# SELF-CONDENSATION OF *p*-CHLOROPHENACYL CHLORIDE IN THE PRESENCE OF GRIGNARD REAGENT

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## ABSTRACT

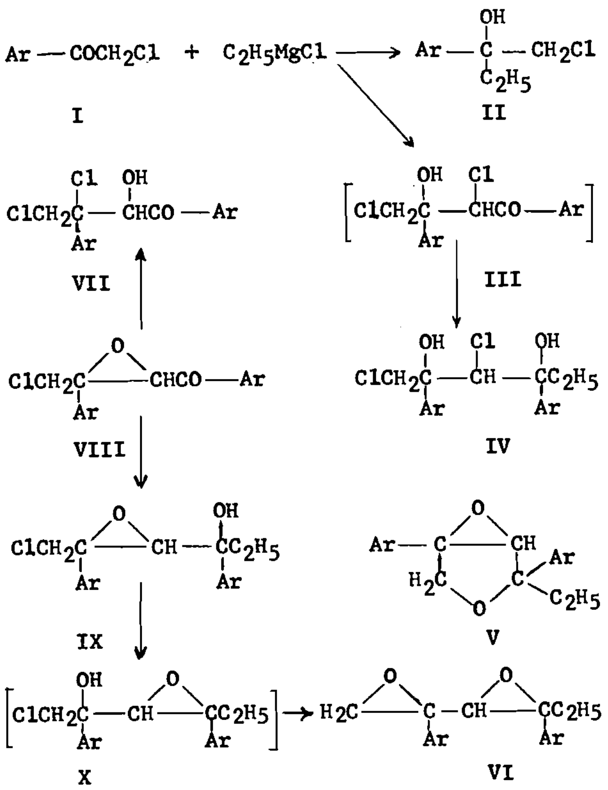
A crystalline by-product, formed in the reaction of *p*-chlorophenacyl chloride (I) with ethylmagnesium chloride, has been identified as 1,3-dichloro-2,4-bis(*p*-chlorophenyl)-2,4-hexanediol (IV). Its formation has been attributed to aldolization of I followed by reaction with Grignard reagent at the carbonyl function. The dehydrochlorination of IV yielded one of two possible compounds to which the diepoxide structure VI was assigned on the basis of n.m.r. spectra. The dehydrochlorinated product (VI) was synthesized from 1-chloro-2,3-epoxy-2,4-bis(*p*-chlorophenyl)-4-butanone (VIII) by treatment with ethylmagnesium chloride followed by reaction of the resulting epoxy alcohol IX with alcoholic alkali. It is suggested that the epoxy alcohol IX did not dehydrochlorinate directly to the 3,4-epoxytetrahydrofuran derivative V but instead rearranged first by epoxide alcohol transposition to X and then dehydrochlorinated to 1,2,3,4-diepoxy-2,4-bis(*p*-chlorophenyl)hexane (VI).

The condensation of *p*-chlorophenacyl chloride (I) with ethylmagnesium chloride produced the normal compound, 1-chloro-2-*p*-chlorophenyl-2-butanol (II) (1) as well as a crystalline by-product. The latter was formed in higher yield when the order of addition was reversed and the Grignard reagent was added to I. This investigation describes the properties and identification of this crystalline by-product and provides evidence for the mechanism of its formation.

The infrared spectrum of this compound showed the presence of hydroxyl groups and the absence of carbonyl groups. The OH band appeared at 3.0 $\mu$ (3 333 cm$^{-1}$), a shift from the normal which indicated hydrogen bonding. The reluctance of the compound to react with phenyl isocyanate or with acetic anhydride suggested the presence of tertiary hydroxyl groups. Of the possible modes of formation of the hydroxyl group from the carbonyl group, aldolization appeared to be the most likely. Analysis of the unknown compound provided the formula $(C_9H_9Cl_2O)_n$ with half the chlorine not removable and the other half easily removable by dehydrochlorination with cold methanolic or ethanolic potassium hydroxide. The dehydrochlorination was accompanied by loss of the hydroxyl groups, as evidenced by infrared spectra, and this indicated epoxide formation from a chlorohydrin.

