Summary

1. When Adams catalyst, activated by ferrous chloride, is used, the deuteration of acetone is accompanied by some hydrogen–deuterium exchange. The product here obtained was a mixture containing 55% of 2-deuteropropanol-2.

2. The rate of chromic acid oxidation of this product was only 52% of that of ordinary isopropyl alcohol. On the basis of this result, it is calculated that the rate of chromic acid oxidation of pure 2-deuteropropanol-2 should be about one-sixth that of pure isopropyl alcohol.

3. The lower rate of oxidation of the 2-deutero compound (which arises from differences between the zero point energies of the C–H and C–D bonds) proves that the secondary hydrogen (or deuterium) in isopropyl alcohol is removed in the rate controlling step of the chromic acid oxidation.

CHICAGO, ILLINOIS RECEIVED MAY 13, 1948

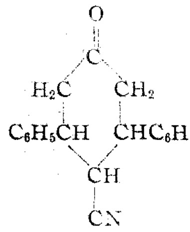
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

1-Cyano-2,6-diphenyl-4-hydroxycyclohexane and Some Related Compounds[1]

BY C. S. MARVEL AND ALLEN C. MOORE[2]

1-Cyano-2,6-diphenyl-4-hydroxycyclohexane (VI) was needed for another synthetic problem and it seemed probable that it could be produced readily by the addition of ethyl cyanoacetate to dibenzalacetone followed by hydrolysis, decarboxylation and reduction.

Kohler and Helmkamp[3] have prepared 1-cyano-2,6-diphenyl-4-cyclohexanone (I) by the addition of methyl cyanoacetate to dibenzalacetone followed by hydrolysis and decarboxylation of the addition product (II, R = CH_3). In our work the addition of ethyl cyanoacetate to dibenzalacetone ran smoothly in the presence of sodium ethoxide to give an 88% yield of the cyclic cyanoester (II R = C_2H_5). Difficulty was experienced in hydrolysis of the ethyl ester although the methyl ester had not been difficult to hydrolyze.[3] It seemed probable that reduction of the carbonyl group would stabilize the cyclohexane ring so no reversal of the Michael reaction would occur under the conditions of alkaline hydrolysis. Accordingly, the keto ester (II, R = C_2H_5) was reduced by the Meerwein–Ponndorf–Verley method.[4] This reduction did not give the simple hydroxy compound but two other products. One was crystalline and proved to be a lactone (III). The other was a noncrystalline polyester (IV). The formation of lactones in this reaction is not unusual.[4] The lactone (III) was undoubtedly formed from the hydroxy ester intermediate with the *cis*-configuration for these groups and the polyester therefore was probably derived from the *trans*-isomer. Hydrolysis of this glassy material gave a 63% yield of the free acid (V) which did not readily form a lactone and this further confirms its *trans*-structure with respect to hydroxyl and carboxyl groups.



I

When the cyanolactone (III) was refluxed for three hours with 40% aqueous sodium hydroxide, the lactone ring was opened and decarboxylation occurred, giving an 80% yield of the hydroxy nitrile (VI). Decarboxylation of the free acid (V) also gave the hydroxynitrile (VI), in 50% yield. By continuing the alkaline hydrolysis of the cyanolactone for a total of thirty-one hours, there was obtained a 94% yield of 2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic acid (VII).

It became evident, from examination of the hydroxy acid (VII) derived from the hydroxynitrile (VI), that the acid had the *cis*-configuration. Thus, the hydroxy acid formed a second lactone (VIII) with ease, in 79% yield, when heated at its melting point. The action of such reagents as acetic anhydride, acetyl chloride and *p*-toluenesulfonyl chloride also brought about lactone formation. By contrast, the strictly analogous *trans*-4-hydroxycyclohexane-1-carboxylic acid prepared by Perkin[5] showed no tendency to yield a lactone when distilled, or when treated with hot 25% sulfuric acid.

When it is considered that the hydroxyl and carboxyl groups of the precursor of the cyanolactone (III) must have been *cis* with respect to one another, it follows that the nitrile and hydroxyl groups must have been in the *trans* configuration originally. It is clear then, that an inversion must have occurred to give a product (VII) of *cis* configuration. This inversion might have occurred during the opening of the lactone ring,[6,7] during

---

[1] This investigation was carried out under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the Government Synthetic Rubber Program.

[2] Present address: Research Laboratories, Parke, Davis and Co., Detroit 32, Michigan.

