2-p-CHLOROPHENYLALKANOLS

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ABSTRACT

2-p-Chlorophenyl-1-butanol (V) has been synthesized by the condensation of p-chlorophenacyl chloride (I) with ethylmagnesium chloride and dehydrochlorination of the resulting 1-chloro-2-p-chlorophenyl-2-butanol (II) to 2-ethyl-2-p-chlorophenyloxirane (III), followed by reduction. It has been discovered that reduction of III with lithium aluminium hydride yielded the tertiary alcohol, 2-p-chlorophenyl-2-butanol (IV), while reduction of III with aluminium hydride yielded the primary alcohol V. The two alcohols IV and V were also prepared by unambiguous methods. Attempts to synthesize the higher homologues of the alcohol V were not very successful.

This paper describes the synthesis of some 2-p-chlorophenylalkanols which were required for evaluation as agricultural chemicals. The method devised for the synthesis of 2-p-chlorophenyl-1-butanol (V) comprised the condensation of p-chlorophenacyl chloride (I) with ethylmagnesium chloride, dehydrochlorination of the resulting 1-chloro-2-pchlorophenyl-2-butanol (II) to 2-ethyl-2-p-chlorophenyl oxirane (III), and reduction of the oxirane (III) to V. In the condensation of ethylmagnesium chloride with I the order of addition was important. Best results were obtained when p-chlorophenacyl chloride (I) was added to the Grignard reagent. The reverse addition produced considerable amounts of a second component, a study of which is reported in another communication (1).

Theoretically the hydrogenation of the oxirane III could follow two reaction paths, one leading to the tertiary alcohol, 2-p-chlorophenyl-2-butanol (IV) and the other to the primary alcohol, 2-p-chlorophenyl-1-butanol (V). Actually it was found that catalytic hydrogenation of the oxirane III in the presence of Raney nickel catalyst gave a complex mixture from which the primary alcohol V was isolated in 30% yield. On the other hand, reduction with lithium aluminium hydride produced the tertiary alcohol IV in 80% yield. Finally reduction with a mixture of lithium aluminium hydride gave the primary alcohol V in 80% yield. These results are in accord with those of Eliel and co-workers (2, 3) who have shown that reduction of 2,2,3-triphenyloxirane with lithium aluminium hydride alone led to diphenyl-benzylcarbinol by attack at the least substituted carbon of the epoxide, whereas reduction with aluminium hydride produced phenylbenzhydrylcarbinol through ring opening and attack of hydride at the tertiary carbon atom.

The two reference compounds required in this investigation were synthesized by unambiguous methods. The tertiary alcohol IV was obtained through the condensation of p-chloroacetophenone with ethylmagnesium bromide. The primary alcohol, 2-p-chlorophenyl-1-butanol (V) was synthesized from p-chlorobenzyl cyanide by a number of steps which included ethylation with ethyl bromide in the presence of quaternary ammonium base, hydrolysis of the resulting 2-p-chlorophenylbutyronitrile (VII, R = ethyl) (4) to the acid VIII (R = ethyl), and reduction of the ester VI to V.

Attempts to prepare higher homologues of 2-p-chlorophenyl-1-butanol (V) by the Grignard method were not successful because alkylmagnesium halides higher than ethyl

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reacted with I to form complex mixtures. The abnormal behavior of long- or branchedchain alkylmagnesium halides in reactions with ketones has been observed by other workers (5–7). The cyanide method also found limitation because long chain substituted p-chlorobenzyl cyanides (VII, R = n-dodecyl and hexadecyl) could not be hydrolyzed to the corresponding acids even on prolonged heating with aqueous-alcoholic alkali. However 2-p-chlorophenylhexanoic acid (VIII, R = n-butyl) was obtained from the cyanide VII, (R = n-butyl) by prolonged hydrolysis. The reduction of its ester yielded 2-p-chlorophenyl hexanol.

