an ethanolic solution of 2,4-dinitrophenylhydrazine containing sulphuric acid and soon deposited the 2,4-dinitrophenylhydrazone of the rearranged ketone, 2-*p*-phenetylcyclohexanone; however, (ii) it did not form the semicarbazone of the same ketone at room temperature (semicarbazide-hydrochloride and sodium acetate in aqueous ethanol); (iii) on heating to approximately 100° it darkened rapidly, evolving hydrogen chloride. The main bulk of the product was distilled, giving *2-p-phenetylcyclohexanone* as a viscous yellow oil, b.p. 163–165°/0.5 mm. (11.2 g.), which deposited crystals in contact with chilled petroleum (50–70°). Recrystallization from the same solvent afforded clusters of colorless needles, m.p. 70–71°.

Anal. Calc'd for $C_{14}H_{18}O_2$: C, 77.0; H, 8.31.

Found: C, 77.2; H, 8.51.

The *2,4-dinitrophenylhydrazone* crystallized from ethanol in slender orange-colored needles, m.p. 158.5–160°.

Anal. Calc'd for $C_{20}H_{22}N_4O_5$: C, 60.3; H, 5.57; N, 14.1.

Found: C, 60.4; H, 5.77; N, 14.4.

Its *semicarbazone*, formed rapidly at room temperature, separated from ethanol in colorless prisms, m.p. 204–206°.

Anal. Calc'd for $C_{15}H_{21}N_3O_2$: C, 65.4; H, 7.69; N, 15.3.

Found: C, 65.3; H, 7.84; N, 15.0.

Reaction of I *with p-tolylmagnesium bromide.* Compound I (8 g., 0.061 mole) in ether (10 cc.) was added to a solution of *p*-tolylmagnesium bromide (0.092 mole) in ether (80 cc.) with stirring and cooling, and the reaction product was worked up the following day as previously described. The product on heating evolved hydrogen chloride, and on distillation gave *2-p-tolylcyclohexanone*, b.p. 126–130°/1 mm. (5.5 g.), n_D^{24} 1.5510, which crystallized on

trituration with petroleum ether (50–70°), and was obtained from this solvent in long thin needles, m.p. 50°.

Anal. Calc'd for $C_{13}H_{16}O$: C, 82.9; H, 8.57.

Found: C, 82.5; H, 8.56.

The *2,4-dinitrophenylhydrazone* separated from ethanol in orange straw-like crystals, m.p. 153°.

Anal. Calc'd for $C_{19}H_{20}N_4O_4$: C, 61.9; H, 5.47.

Found: C, 62.2; H, 5.65.

Reaction of I *with p-chlorophenylmagnesium bromide.* A solution of I (22 g., 0.16 mole) in ether (50 cc.) was added to *p*-chlorophenylmagnesium bromide (0.25 mole in 150 cc. of ether) during half an hour, at the end of which time the mixture had become a whitish paste, which was further stirred for two hours and worked up the following day as previously described. A light amorphous solid with a bluish fluorescence was present with the ethereal extract and this was removed by filtration. The ethereal extract was then concentrated and distilled, giving a pale yellow liquid b.p. 146–150°/2 mm. (19.0 g.), n_D^{28} 1.5620, which was mostly *1-p-chlorophenyl-2-chlorocyclohexanol*. Redistillation with a short Vigreux column afforded a colorless liquid, b.p. 112–113°/0.5 mm., n_D^{28} 1.5613, which however was contaminated with traces of the ketone *p*-2-chlorophenylcyclohexanone, and was not obtained analytically pure even after repeated distillations (Found: Cl, 28.0; 27.2%). A portion (3 g.) was therefore treated with Girard reagent P (1 g.) as described by Girard and Sandulesco (12). The non-ketonic fraction on evaporative distillation gave the pure product, b.p. 115° (Bath)/0.2 mm., n_D^{28} 1.5601.

Anal. Calc'd for $C_{12}H_{14}Cl_2O$: C, 58.8; H, 5.72; Cl, 28.95.

Found: C, 59.1; 59.1; H, 5.94; 5.83; Cl, 29.1.

It did not react with 2,4-dinitrophenylhydrazine.

The ketonic fraction, consisting of *2-p-chlorophenylcyclohexanone* was obtained in a very small yield in the form of an oil, and was characterized through its *2,4-dinitrophenylhydrazone* which crystallized in yellow-orange needles from ethanol, m.p. 154–156°.