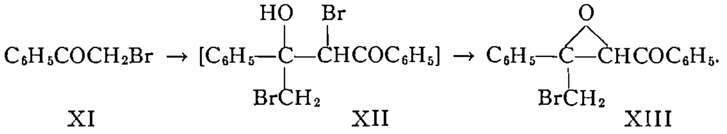
The molecular weight of the unknown compound could not be determined by the Rast method because it liberated hydrogen chloride on heating. The dehydrochlorinated compound, on the other hand, though sensitive to acids and bases, was more stable to heat and could be distilled *in vacuo*. Analysis and molecular weight determinations of the dehydrochlorinated compound gave the empirical formula $(C_9H_8ClO)_2$ from which the formula $(C_9H_9Cl_2O)_2$ could be deduced for the chlorohydrin. On the basis of the above evidence the structure IV was assigned to the by-product of the Grignard reaction and the structure V or VI to the dehydrochlorinated product. Degradation studies showed that IV could be cleaved by phosphorus pentoxide in boiling benzene to *p*-chlorophenacyl chloride (I) in 80% yield. This cleavage was attributed to retrograde aldolization.

The formation of 1,3-dichloro-2,4-bis(*p*-chlorophenyl)-2,4-hexanediol (IV) in the Grignard reaction can be explained by aldolization of two molecules of *p*-chlorophenacyl chloride (I) followed by attack of the intermediate hydroxyketone III by ethylmagnesium



Ar = p-chlorophenyl

chloride at the carbonyl function. A similar aldolization occurs in the Darzens reaction but the intermediate halohydrin cannot survive the strong alkaline conditions and is converted into an epoxide by intramolecular displacement. The Darzens reaction (2, 3, 4) is illustrated by the self-condensation of phenacyl bromide (XI), catalyzed by alcoholic sodium alkoxides, to form the two geometrical isomers of 4-bromo-1,3-diphenyl-2,3-epoxy-1-butanone (XIII) (5–8).



$$\underset{\text{XI}}{C_6H_5COCH_2Br} \rightarrow \underset{\text{XII}}{[C_6H_5\text{—}\overset{\text{HO}}{\underset{\text{BrCH}_2}{C}}\text{—}\overset{\text{Br}}{C}HCOC_6H_5]} \rightarrow \underset{\text{XIII}}{C_6H_5\text{—}\underset{\text{BrCH}_2}{C}\overset{\text{O}}{\text{—}}CHCOC_6H_5}.$$

The intermediate bromohydrin XII has never been isolated. However there is one report (3) of the isolation of a fluorohydrin. In this investigation the isolation of the chlorohydrin IV was made possible through the stabilization of the aldolization product III by reaction with ethylmagnesium chloride.

The structure of 1,3-dichloro-2,4-bis(*p*-chlorophenyl)-2,4-hexanediol (IV) was confirmed by synthesis of its dehydrochlorination product. The starting material was 4-chloro-2,3-epoxy-1,3-bis(*p*-chlorophenyl)-1-butanone (VIII) which was obtained from *p*-chlorophenacyl chloride (I) by the Darzens method using sodium ethylate as catalyst. The recent confirmation (5, 6) of the structure of the epoxyketone XIII obtained from phenacyl bromide under similar conditions validates the structure VIII. The first approach to IV failed because in the presence of hydrogen chloride the oxirane ring of VIII opened in the undesired direction to form 3,4-dichloro-2-hydroxy-1,3-bis(*p*-chlorophenyl)-1-butanone (VII) and not the required isomer III. That epoxyketone VIII yielded the secondary alcohol VII was established by infrared spectra and by the analogous behavior of 2,3-epoxy-1,3-diphenyl-1-butanone which yielded 3-chloro-2-hydroxy-1,3-diphenyl-1-butanone under similar conditions (9).

The second approach to IV consisted of the reaction of 4-chloro-2,3-epoxy-1,3-bis(*p*-chlorophenyl)-1-butanone (VIII) with ethylmagnesium bromide. In previously studied reactions of α,β-epoxyketones with Grignard reagents it had been observed that epoxyalcoholates are formed which undergo cleavage easily unless stabilized by very low temperatures or by introduction of an alpha substituent (10, 11). When the epoxyketone VIII was treated with ethylmagnesium bromide at −10° followed by decomposition with dilute acid, the epoxyalcohol IX was formed. Since epoxyalcohols are labile compounds (12) no attempt to purify IX was made. Instead, the crude IX was treated with methanolic potassium hydroxide to form a crystalline compound which proved to be identical in all respects with the dehydrochlorinated product V or VI obtained from the unknown compound IV by a similar treatment.