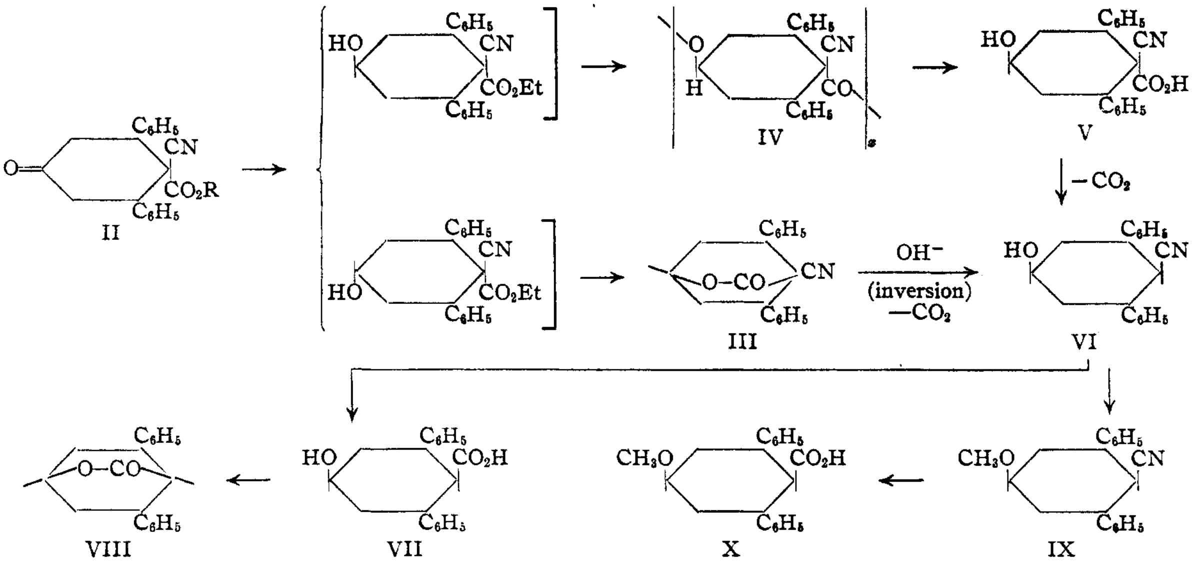
[3] Kohler and Helmkamp, THIS JOURNAL, **46**, 1018 (1924).

[4] Wilds, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 178 (1944).

[5] Perkin, *J. Chem. Soc.*, **85**, 416 (1904).

[6] Olson and Miller, THIS JOURNAL, **60**, 2687 (1938).

[7] Kohler and Jansen, *ibid.*, **60**, 2142 (1938).



decarboxylation, or during hydrolysis of the nitrile group. An exact interpretation of the site of inversion does not appear to be possible on the basis of the present facts since the configuration of the phenyl groups with respect to one another and with respect to the nitrile is not definitely known.

If one assumes, however, that the most plausible form of II is one in which the two phenyl groups and the nitrile are *cis* with respect to one another, then an inversion at carbon 4 during hydrolysis of the lactone (III) would serve to explain the foregoing data. This would, of course, necessitate the anomalous assumption that the alcohol C–O bond must have been broken, instead of the ester C–O bond.

If, on the other hand, one assumes that no inversion occurred at carbon 4, it becomes more difficult to explain why the same hydroxy nitrile (VI) was obtained by decarboxylation of the hydroxy acid (V) and the lactone (III).

Under the drastic alkaline conditions used to effect hydrolysis and decarboxylation of the lactone (III), racemization of the nitrile group of the hydroxy nitrile (VI) might be anticipated. That this clearly did not occur is probably best explained by the assumption that the two phenyl groups being in *cis* configuration hindered free approach to one side of the cyclohexane ring. Hence, in the event that an intermediate imino tautomer formed after the loss of carbon dioxide by the initial hydrolysis product of the lactone (III), the shift of the proton would probably be restricted so that retention or inversion rather than racemization would be favored.

Methylation of the hydroxynitrile (VI) was brought about by a modification of Purdie's technique for alkylating sugars,[8] in which benzene was substituted for the usual alcoholic solvent. A yield of 66% of 1-cyano-2,6-diphenyl-4-methoxycyclohexane (IX) was thus obtained. When this methoxynitrile was subjected to the same conditions used previously to hydrolyze the hydroxynitrile, no reaction occurred. Hot 50% sulfuric acid also failed to bring about a reaction, yet when the strength was increased to 75%, the hot acid appeared to cause extensive decomposition and nothing could be isolated from the mixture. Similar results were obtained with cold concentrated sulfuric acid. By refluxing the methoxynitrile (IX) for two days with saturated alcoholic potassium hydroxide, it was eventually possible to isolate a very small yield of 2,6-diphenyl-4-methoxycyclohexane-1-carboxylic acid (X). This greatly increased stability of the nitrile group following methylation of the hydroxyl is very difficult to explain since there appears to be no reason to assume that an increase in hindrance of the nitrile should occur.

The *p*-toluenesulfonic ester of the hydroxynitrile (VI) was prepared in 84% yield by modification of a procedure used previously for preparing cholesteryl *p*-toluenesulfonate.[9] This ester appeared to be completely inert in the presence of boiling methanol[10] which would have been expected to bring about ether formation. The *p*-toluenesulfonate ester did react when it was refluxed in alcoholic solution with sodium methoxide to produce a small yield of Δ^1- and/or Δ^2-1-cyano-2,6-diphenylcyclohexene.

Acetylation of the hydroxynitrile gave an 85% yield of 4-acetoxy-1-cyano-2,6-diphenylcyclohexane which, oddly enough, melted in the same range, 140–143°, as both the hydroxynitrile and its *p*-toluenesulfonate. Hydrolysis of the acetoxynitrile by hot 40% aqueous sodium hydroxide gave the lactone of 2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic acid (VIII).