EXPERIMENTAL

1-Chloro-2-p-chlorophenyl-2-butanol (II)

To a Grignard solution prepared from magnesium (10 g), dry ether (250 ml), and ethyl chloride (30 g) was added dropwise with stirring a solution of *p*-chlorophenacyl chloride (1) (50 g) in dry benzene (300 ml) over about 0.5 h. The temperature was kept at 10–15° by cooling. The reaction mixture was stirred for 5 h and then decomposed with dilute hydrochloric acid. The organic layer was separated, washed with water, and the solvent removed. The residue distilled at 92–95° (0.5 mm); $n_{\rm D}^{23} = 1.5472$. The yield was 50 g or 86%.

Anal. Calcd. for C10H12Cl2O: C, 54.80; H, 5.48. Found: C, 54.81, 55.00; H, 5.29, 5.40.

In another experiment when the Grignard reagent was added to the p-chlorophenacyl chloride the yield of II dropped and 1,3-dichloro-2,4-bis(p-chlorophenyl)-2,4-hexanediol formed (1).

1-Chloro-2-p-chlorophenyl-2-propanol

This was prepared in 30% yield as above from *p*-chlorophenacyl chloride (I) and methylmagnesium bromide. It boiled at 92–95° (1 mm); $n_D^{22} = 1.5576$.

Anal. Calcd. for C9H10Cl2O: C, 52.68; H, 4.88; Cl, 34.61. Found: C, 52.85, 52.96; H, 4.82, 4.87; Cl, 34.35, 34.64

2-Ethyl-2-p-chlorophenyloxirane (III)

To a stirred solution of 1-chloro-2-p-chlorophenyl-2-butanol (II) (62 g) in methanol (300 ml) was added dropwise at 15° a solution of potassium hydroxide (21 g) in methanol (150 ml). The reaction mixture was stirred 1 h at 15° and 1 h at room temperature. The solution was decanted from the precipitated potassium chloride, the solvent was removed, and the residue combined with the potassium chloride was treated with water. The precipitated oil was extracted with benzene, the extract washed with water, and the solvent removed. The residue distilled at $110-112^{\circ}$ (11 mm) yielding 44 g or 88% of a colorless liquid; $n_{\rm D}^{20} = 1.5315$.

Anal. Calcd. for C10H11CIO: C, 65.74; H, 6.03. Found: C, 65.94, 66.10; H, 5.93, 6.11.

2-Methyl-2-p-chlorophenyloxirane

This was prepared in 85% yield by the dehydrochlorination of 1-chloro-2-*p*-chlorophenyl-2-propanol as above, b.p. (11 mm) 106-108°; $n_D^{22} = 1.5390$.

Anal. Calcd. for C₉H₉ClO: C, 64.09; H, 5.34; Cl, 21.04. Found: C, 63.72, 64.06; H, 5.37, 5.47; Cl, 21.04, 21.18

2-p-Chlorophenyl-1-butanol (V)

(a) By Catalytic Reduction of 2-p-Chlorophenyl-2-ethyloxirane

A mixture of 2-p-chlorophenyl-2-ethyloxirane (III) (30 g), methanol (100 ml), anhydrous sodium carbonate (0.5 g), and Raney nickel catalyst (ca. 0.5 g) was shaken under 50 lb of hydrogen pressure until there was a drop in pressure of 12 lb (ca. 5 h). The catalyst was filtered off and the filtrate distilled. The fraction distilling at 134-137° (11 nm) weighed 10 g (30%); $p_{D}^{21} = 1.5372$. This was identical with 2-p-chlorophenyl-1-butanol (V) obtained by an unambiguous method (see (c)).

Anal. Calcd. for C10H13CIO: C, 65.04; H, 7.05. Found: C, 64.87, 64.80; H, 7.02, 7.12.

(b) By reduction of 2-p-Chlorophenyl-2-ethyloxirane (III) with Aluminium Hydride

To a stirred suspension of pulverized lithium aluminium hydride (5 g) in dry ether (100 ml) was added, with cooling, aluminium chloride (7 g). This reaction mixture was stirred for about 15 min and then a solution of 2-p-chlorophenyl-2-ethyloxirane (III) (15 g) in dry ether (50 ml) was added dropwise with cooling on a water bath. After heating under reflux for 0.5 h the reaction mixture was cooled, and decomposed first with wet ether and then with dilute acid. The ether layer was washed, the solvent removed, and the residue distilled. The main fraction boiled at 140–142° (13 mm) yielding a colorless liquid (12 g or 80%): $n_D^{25} = 1.5350$, which gave an infrared spectrum identical with that given by the product of catalytic hydrogenation (a).