The structure of the compound IV was thus established as 1,3-dichloro-2,4-bis(*p*-chlorophenyl-2,4-hexanediol by the deductive reasoning based on the fact that IV dehydrochlorinated to V or VI, the compound which also resulted from the reaction sequence VIII → IX → V or VI. There remained the task of assigning a structure to the product of dehydrochlorination, V or VI. A casual examination of the reaction sequence VIII → IX → V or VI would favor the assignment of the structure V. Such a structure would not be unreasonable because the 3,4-epoxytetrahydrofuran system is not very strained and has been prepared in the unsubstituted form (14, 15) as well as in the sugar series (16, 17). However, it is necessary to consider the remarkable ease of rearrangement of α,β-epoxyalcohols analogous to IX by transposition of hydroxyl and epoxide (β-oxanol rearrangement) (13). Thus 2,3-epoxy-1-chloro-2,4-bis(*p*-chlorophenyl)-4-hexanol (IX) on treatment with alcoholic alkali could first rearrange by alcohol epoxide transposition to 3,4-epoxy-1-chloro-2,4-bis(*p*-chlorophenyl)-2-hexanol (X) and then dehydrochlorinate to 1,2,3,4-diepoxy-2,4-bis(*p*-chlorophenyl)hexane (VI). Nuclear magnetic resonance (n.m.r.) spectra studies favor the assignment of structure VI to the dehydrochlorinated product of IV and this supports the suggestion that the rearrangement of IX to X does occur before the dehydrochlorination to VI.

The n.m.r. spectra of VI (or V) and of two model compounds are shown in Fig. 1. The peaks for the protons of epoxide methylenes in the spectra of VI (or V) and 2-*p*-chlorophenyl-2-ethyloxirane (XV) are upfield of where one would normally expect to find such resonances. This upfield shift is quite typical of strained three-membered systems which are pseudoaromatic because of some delocalization of electrons. The methylene proton peaks as shown in the spectra of the tetrahydrofuran model compound XIV (14, 15) are downfield and are more typical of protons on carbons directly bonded to oxygen. The geminal methylene protons of the epoxide VI (5.5 c.p.s.) as well as those of the model epoxide compound XV (5.5 c.p.s.) show small coupling constants as compared to those of the tetrahydrofuran model compound XIV (11 c.p.s.). On the basis of this evidence the diepoxide structure VI and not the epoxytetrahydrofuran structure (V) is assigned to the dehydrochlorinated product of IV.

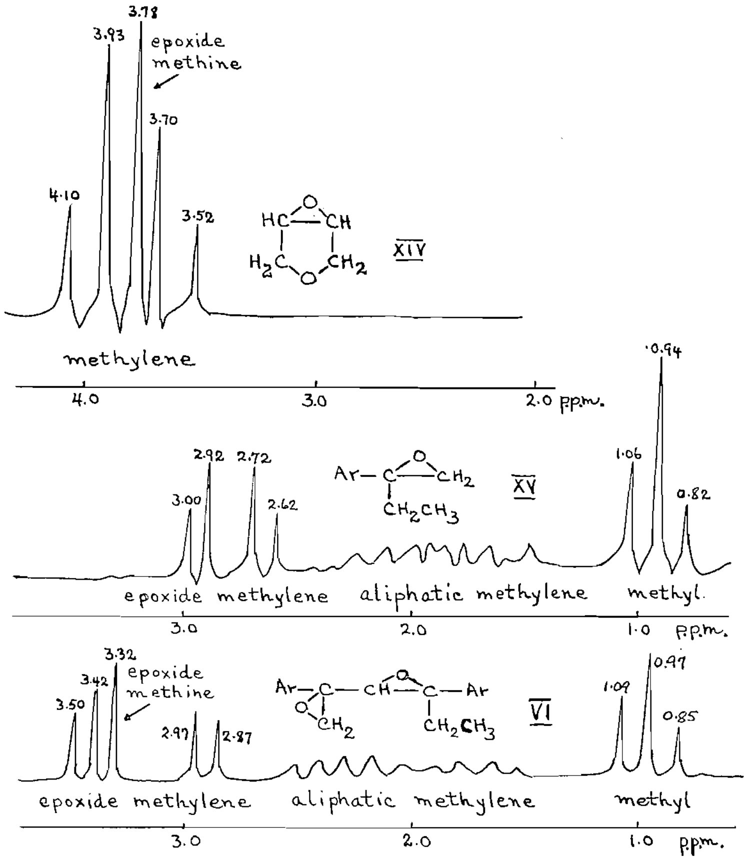


FIG. 1. Nuclear magnetic resonance spectra determined in deuterochloroform at 60 Mc referred to tetramethylsilane as standard.