The hydroxynitrile reacted with phosphorus

---

[8] Purdie and Irvine, *J. Chem. Soc.*, **83**, 1021 (1903).

[9] Wallis, Fernholz and Gephart, This Journal, **59**, 137 (1937).

[10] Stoll, *Z. physiol. Chem.*, **207**, 147 (1932).

pentachloride and thionyl chloride in the presence of pyridine to give small yields of a chloronitrile, m. p. 150°, of unknown configuration.

Experimental

Ethyl 1-Cyano-2,6-diphenyl-4-ketocyclohexane-1-carboxylate (II, R = C_2H_5).—One hundred and three grams (0.44 mole) of recrystallized dibenzalacetone, m. p. 110–111°, and 58.6 g. (0.52 mole) of ethyl cyanoacetate were mixed with 1500 cc. of dry ethyl ether in a 2000-cc. Erlenmeyer flask and the mixture swirled until maximum solution had been effected.

A solution of sodium ethoxide was prepared by allowing 1.5 g. of clean, freshly-cut sodium to react with 50 cc. of absolute ethanol, then diluting with 50 cc. of dry ether.

While the ether mixture of the reactants was swirled, the sodium ethoxide solution was added dropwise intermittently until the tendency toward turbidity had ceased and a clear yellow solution resulted (10–20 cc. of catalyst solution was usually required). The reaction mixture became warm at this point, and small, feathery, white needles began to form. Additional catalyst solution was added dropwise with swirling, and the mixture transferred to a beaker. Under continued stirring, the mixture set up to a semi-solid mass. This was diluted with about 200 cc. of dry ether, stirred again, then set aside for thirty minutes in the ice-box. The solid was collected on a filter, pressed by a rubber dam, and finally washed twice with dry ether. The white material, after air-drying overnight, weighed 116 g., a yield of 76%, m. p. 132–134°. When the ethereal filtrate was concentrated, a second crop of solid weighing 18 g. was obtained, bringing the over-all yield to 134 g., or 88% of theoretical. Complete removal of solvent from the mother liquor left a thick brown oil weighing 17 g.

After two recrystallizations of a portion of the first crop from absolute ethanol, the melting point remained constant at 137–138°. The white compound failed to take up bromine, indicating that ring closure must have occurred.

Anal.[11] Calcd. for $C_{22}H_{21}O_3N$: C, 76.08; H, 6.06; N, 4.03. Found: C, 76.08; H, 5.94; N, 3.97.

The infrared absorption spectra[12] showed a very weak band at 2250 cm.$^{-1}$, the nitrile region, and strong bands at 1724 cm.$^{-1}$ and 1736 cm.$^{-1}$, the keto and ester group regions, respectively.

1-Cyano-2,6-diphenyl-4-ketocyclohexane-1-carboxylic Acid (II, R = H).—To a solution of 173 g. (0.5 mole) of ethyl 1-cyano-2,6-diphenyl-4-ketocyclohexane-1-carboxylate in 2 l. of hot ethanol, there was added 75 g. of potassium hydroxide in one liter of distilled water. The mixture was refluxed on the steam cone for nineteen hours, then the resulting wine-red reaction mixture was carefully neutralized while hot with dilute (1:2) hydrochloric acid. The clear, light yellow, neutral solution was concentrated to 2 l. and added dropwise, with stirring, to 2 l. of hot water. The mixture was warmed until most of the turbidity disappeared, then the dissolved portion was decanted from a brown, gummy insoluble residue. The gum solidified and, when dry, weighed 57 g.

The dissolved portion was treated with Darco, filtered, then added while hot to one liter of a stirred solution of dilute (1:2) hydrochloric acid. An off-white solid settled out readily and was removed on a filter, washed with water, and dried overnight at 80°. The product thus obtained melted with decomposition at 201° and weighed 66 g., a yield of 41% of theoretical.

A portion of this solid was recrystallized twice from benzene, then again from aqueous ethanol, giving a solid melting at 219–220° with rapid decomposition.

Anal. Calcd. for $C_{20}H_{17}O_3N$: C, 75.24; H, 5.33; N, 4.39. Found: C, 74.66; H, 5.48; N, 4.36.

1-Cyano-2,6-diphenyl-4-ketocyclohexane-1-carboxylic acid has been previously reported[8]; however, no melting point was recorded and the compound analyzed contained acetone of crystallization.

Attempted Decarboxylation of 1-Cyano-2,6-diphenyl-4-ketocyclohexane-1-carboxylic Acid.—Twenty-six grams (0.082 mole) of 1-cyano-2,6-diphenyl-4-ketocyclohexane-1-carboxylic acid, m. p. 208–209° dec., was heated under reduced pressure at 200–210° in an oil-bath until effervescence had ceased. The brown melt was cooled, then dissolved in ethanol and treated with Darco. A buff solid separated from the filtrate. After one recrystallization from ethanol, and two recrystallizations from benzene, this material melted with decomposition at 203–209°, indicating that it was most probably starting material. The filtrate could not be induced to yield any crystals.