(c) By Reduction of Ethyl 2-p-Chlorophenylbutyrate (VI) with Lithium Aluminium Hydride

To a stirred suspension of pulverized lithium aluminium hydride (3 g) in dry ether (100 ml) was added dropwise a solution of ethyl 2-p-chlorophenylbutyrate (VI) (prepared from the nitrile VII (R = ethyl) by alkaline hydrolysis followed by esterification (4)) (12 g) in dry ether over about 15 min. The reaction mixture was heated under reflux for 30 min, cooled, and decomposed by addition of wet ether followed by dilute hydrochloric acid. The ether solution was washed with water, the solvent removed, and the residue distilled, b.p. 140-141° (13 mm); $n_{\rm D}^{z_3} = 1.5342$. The yield of colorless liquid was 9.5 g or 85%. The infrared spectrum of this alcohol was identical with that of the alcohol obtained in (a).

2-p-Chlorophenyl-2-butanol (IV)

(a) By reduction of 2-p-Chlorophenyl-2-ethyloxirane (III)

To a suspension of powdered lithium aluminium hydride (6 g) in dry ether (150 ml) was added dropwise with stirring a solution of 2-p-chlorophenyl-2-ethyloxirane (III) (15 g) in dry ether (50 ml). After heating under reflux for 1 h the reaction mixture was decomposed in the usual manner and the product distilled. It boiled at $120-121^{\circ}$ (10 mm) and weighed 12 g (80%); $n_D^{25} = 1.5330$. That this was the tertiary alcohol IV and not the primary alcohol V was shown by comparison of its properties and infrared spectra with those of IV prepared unambiguously (see (b) below).

(b) By the Reaction of Ethylmagnesium Bromide with p-Chloroacetophenone

To a Grignard solution prepared from magnesium (16 g), ethyl bromide (25 g), and dry ether (200 ml) was added dropwise with stirring and cooling a solution of p-chloroacetophenone (30 g) in dry ether (50 ml). The reaction mixture was decomposed with dilute sulfuric acid, the ether layer washed with water, and the solvent removed. The residue distilled at $120-121^{\circ}$ (10 mm); $n_D^{25} = 1.5318$. The yield was 31 g or 80%. Anal. Calcd. for C10H13ClO: C, 65.04; H, 7.05. Found: C, 64.90, 65.08; H, 7.30, 7.08.

2-p-Chlorophenylcapronitrile (VII, R = n-Butyl)

To a stirred solution of potassium hydroxide (100 g) in water (60 ml) was added benzyl triethylammonium chloride (5 g) followed by p-chlorobenzyl cyanide (100 g). This was cooled to 10° and n-butyl chloride (90 g) was added. The resulting reaction mixture was stirred at 12 to 15° for 24 h, diluted with water, and extracted

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with benzene. The benzene extract was washed with water, the solvent removed, and the residue distilled. The distillate which boiled at $142-170^{\circ}$ (11 mm) was dissolved in a solution of sodium (7 g) in methanol (200 ml) and treated with benzaldehyde (40 ml). After standing overnight the reaction mixture was filtered to separate the precipitated α -p-chlorophenyl- β -phenylacrylonitrile. The filtrate was diluted with water and extracted with benzene; the benzene solution was washed with water, with aqueous sodium bisulfite, and with water. The solvent was removed and the residue distilled yielding 42 g (32%) of nitrile boiling at 158-164° (12 mm); $n_{\rm D}^{22} = 1.5192$.

Anal. Calcd. for C12H14NC1: C, 69.40; H, 6.75. Found: C, 69.03, 69.32; H, 6.92, 6.78.