## EXPERIMENTAL

### *1,3-Dichloro-2,4-bis(p-chlorophenyl)-2,4-hexanediol (IV) and 1-Chloro-2-p-chlorophenyl-2-butanol (II)*

A Grignard solution was prepared from magnesium turnings (30 g), dry ether (600 ml), and ethyl chloride (100 g) and decanted from the excess magnesium. Three quarters of this solution was added dropwise over 6 h to a cooled and stirred solution of *p*-chlorophenacyl chloride (I) (150 g) in dry benzene (850 ml). The temperature was kept at 10° by cooling on an ice bath. The reaction mixture was allowed to stand overnight and then treated at 10–15° with the other quarter of the Grignard solution. The resulting solution was decomposed with a cold solution of concentrated hydrochloric acid (120 ml) in water (200 ml) at 10–15°. The organic layer was separated, washed with water, concentrated *in vacuo* to about 200 ml, and allowed to cool. The white precipitate was removed by filtration, washed, and dried. The yield of IV from two crops was 46 g (28%), m.p. 180–182° with decomposition. Crystallization from benzene yielded white prisms melting at 185–186° with decomposition.

Anal. Calcd. for $C_{18}H_{18}Cl_4O_2$: C, 52.94; H, 4.41; Cl, 34.80. Found: C, 52.51, 52.82; H, 4.47, 4.63; Cl, 35.89.

The infrared spectrum of this compound showed the OH band at 3.0 $\mu$ (3 333 $cm^{-1}$). This is a shift from the free hydroxyl range and indicates hydrogen bonding.

The mother liquors from the above crystallizations were combined, taken to dryness *in vacuo*, and the residue distilled. The distillate of 1-chloro-2-*p*-chlorophenyl-2-butanol (II) (1) was a colorless liquid boiling at 92–95° (0.5 mm); $n_D^{27}$ = 1.5465. The yield of II was 53 g or 30%.

Anal. Calcd. for $C_{10}H_{12}Cl_2O$: C, 54.80; H, 5.48. Found: C, 54.81, 55.00; H, 5.29, 5.40.

### *1,2,3,4-Diepoxy-2,4-bis(p-chlorophenyl)hexane (VI)*

*(a) From 1,3-Dichloro-2,4-bis(p-chlorophenyl)-2,4-hexanediol (IV)*

To a solution of 1,3-dichloro-2,4-bis(*p*-chlorophenyl)-2,4-hexanediol (IV) (25 g) in methanol (500 ml) at 30° was added a solution of potassium hydroxide (10 g) in methanol (100 ml). Precipitation soon began.

After allowing the reaction mixture to stand for 3 h the precipitate was removed by filtration, washed well with water to wash out the potassium chloride, and dried, yielding 15 g of white crystals. The methanol filtrate on concentration gave a second crop weighing 2.5 g. The total yield of VI was 17.5 g or 85%, melting at 132–134°. Crystallization from methanol yielded sparkling white prisms melting at 133–134°.

Anal. Calcd. for $C_{18}H_{16}Cl_2O_2$: C, 64.48; H, 4.77; Cl, 21.19. Found: C, 64.70, 65.04; H, 4.86, 4.83; Cl, 21.27, 21.75.

### *(b) From 1-Chloro-2,3-epoxy-2,4-bis(p-chlorophenyl)-4-hexanol (IX)*

To a solution of 1-chloro-2,3-epoxy-2,4-bis(*p*-chlorophenyl)-4-hexanol (IX) (see below) (2 g) in methanol (25 ml) was added a solution of potassium hydroxide (0.5 g) in methanol (5 ml). The resulting solution was allowed to stand overnight. The white crystals (1.2 g or 75%) were removed by filtration, washed with water and with methanol, and dried, m.p. 132–134°. Crystallization from methanol yielded white prisms melting at 132–134° alone or in admixture with the compound obtained in (*a*). The infrared spectra of the compounds obtained in (*a*) and (*b*) were identical. This compound could be easily distilled at 0.5 mm pressure at a bath temperature of 180°.

Anal. Calcd. for $C_{18}H_{16}Cl_2O_2$: C, 64.48; H, 4.77. Found: C, 64.83, 65.03; H, 4.63, 4.67.

### *1-Chloro-2,3-epoxy-2,4-bis(p-chlorophenyl)-4-butanone (VIII)*

To a stirred solution of *p*-chlorophenacyl chloride (I) (40 g) in methanol (1 400 ml) cooled at 5 to 10° was added dropwise a solution of sodium (3 g) in methanol (150 ml) over 0.5 h. The resulting yellow solution was stirred at 10° for 2 h and then allowed to stand overnight. It was concentrated *in vacuo* to 500 ml and then poured into water. The sticky solid was extracted with benzene, washed with water, and the solvent removed. The residue on crystallization from methanol yielded white prisms (15 g or 42%), melting at 134–136°.