1-Cyano-2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic Acid, δ-Lactone (III).—A solution of 260 g. (0.75 mole) of ethyl 1-cyano-2,6-diphenyl-4-ketocyclohexane-1-carboxylate in 1340 cc. of hot isopropyl alcohol was mixed while warm with 274 g. (1.34 moles) of freshly distilled aluminum isopropoxide. A gelatinous precipitate separated. The mixture, in a 3-l., round-bottomed flask, was refluxed under an 18-in. bead-packed column, mounted with a partial take-off type distillation head. Distillate was taken off slowly as reflux continued for approximately twenty-four hours, or until the distillate repeatedly failed to give a positive test for acetone with 2,4-dinitrophenylhydrazine.[4] The alcohol was then removed by distillation until the volume was reduced to about one-half that of the original. The mixture remaining was then transferred to a beaker surrounded by ice, and when cold, acidified with approximately one liter of dilute hydrochloric acid (220 cc. concentrated acid to 1100 cc. of water). The mixture was stirred and let stand until all gelatinous material had dissolved. If, at this point two layers resulted, additional isopropyl alcohol was added with stirring until only one liquid phase remained. After standing in the ice-box to allow for complete sedimentation, the liquid portion was carefully decanted, leaving a slurry of white granular crystals. This was diluted with 50% aqueous isopropyl alcohol containing some hydrochloric acid, and the solid removed on a filter. The crystals were washed on the filter, first with more acidified aqueous isopropyl, alcohol then with cold isopropyl alcohol and finally with water. The product, after drying at 80° for three hours, was a fine white crystalline powder, m. p. 226–227°, weighing 110 g. or 48.5%. Recrystallization from acetone gave a solid melting at 227–228°.

Anal. Calcd. for $C_{20}H_{17}O_2N$: C, 79.18; H, 5.65; N, 4.62. Found: C, 79.45; H, 5.63; N, 4.74.

The infrared absorption spectra showed a very weak band at 2265 cm.$^{-1}$, the nitrile region, and a strong band at 1766 cm.$^{-1}$, the lactone region.

In a run similar to the one above, the decanted solution was combined with washings and then concentrated until two layers formed. These were separated and the bottom layer extracted twice with benzene. The top layer was diluted with benzene, then separated. The combined benzene extract was washed with water, with dilute hydrochloric acid, then with dilute sodium hydroxide solution, and finally with water again. The extract was separated, stirred with anhydrous sodium sulfate, then boiled with Darco, and filtered while hot. Solvent was completely removed on the steam cone, vacuum being applied after the substance became rather viscous. A thick, light brown sirup remained, which solidified to a clear glass when cooled. All attempts to crystallize this substance failed. From 434 g. (1.25 moles) of ethyl 1-cyano-2,6-diphenyl-4-ketocyclohexane-1-carboxylate, there was obtained 240 g. of this non-crystalline residue.

1-Cyano-2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic Acid (V).—Two hundred and fourteen grams (0.613 mole, calculated as ethyl 1-cyano-2,6-diphenyl-4-hydroxycyclohexane-1-carboxylate) of the non-crystalline residue from the reduction described above, was dissolved in one liter of 95% ethanol, a solution of 67 g. (1.2 moles) of potassium hydroxide in 100 cc. of water was added, and the mixture refluxed for two hours. The cooled reaction

---

[11] All microanalyses were done by the Clark Microanalytical Laboratories.

[12] We are indebted to Mrs. J. L. Johnson for the infrared absorption data and its interpretation.

mixture was acidified with concentrated hydrochloric acid, boiled with Norit, filtered and the alcohol removed. The resulting gum was washed with water to remove sodium chloride, and then dissolved in hot benzene. White granular crystals, which deposited out of the cooled solution, were removed on a filter and desiccated under vacuum. There was thus obtained 125 g. of solid, m. p. 189–190° dec., a yield of 63% of theoretical. After two recrystallizations from 25–35% aqueous ethanol, the product melted at 204° dec.

Anal. Calcd. for $C_{20}H_{19}O_3N$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.36, 74.99; H, 5.74, 5.50; N, 4.36.

The infrared absorption spectra showed a weak band at 2247 cm.$^{-1}$, the nitrile region, and strong bands at 1750 cm.$^{-1}$ and 3445 cm.$^{-1}$, the carboxyl and hydroxyl regions, respectively. The lower melting product, 189–190° dec., showed extra bands at 2260 cm.$^{-1}$, 1717 cm.$^{-1}$, and 3362 cm.$^{-1}$. Removal of solvent from the mother liquor left a viscous brown oil weighing 61 g.

Attempted Hydrolysis of 1-Cyano-2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic Acid, δ-Lactone. (A).—Two grams (0.007 mole) of the δ-lactone was dissolved in a solution of 10 g. of potassium hydroxide in 100 cc. of ethanol. After being boiled with Norit, the solution was filtered and mixed with 200 cc. of water, cooled and added with stirring to 300 cc. of 1:5 hydrochloric acid. The milky suspension which resulted was allowed to settle overnight in the ice-box. A white solid separated and this was removed on a filter and air-dried. The solid, weighing approximately 1 g., was recrystallized from ethanol, giving well-defined crystals, m. p. 225–226°. A mixed melt with the starting material showed no depression.