Anal. Calc'd for $C_{18}H_{17}ClN_4O_4$: C, 55.6; H, 4.38; N, 14.4.

Found: C, 55.6; H, 4.44; N, 14.3.

Action of heat on 1-p-chlorophenyl-2-chlorocyclohexanol. A solution of the chlorohydrin (2 g.) in ethylbenzene (10 cc.) was heated under reflux for six hours. It was then diluted with ether and washed with water and then aqueous sodium bicarbonate, dried, and concentrated. Distillation *in vacuo* gave several fractions all of which showed the same refractive index as the starting material.

III (1.4 g.) was refluxed in *p*-cymene for six hours and worked up as before. Evaporative distillation at 1 mm. gave the following fractions (temperatures of bath in parenthesis): (i) 0.2 g. of a very mobile liquid (130°); (ii) 0.17 g. of a mobile oil (130–140°); (iii) 0.79 g. of a somewhat viscous liquid n_D^{28} 1.5637 (140–152°); (iv) 0.3 g. of a residue. (i) and (ii) gave a deep red precipitate with 2,4-dinitrophenylhydrazine; (iii) did not react.

Reaction of I *with m-chlorophenylmagnesium bromide.* The product from the reaction of I (9 g., 0.07 mole) and *m*-chlorophenylmagnesium bromide (0.17 mole) under the usual conditions gave on fractional distillation *1-m-chlorophenyl-2-chlorocyclohexanol* b.p. 139–140°/1 mm. (6.6 g.), n_D^{28} 1.5655. Further distillation yielded an analytically pure product, a colorless oil of n_D^{28} 1.5632.

Anal. Calc'd for $C_{12}H_{14}Cl_2O$: C, 58.8; H, 5.72; Cl, 28.95.

Found: C, 58.7; H, 5.76; Cl, 28.8.

The ketone IV, present in the previous preparation as a by-product, was not encountered here probably owing to the large excess of Grignard reagent used in this case.

A fluorescent amorphous solid (1.2 g.) was also encountered in this experiment. After purification by precipitation from a mixture of ethanol and benzene, it had m.p. 190–200° (cloudy) and a molecular weight of 703 (cryoscopic).

Action of heat on 1-m-chlorophenyl-2-chlorocyclohexanol. The chlorohydrin (2.7 g.) obtained above was heated with *p*-cymene under reflux for six hours and worked up in the

usual manner. Distillation gave two main fractions of n_D^{28} 1.5632 and 1.5635 respectively, and a small residue (ca. 0.5 g.) of n_D^{28} 1.5657.

Reaction of I with o-anisylmagnesium bromide. The product from I (19 g., 0.14 mole) and o-anisylmagnesium bromide (0.29 mole) gave on distillation the following fractions: (i) b.p. 40–130°/2 mm. (ca. 8 g.), (ii) b.p. 130–148°/2 mm. (ca. 4 g.), (iii) b.p. 148–150°/2 mm., n_D^{27} 1.5520 (16.2 g.), and (iv) a very viscous residue.

Fraction (iii), which crystallized overnight, was *1-o-anisyl-2-chlorocyclohexanol.* It was very soluble in light petroleum and in methanol and crystallized slowly from the latter in large colorless prisms, m.p. 75–77°.

Anal. Calc'd for $C_{13}H_{17}ClO_2$: C, 64.8; H, 7.10; Cl, 14.7.
    Found: C, 64.8; H, 7.14; Cl, 14.6.

It did not react with 2,4-dinitrophenylhydrazine nor with hydroxylamine. The residue (iv) on trituration with methanol and chilling deposited prismatic crystals, m.p. 111–120° (2.6 g.), which were soluble in benzene and cyclohexane, but only slightly so in ethanol. Repeated recrystallization from a mixture of benzene and ethanol, followed by cyclohexane afforded pure *1,2-di-o-anisylcyclohexanol* (VII), m.p. 130–131°.

Anal. Calc'd for $C_{20}H_{24}O_3$: C, 76.9; H, 7.74; Mol. wt., 312.
    Found: C, 76.9; H, 7.84; Mol. wt., 260 (cryoscopic).

It did not react with 2,4-dinitrophenylhydrazine nor give qualitative tests for halogen.

Action of heat on 1-o-anisyl-2-chlorocyclohexanol. The chlorohydrin (2 g.) was refluxed in ethylbenzene (10 cc.) for six hours, and was worked up as described previously. Distillation *in vacuo* gave several fractions all of which crystallized, and were found to be unchanged material.