The known compounds 2-phenylbutyronitrile (8, 9) (54%), 2-p-chlorophenylbutyronitrile (4) (60%), and 2-phenylcapronitrile (10) (41%) were prepared in the same manner as was VII (R = n-butyl).

α -n-Dodecyl-p-chlorobenzyl Cyanide (VII, R = n-Dodecyl)

This was prepared in 56% yield by the alkylation of *p*-chlorobenzyl cyanide with *n*-dodecyl bromid as above. The crude product distilled at 180-185° (0.5 mm); $n_{D}^{27} = 1.4959$.

Anal. Calcd. for C20H30ClN: C, 75.12; H, 9.39. Found: C, 75.30, 74.94; H, 9.09, 9.17.

The residue from the distillation of the above product was crystallized from benzene-methanol to yield (15%) white prisms of α, α -di-*n*-dodecyl-*p*-chlorobenzyl cyanide melting at 56-58°.

Anal. Calcd. for C32H54CIN: C, 78.77; H, 11.08. Found: C, 78.20, 78.79; H, 10.79, 10.99.

α -n-Hexadecyl-p-chlorobenzyl Cyanide (VII, R = n-Hexadecyl)

This was prepared in 49% yield by the alkylation of *p*-chlorobenzyl cyanide with *n*-hexadecyl bromide as above. It distilled at 211-215° (0.5 mm) and the distillate on crystallization from petroleum ether (30-60°) melted at 38-40°.

Anal. Calcd. for C24H38ClN: C, 76.70; H, 10.12. Found: C, 76.53, 76.45; H, 9.91, 9.90.

The residue from the above distillation on crystallization from methanol-benzene yielded (12%) almost white prisms of α, α -di-*n*-hexadecyl-*p*-chlorobenzyl cyanide melting at 56-58°.

Anal. Calcd. for C40H70ClN: C, 80.07; H, 11.68. Found: C, 79.63, 80.19; H, 11.54, 11.42.

2-p-Chlorophenylcaproic Acid (VIII, R = n-Butyl)

To a solution of sodium hydroxide (20 g) in water (200 ml) and ethanol (15 ml) was added 2-p-chlorophenylcapronitrile (VII, R = n-butyl) (30 g), and the reaction mixture was heated under reflux for 5 days. The resulting solution was acidified and extracted with benzene; the benzene solution was washed with water and the solvent removed. The residue distilled at 135–137° (0.5 mm) as a colorless liquid (29 g or 90%) which soon solidified; $n_{D^{25}} = 1.5215$. A small portion when crystallized from petroleum ether (30-60°) yielded white prisms which melted at 63-65°.

Anal. Calcd. for C12H15ClO2: C, 63.72; H, 6.64. Found: C, 63.80, 63.95; H, 6.94, 6.69.

2-p-Chlorophenylmyristic Acid Amide

When α -n-dodecyl-p-chlorobenzyl cyanide (VII, R = n-dodecyl) was subjected to alkaline hydrolysis as above, no acid was obtained. Instead the amide was formed. It crystallized from methanol as white prisms melting at 90-92°.

Anal. Calcd. for C20H32NClO: C, 71.11; H, 9.48. Found: C, 71.31, 71.37; H, 9.31, 9.25.

2-Phenyl-1-hexanol

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The ethyl ester of 2-phenylcaproic acid (prepared from 2-phenylcapronitrile, but not purified) (10, 11) was reduced with lithium aluminium hydride to form a colorless liquid boiling at $134-135^{\circ}$ (11 mm); $n_{D^{26}} =$ 1.5085. The yield was 90%.

Anal. Calcd. for C₁₂H₁₈O: C, 80.90; H, 10.11. Found: C, 80.23, 80.36; H, 9.68, 9.67.

2-p-Chlorophenyl-1-hexanol

This was prepared in 80% yield by the reduction of ethyl 2-p-chlorophenylcaproate with lithium aluminium hydride. It boiled at 158–160° (11 mm); $n_{D^{22}} = 1.5235$.

Anal. Calcd. for C12H17CIO: C, 67.76; H, 8.00. Found: C, 68.01, 68.13; H, 7.98, 8.00.

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