In the absence of potassium hydroxide, 2 g. of crystalline δ-lactone failed to dissolve in 100 cc. of ethanol.

(B).—Approximately 1–2 g. of the δ-lactone was powdered and dissolved with stirring in cold concentrated sulfuric acid. Careful dilution of this solution with water gave a white precipitate which was removed on a filter. The solid thus obtained, after being washed with water and air-dried, melted at 225° and showed no depression in a mixed melt with the starting material.

1-Cyano-2,6-diphenyl-4-hydroxycyclohexane (VI) (A).—One hundred grams (0.33 mole) of 1-cyano-2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic acid, δ-lactone was refluxed with 1000 g. of 40% aqueous sodium hydroxide for three hours. At the end of the heating period, ammonia was first noted at the top of the reflux condenser. The reaction mixture was allowed to cool and the hardened organic layer was separated and washed with water. The solid was dissolved in ethanol, and the hot solution was treated with Darco, then filtered. Chilling brought out granular crystals which were removed on a filter and dried by vacuum desiccation. Sixty-three grams of solid, melting at 130–135°, and a second crop of 10 g., melting at 140–142°, were obtained. The total of 73 g. represents a yield of 80% of theoretical. Recrystallization of the solid from ethanol gave well-defined crystals, melting at 143–144°.

Anal. Calcd. for $C_{19}H_{19}ON$: C, 82.28; H, 6.91; N, 5.05. Found: C, 82.20; H, 6.70; N, 5.15.

The infrared absorption spectra showed a weak band at 2260 cm.$^{-1}$, the nitrile region, and a strong band at 3440 cm.$^{-1}$, the hydroxyl region.

Following the above method it was sometimes observed that the product resulting showed a melting range of 120–125°. Thus, in a representative case, there was obtained from 150 g. (0.495 mole) of 1-cyano-2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic acid, δ-lactone, 109 g. of solid melting at 120–125°, a yield of 80%. Recrystallization of this from 95% ethanol gave granular crystals melting at the same temperature. Doubling the volume of ethanol was without effect, so the solution was made alkaline with 2–5 g. of potassium hydroxide, boiled with Darco and filtered. The solid which was deposited melted in the same range, 120–125°.

The investigation of other solvents failed to indicate one better than ethanol.

(B).—A solution of 16 g. (0.05 mole) of recrystallized 1-cyano-2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic acid, m. p. 202° dec., in 125 cc. of crude quinoline was refluxed for one hour to effect decarboxylation. The cooled reaction mixture, after acidification with 500 cc. of 1:1 hydrochloric acid, was extracted twice with benzene and the resulting benzene extracts combined and treated with Norit. Following filtration, the solvent was removed, leaving a brown oil which was dissolved in ethanol and treated with Norit and Darco, then filtered. From the chilled solution there was obtained 6 g. of crystals, m. p. 142–143°, and a second crop of 1 g., m. p. 122–125°. The total of 7 g. represents a yield of 50% of theoretical.

2,6-Diphenyl-4-hydroxycyclohexane-1-carboxylic Acid (VII).—A mixture of 70 g. (0.23 mole) of 1-cyano-2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic acid, δ-lactone, and 1000 g. of 40% aqueous sodium hydroxide was refluxed for thirty-one hours. At the end of the heating period, *i.e.*, when ammonia ceased to be evolved, a gummy upper layer remained in the flask. This solidified when cool and was removed, washed with water and dissolved in ethanol. After being filtered, the warm solution was carefully neutralized with hydrochloric acid, then boiled, and again filtered to remove sodium chloride.

The alkali portion of the original reaction mixture was diluted with an equal volume of water, then carefully acidified with concentrated hydrochloric acid. The resulting solid was removed on a filter, and the wet cake, consisting chiefly of hydrated silica, was extracted with hot ethanol. After removal of the ethanol-insoluble material on a filter, the solution was combined with the one prepared initially.

The alcoholic solution was boiled with Norit, filtered, then concentrated somewhat to insure ease of crystallization. Chilling brought out fine, white needles, which were removed on a filter and dried in a vacuum desiccator. A second crop of crystals was obtained by concentrating and chilling the mother liquor. The first crop, weighing 58 g., melted at 172–173° dec., and the second crop, weighing 6 g., melted at 157–168° dec. The total of 64 g. represents a 94% yield.

After two recrystallizations from water containing 10% ethanol, the solid melted at 173–174° dec.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.97; H, 7.00.

The infrared absorption spectra showed strong bands at 1708 cm.$^{-1}$, the carboxyl region, and at 3365 cm.$^{-1}$, the hydroxyl region.

2,6-Diphenyl-4-hydroxycyclohexane-1-carboxylic Acid, δ-Lactone (VIII).—Twenty-five grams (0.084 mole) of 2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic acid was warmed at 135° under reduced pressure for approximately thirty minutes. The temperature was then raised to 170° for about twenty minutes (*i.e.*, until effervescence had ceased). After the light brown product had cooled somewhat, it was taken up in ethanol, decolorized with Darco, filtered and cooled until crystals formed. The white needles which deposited were removed on a filter, and the mother liquor concentrated to recover a second crop. By this means there was obtained a total of 18.5 g. of solid, m. p. 125–126°, 79% of theoretical.