Anal. Calcd. for $C_{16}H_{11}Cl_3O_2$: C, 56.22; H, 3.22. Found: C, 56.62, 56.57; H, 3.21, 3.49.

The infrared spectrum of this compound showed a strong carbonyl band at 5.9 $\mu$.

### *1-Chloro-2,3-epoxy-2,4-bis(p-chlorophenyl)-4-hexanol (IX)*

A Grignard solution prepared from magnesium turnings (2 g), dry ether (100 ml), and ethyl chloride (6 g) was added dropwise over 0.5 h to a cooled and stirred solution of 2,4-bis(*p*-chlorophenyl)-1-chloro-2,3-epoxy-4-butanone (VIII) (4 g) in dry ether (100 ml). The temperature was kept at −8 to −10° by cooling on an ice–salt bath. The reaction mixture was stirred at −10° for 0.5 h and then decomposed at −10° first with wet ether and then with 1 *N* hydrochloric acid. The ether layer was washed with water and then the solvent was removed, the last traces *in vacuo*. The residual viscous liquid (4 g or 93%) would not crystallize.

Anal. Calcd. for $C_{18}H_{17}Cl_3O_2$: C, 58.14; H, 4.58. Found: C, 58.39, 58.44; H, 4.97, 4.82.

The infrared spectrum of this compound showed a strong band at 2.8 $\mu$.

### *1,2,3,4-Diepoxy-2,4-bis(p-chlorophenyl)pentane*

This was prepared in 1% yield by the condensation of *p*-chlorophenacyl chloride (I) with methylmagnesium bromide followed by treatment of the crude oily product with methanolic potassium hydroxide, following the method used for the preparation of 1,2,3,4-diepoxy-2,4-bis(*p*-chlorophenyl)hexane (VI) above. The intermediate 1,3-dichloro-2,4-bis(*p*-chlorophenyl)-2,4-pentanediol could not be isolated in pure form. The crude 1,2,3,4-diepoxy-2,4-bis(*p*-chlorophenyl)pentane distilled at 160–200° (0.5 mm) and the distillate when crystallized from methanol–benzene yielded white prisms melting at 153–154°.

Anal. Calcd. for $C_{17}H_{14}Cl_2O_2$: C, 63.55; H, 4.36; Cl, 22.1. Found: C, 63.46; H, 4.07; Cl, 23.82.

### *Degradation of 1,3-Dichloro-2,4-bis(p-chlorophenyl)-2,4-hexanediol (IV) to p-Chlorophenacyl Chloride (I)*

To a stirred solution of 1,3-dichloro-2,4-bis(*p*-chlorophenyl)2,4-hexanediol (IV) (10 g) in dry benzene (500 ml) was added phosphorus pentoxide (25 g) and the resulting mixture was stirred and heated under reflux for 2 h. The benzene solution was decanted from the dark residue, washed with cold water, and the solvent removed. The residual semisolid was crystallized from carbon tetrachloride – petroleum ether (30–60°), yielding white prisms (3.5 g or 80%) melting at 99–100° alone or in admixture with *p*-chlorophenacyl chloride.

### *1,2-Dichloro-2,4-bis(p-chlorophenyl)-3-hydroxy-4-butanone (VII)*

Into a solution of 1-chloro-2,3-epoxy-2,4-bis(*p*-chlorophenyl)-4-butanone (VIII) (10 g) in glacial acetic acid (150 ml) at 30° was passed hydrogen chloride until saturated and the solution was allowed to stand overnight. The solvent was removed *in vacuo* below 40° and the residue was crystallized from benzene – petroleum ether (30–60°). The white prisms (6.0 g or 55%) melted at 133–134° with decomposition. One recrystallization from the same solvent raised the melting point to 136–137° with decomposition.

Anal. Calcd. for $C_{16}H_{12}Cl_4O_2$: C, 50.79; H, 3.17. Found: C, 50.96, 50.68; H, 3.46, 3.29.

The infrared spectrum of this compound showed the ketone band at 5.95 $\mu$ and the secondary hydroxyl bands at 7.85 and 9.1 $\mu$. This compound when treated with phosphorus pentoxide in benzene did not yield *p*-chlorophenacyl chloride. Also it did not react with ethyl magnesium bromide at 5°; at room temperature it reacted to give an intractable product.

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