The chlorohydrin (1 g.) was refluxed in p-cymene (5 cc.) for six hours, diluted with ether, and washed with water. The washings were acid to litmus and gave a positive test for chloride. Evaporative distillation at 1 mm. gave the following fractions (temperature of bath in parenthesis): (i) a mobile yellow liquid (110°); (ii) a pale yellow oil (140–150°); (iii) a viscous yellowish oil n_D^{27} 1.5570, 0.4 g. (140–150°) and (iv) a brown residue, ca. 0.2 g.) Fractions (i) and (ii) but not (iii) reacted rapidly with 2,4-dinitrophenylhydrazine to give a deep red precipitate.

Reaction of I with 1-naphthylmagnesium bromide. The product from I (19.8 g., 0.15 mole) and 1-naphthylmagnesium bromide (0.23 mole) was treated as before with Girard reagent P, and thereby separated into two fractions: (a) a ketonic fraction, which was 2-(1-naphthyl)cyclohexanone (IV). Recrystallized from light petroleum it had m.p. 85–87° (1.6 g.) and it formed a semicarbazone of m.p. 214° (decomp.). Orchin (11) reports m.p. 83.5–85° and 213–215° respectively. The *2,4-dinitrophenylhydrazone* which separated from ethanol in orange needles, melted at 137.5–139°:

Anal. Calc'd for $C_{22}H_{20}N_4O_4$: C, 65.3; H, 4.99.
    Found: C, 65.3; H, 5.02.

(b) A non ketonic fraction, which on distillation gave (i) naphthalene (ca. 5 g.) and (ii) *1-(1-naphthyl)-2-chlorocyclohexanol,* b.p. 171–173°/2 mm. (13 g.) a pale yellow viscous liquid which set to a glass. It was soluble in petroleum and in ethanol but attempts to induce crystallization failed. A portion was evaporatively distilled, b.p. 130° (Bath)/0.2 mm., giving a pale yellow glass.

Anal. Calc'd for $C_{16}H_{17}ClO$: C, 73.7; H, 6.53.
    Found: C, 74.0; H, 6.27.

Reaction of I with o-tolylmagnesium bromide. The product from I (12 g., 0.09 mole) and the Grignard reagent (0.22 mole) on fractional distillation gave as the main fraction a pale yellow liquid, b.p. 126–127°/2 mm. (6 g.), n_D^{24} 1.5444, which was mostly *2-o-tolylcyclohexanone.*

It readily formed the 2,4-dinitrophenylhydrazone and oxime of the ketone, but contained traces of halogen (probably the chlorohydrin) which could not be effectively removed by further distillations. Treatment with Girard's reagent P gave an analytically pure specimen: b.p. 110–112° (Bath)/0.7 mm., n_D^{24} 1.5424.

Anal. Calc'd for $C_{13}H_{16}O$: C, 82.9; H, 8.57.
    Found: C, 82.9; H, 8.73.

The *2,4-dinitrophenylhydrazone* crystallized from ethanol in yellow-orange needles, m.p. 145–147°.

Anal. Calc'd for $C_{19}H_{20}N_4O_4$: C, 61.9; H, 5.47.

Found: C, 61.6; H, 5.55.

The *oxime*, formed by refluxing the product with hydroxylamine hydrochloride in a mixture of absolute ethanol and pyridine, crystallized from ethanol in stout needles, m.p. 195°.

Anal. Calc'd for $C_{13}H_{17}NO$: N, 6.89. Found: N, 6.86.

SUMMARY

The reaction of 2-chlorocyclohexanone with aryl Grignard reagents (RMgX) has been shown to involve as the initial step an addition of the reagent to the carbonyl group. This is supported by the isolation in several cases of the chlorohydrins (III, R = *p*- and *m*-chlorophenyl, *o*-anisyl, and 1-naphthyl). In general, however, rearrangement may occur, the ultimate product of the reaction depending on the nature of R. With groups of low electropositivity (*p*- and *m*-chlorophenyl) the thermally stable Grignard products give unrearranged chlorohydrins (III). With groups of high electropositivity (*p*-phenetyl and *p*-tolyl) rearranged ketones (IV) are produced. *ortho*-Substituted groups (*o*-anisyl, *o*-tolyl, 1-naphthyl) do not behave in simple conformity with their polarity, the *o*-tolyl group leading unexpectedly to much rearrangement.

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