After two recrystallizations from absolute ethanol, the solid melted at 126–127°.

Anal. Calcd. for $C_{19}H_{18}O_2$: C, 82.01; H, 6.48. Found: C, 81.95; H, 6.54.

The infrared absorption spectra showed a strong band at 1755 cm.$^{-1}$, the lactone region.

A solution of 6 g. (0.02 mole) of 2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic acid in 20 cc. of acetic anhydride was refluxed for five hours. The acetic anhydride was removed under reduced pressure and the solid residue dissolved in ethanol and decolorized with Norit. Fine white needles, m. p. 125°, were obtained from the cooled filtrate. A mixed melt with the δ-lactone, m. p. 125–126°, showed no depression.

To a solution of 5 g. (0.017 mole) of 2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic acid in 25 cc. of dry pyridine there was added, with caution, 2.6 cc. (3.84 g., 0.034

mole) of acetyl chloride. The mixture was allowed to stand overnight, then was diluted with water and extracted with chloroform. After the extract was dried over anhydrous sodium sulfate, the chloroform was removed and the residual oil dissolved in ethanol and the solution chilled. Crystals, m. p. 123°, were removed on a filter. Recrystallization from ethanol gave a solid melting at 124–125°. A mixed melt with the δ-lactone showed no depression.

To a solution of 5 g. (0.017 mole) of 2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic acid in 15 cc. of dry pyridine, there was added 6.85 g. (0.036 mole) of *p*-toluenesulfonyl chloride. The mixture, which became quite hot, was allowed to stand overnight. The crystalline mass which was formed was diluted with ethanol to effect solution, then enough water was added dropwise to induce recrystallization. Two and one-half grams of solid was removed on a filter and recrystallized, giving needles, m. p. 125°. A mixed melt with the δ-lactone showed no depression.

1-Cyano-2,6-diphenyl-4-methoxycyclohexane (IX).—The method used by Purdie and Irvine[8] in the alkylation of sugars, was followed with modification. To a solution of 10 g. (0.036 mole) of recrystallized 1-cyano-2,6-diphenyl-4-hydroxycyclohexane, m. p. 142–143°, in 100 cc. of dry benzene in a 500-cc., three-necked, round-bottomed flask, fitted with Hershberg stirrer, and cold finger-type condenser, was added 22.5 cc. (51.3 g., 0.36 mole) of methyl iodide, and 5–10 g. of a 30-g. portion of freshly prepared silver oxide. Two cubic centimeters of methanol was added, the stirrer was started, and the mixture was brought to reflux. The rest of the silver oxide was added in three or four approximately equal-sized batches at two-hour intervals. Reflux was maintained for an over-all period of ten hours.

The hot mixture was filtered to remove the silver residues, and these were washed on the filter with hot benzene, then transferred to a beaker and boiled with fresh benzene. The combined benzene extracts were decolorized with Darco, then evaporated. The residual oil was taken up in absolute ethanol, from which white plates separated immediately. Seven grams of crystalline solid, m. p. 105–106°, was obtained, a yield of 66.5%. The second crop from the concentrated mother liquor weighed less than 0.5 g. A portion of the concentrated mother liquor weighed less than 0.5 g. A portion of the product, after two recrystallizations from absolute ethanol, gave hexagonal plates, m. p. 106–107°.

Anal. Calcd. for $C_{20}H_{21}ON$: C, 82.43; H, 7.27; N, 4.81. Found: C, 82.38; H, 7.49; N, 4.85.

The infrared absorption spectra showed a weak band at 2247 cm.$^{-1}$, the nitrile region, and a strong band at 1104 cm.$^{-1}$, the ether C–O region.

Attempted Hydrolysis of 1-Cyano-2,6-diphenyl-4-methoxycyclohexane. (A).—A mixture of 2 g. (0.007 mole) of 1-cyano-2,6-diphenyl-4-methoxycyclohexane, m. p. 103–105°, and 50 g. of 40% aqueous sodium hydroxide was refluxed for twenty-four hours. After the mixture was cooled, the organic portion was separated and dissolved in 95% ethanol, treated with Darco, and the solution filtered. The filtrate was acidified with concentrated hydrochloric acid, boiled, again filtered, and finally concentrated. A solid which separated from the chilled solution was collected on a filter, air-dried, and recrystallized from ethanol, giving material melting at 103–104°. A mixed melt with the starting material showed no depression.

(B).—Five grams (0.017 mole) of the methoxynitrile, m. p. 101–103°, was added in small portions to 50 cc. of 75% sulfuric acid at 140–150°. The mixture became orange and all the organic material appeared to disperse after one-half hour. Heating was continued, with frequent shaking, for a total of one hour. The acid mixture, when poured onto cracked ice, deposited a yellow precipitate which was removed on a filter and dissolved in ethanol. After treatment with Norit, the solution was filtered, concentrated, and the resulting oil dissolved in dilute aqueous sodium hydroxide. Acidification of the orange solution with 1:1 hydrochloric acid failed to cause any precipitation.

(C).—A mixture of 2 g. (0.007 mole) of the methoxynitrile and 76 cc. of 50% sulfuric acid was refluxed for five hours. After the mixture had cooled, the solidified organic layer was separated, dissolved in ethanol, treated with Darco and the solution filtered. Crystals which separated from the chilled concentrated solution were collected on a filter and air-dried. In this manner there was obtained approximately 1 g. of material, m. p. 102–104°, which failed to show any depression in a mixed melt with a sample of starting material.

(D).—One gram of the powdered methoxynitrile was added slowly to 50 cc. of cold concentrated sulfuric acid over a period of fifteen to twenty minutes. The solid went into solution, imparting a brown coloration to the acid. While surrounded by ice, the mixture was carefully diluted by dropping in chipped ice until precipitation occurred. The gum which resulted was dissolved in ethanol, from which it failed to crystallize. After removal of the solvent, the concentrate was warmed with dilute aqueous sodium hydroxide, and the solution obtained treated with Darco and filtered. Acidification of the alkaline filtrate failed to cause precipitation.

2,6-Diphenyl-4-methoxycyclohexane-1-carboxylic Acid (X).—A solution of 4 g. (0.014 mole) of 1-cyano-2,6-diphenyl-4-methoxycyclohexane in 100 cc. of saturated alcoholic potassium hydroxide was refluxed for forty-eight hours. Ammonia was evolved and a small amount of an insoluble layer formed at the bottom of the flask. The reaction mixture was diluted with an equal volume of water, acidified with concentrated hydrochloric acid, then extracted twice with benzene. After treatment of the benzene extract with Norit and filtering, the solvent was removed completely, leaving a clear yellow oil which was then dissolved in ethanol, again treated with Norit and filtered. The clear yellow solution ultimately deposited crystals which were removed on a filter and air-dried. There was thus obtained 0.5 g. of solid melting at 176–178°. After two recrystallizations from absolute ethanol, crystalline rectangular parallelepipeds melting at 186–187° were obtained.

Anal. Calcd. $C_{20}H_{22}O_3$: C, 77.39; H, 7.15. Found: C, 77.18; H, 7.09.

The infrared absorption spectra showed strong bands at 1730 cm.$^{-1}$, the carboxyl region, and at 1128 cm.$^{-1}$, the ether C–O region.

***p*-Toluenesulfonate of 1-Cyano-2,6-diphenyl-4-hydroxycyclohexane.**—The procedure followed was a modification of the method used by Wallis, Fernholz and Gephart[9] for the preparation of cholesteryl *p*-toluenesulfonate. Five grams (0.018 mole) of recrystallized 1-cyano-2,6-diphenyl-4-hydroxycyclohexane was dissolved in 15 cc. of anhydrous pyridine and 6.85 g. (0.036 mole) of *p*-toluenesulfonyl chloride added. The solution immediately became hot and fumes were evolved. After standing at room temperature overnight, large needles had separated and the liquid portion had become sirupy. Absolute ethanol (about 20 cc.) was added dropwise to the stirred solution to induce crystallization again. The crystals were removed on a filter and dried by vacuum desiccation. There was thus obtained 6.5 g. of solid melting at 133–134°, a yield of 84% of theoretical.

Recrystallization from ethanol gave long white needles, melting at 140–142°. A mixture of starting material, m. p. 140–142°, and recrystallized product, showed a melting point depression of 20°. A sodium fusion test for sulfur was clearly positive.

Anal. Calcd. for $C_{26}H_{25}NO_3S$: C, 72.36; H, 5.84; N, 3.25. Found: C, 72.52; H, 5.68; N, 3.27.

The infrared absorption spectra showed a very weak band at 2247 cm.$^{-1}$, the nitrile region, and strong bands at 1180 cm.$^{-1}$, and 1193 cm.$^{-1}$, the sulfonyl region.

The ester was recovered unchanged after being refluxed with methanol for three hours.

Reaction of *p*-Toluenesulfonate of 1-Cyano-2,6-diphenyl-4-hydroxycyclohexane with Sodium Methoxide.—A solution of sodium methoxide, prepared by dissolving 1.5 g. of sodium in 30 cc. of methanol, was added to 8 g.

(0.019 mole) of the *p*-toluenesulfonate in 125 cc. of absolute ethanol, and the mixture refluxed for twenty-three hours. Glistening white plates were deposited during the reflux period. The reaction mixture, after careful acidification with concentrated hydrochloric acid, was chilled and the crystals removed on a filter. Washing of the filtered solid with water left only a small portion of water-insoluble material, which was then dissolved in ethanol and combined with the initial filtrate. As this solution, when chilled, showed a tendency to deposit more water-soluble plates, the solvent was completely removed and the residual semi-solid boiled for one-half hour with dilute aqueous sodium hydroxide solution. The organic material was separated from the cooled mixture and redissolved in ethanol, treated with Darco, filtered and finally chilled. The fine white needles resulting were removed on a filter and after air-drying, weighed approximately 1 g. The material thus obtained sintered at 185° but failed to show a definite melting point. After three recrystallizations from ethanol, a solid melting sharply at 207–208° was obtained.

Anal. Calcd. for $C_{19}H_{17}N$: C, 87.99; H, 6.61; N, 5.40. Found: C, 88.37; H, 6.44; N, 5.47.

The infrared absorption spectra of the 185° product showed twinned weak bands at 2217 cm.$^{-1}$ and 2247 cm.$^{-1}$, which indicate a conjugated nitrile group. The recrystallized material showed less of the second band at 2217 cm.$^{-1}$ and a more prominent band at 1585 cm.$^{-1}$, the conjugated phenyl frequency.

These data, together with the observation that the product reacted slowly to decolorize bromine in carbon tetrachloride, indicated that the compound was a mixture of Δ^1- and Δ^2-1-cyano-2,6-diphenylcyclohexene.

Similar results were obtained when the *p*-toluenesulfonates were refluxed in ethanol with sodium ethoxide for eighty minutes.

4-Acetoxy-1-cyano-2,6-diphenylcyclohexane.—A solution of 20 g. (0.072 mole) of 1-cyano-2,6-diphenyl-4-hydroxycyclohexane in 200 cc. of acetic anhydride was refluxed for six hours. The acetic anhydride was distilled off under reduced pressure and the solid residue dissolved in ethanol, decolorized with Norit and filtered. Chilling brought out long white needles which were removed on a filter and dried by vacuum desiccation. There was thus obtained 19.5 g. of material melting at 141–142°, a yield of 85% of theoretical.

Two recrystallizations from absolute ethanol failed to raise the melting point. A mixed melt with starting material, m. p. 140–141°, showed a depression of 40°.

Anal. Calcd. for $C_{21}H_{21}O_2N$: C, 78.97; H, 6.63; N, 4.39. Found: C, 79.08; H, 6.55; N, 4.23.

The infrared absorption spectra showed a weak band at 2247 cm.$^{-1}$, the nitrile region, and a strong band at 1723 cm.$^{-1}$, the ester region.

Hydrolysis of 4-Acetoxy-1-cyano-2,6-diphenylcyclohexane.—A mixture of 2 g. (0.006 mole) of the acetoxynitrile and 50 g. of 40% aqueous sodium hydroxide was refluxed for twenty-four hours. When the mixture had cooled, the hardened organic layer was separated, washed with water, dissolved in ethanol and the solution treated with Darco and filtered. After acidification with concentrated hydrochloric acid, the solution was boiled and again filtered. Crystals which deposited from the cooled solution were collected on a filter and air-dried. The solid thus obtained melted at 125° and showed no depression in a mixed melt with a sample of 2,6-diphenyl-4-hydroxycyclohexane-1-carboxylic acid, δ-lactone.

4-Chloro-1-cyano-2,6-diphenylcyclohexane. (A).—Four grams (0.019 mole) of phosphorus pentachloride was added to a solution of 5 g. (0.018 mole) of 1-cyano-2,6-diphenyl-4-hydroxycyclohexane in 125 cc. of dry benzene, and the mixture was refluxed for twenty-four hours. The warm reaction mixture was then shaken with an equal volume of water, separated, and shaken with an equal volume of 5% aqueous sodium hydroxide. Following separation, the solution was stirred with anhydrous sodium sulfate, filtered and the solvent removed. The residual oil, after being boiled for one hour with water, was dissolved in ethanol, treated with Norit, and the solution filtered. Chilling caused the deposition of prismatic needles which were then removed on a filter and air-dried. In this manner approximately 1.5 g. of solid was separated, which, after recrystallization from ethanol, melted at 150°. The yield was 26%.

Anal. Calcd. for $C_{19}H_{18}NCl$: C, 77.14; H, 6.13; N, 4.74. Found: C, 77.27; H, 5.97; N, 4.68.

(B).—Two cubic centimeters (3.3 g., 0.028 mole) of thionyl chloride was added to a solution of 5 g. (0.018 mole) of 1-cyano-2,6-diphenyl-4-hydroxycyclohexane in 100 cc. of dry benzene and 10 cc. of dry pyridine. A white precipitate formed immediately. During the subsequent reflux period of twenty-four hours, the white precipitate dissolved and sulfur dioxide was evolved. The reaction mixture was shaken twice with water, then filtered and the solvent removed, leaving a brown oil which was warmed with water for one hour, then separated, dissolved in ethanol, treated with Darco and the solution finally filtered. Chilling brought out a white solid which was collected on a filter and air-dried. There was thus obtained 1 g. of material melting at 143–145°, a yield of 19%. After recrystallization from absolute ethanol, the solid melted at 149–150° and showed no depression in a mixed melt with a sample of 4-chloro-1-cyano-2,6-diphenylcyclohexane.

Summary

1-Cyano-2,6-diphenyl-4-hydroxycyclohexane has been synthesized. An interesting case of *cis-trans* inversion during the hydrolysis and decarboxylation of a cyanolactone has been observed. 1-Cyano-2,6-diphenyl-4-hydroxycyclohexane hydrolyzes with ease but its methyl ether requires rigorous conditions to effect hydrolysis of the nitrile group.

URBANA, ILLINOIS RECEIVED MAY 7, 1948