[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF MARYLAND]

Synthesis of 1-Phenylcyclohexaneacetic Acid

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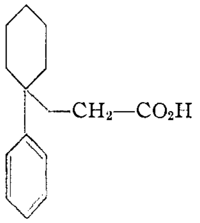
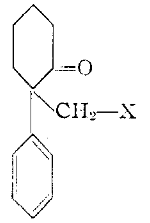
1-Phenylcyclohexaneacetic acid has been prepared by Barbier–Wieland degradation of 1-phenylcyclohexanepropionic acid. The Wolff-Kishner reaction of 2-oxo-1-phenylcyclohexaneacetonitrile led to phenylcyclohexane while the same reaction of 2-oxo-1-phenylcyclohexaneacetic acid led to a cyclic compound. The Friedel–Crafts reaction on ethyl 1-hydroxycyclohexaneacetate with benzene afforded predominately ethyl 4-phenylcyclohexaneacetate and small amounts of ethyl 2-phenylcyclohexaneacetate. Cyclization of 1-phenylcyclohexaneacetic acid occurred readily to yield spirocyclohexane-1,1-indanone-3.

The material reported in this paper is the result of an investigation of several different methods which were studied to develop a synthesis of 1-phenylcyclohexaneacetic acid (I).

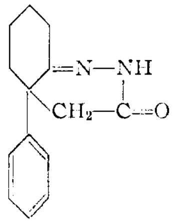
The procedure which was successful started with 1-phenylcyclohexanepropionic acid[1] which was subjected to a Barbier–Wieland degradation. The ethyl ester and the olefin, which resulted from the reaction of the ester with phenylmagnesium bromide, were obtained in good yield. The oxidation of the olefin in the usual manner provided (I) in 58% yield.



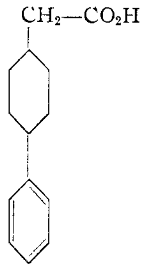
I



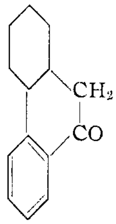
IIA, X = CO₂H
B, X = CN
C, X = CO₂C₂H₅



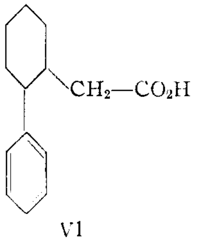
III



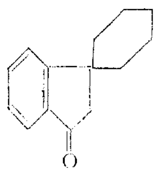
IV



V



VI



VII

Since it has been shown[1] that 2-oxo-1-phenylcyclohexanepropionic acid readily undergoes the Wolff-Kishner reaction to yield 1-phenylcyclohexanepropionic acid, the easiest method to prepare the desired compound 1-phenylcyclohexaneacetic acid appeared to be the use of the same reaction on either 2-oxo-1-phenylcyclohexaneacetic acid (IIa) or the corresponding nitrile (IIb), both of which had been prepared in good yield along with the ester (IIc) of the acid by Boekelheide and Schilling.[2] Some difficulty was encountered in the hydrolysis of the ketonitrile (IIb), while the hydrolysis of the ketoester (IIc) readily afforded the ketoacid (IIa).

The Wolff–Kishner reaction using the Huang-Minlon modification[3] on both the ketonitrile (IIb) and the ketoacid (IIa) was unsuccessful, and led to unexpected results. From the reaction of (IIb), the only product isolated was phenylcyclohexane, identical with the product of the Wolff–Kishner reaction on 2-phenylcyclohexanone. The hydrocarbon was also converted to the known 2,4-dinitrophenylcyclohexane.[4] The same reaction on the ketoacid (IIa) also failed to provide the desired product (I), and instead, a white crystalline compound was obtained whose structural formula is believed to be (III).

A third method started with the product, ethyl 1-hydroxycyclohexaneacetate, obtained from a Reformatsky reaction using cyclohexanone and ethyl bromoacetate. The Friedel–Crafts reaction of the hydroxy ester with benzene proceeded readily and the ester product was hydrolyzed. The acid isolated, melted at 112–114° (after purification) and its amide at 197–198°.[5] Reduction of the amide with lithium aluminum hydride yielded an amine which was isolated as the hydrochloride, m.p. 174–177°.

In an attempt to determine by cyclization whether the above impure acid might contain 1-phenylcyclohexaneacetic acid, the crude acid was dissolved in concentrated sulfuric acid. After working up the product in the usual manner and extracting any acidic products from the ether layer, small amounts corresponding to 5–10% of *trans*-9-keto-1,2,3,4,4a,9,10,10a-octahydrophenanthrene

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[1] W. E. Bachmann and E. J. Fornefeld, THIS JOURNAL, **73**, 51 (1951).

[2] V. Boekelheide and W. M. Schilling, *ibid.*, **72**, 712 (1950).

[3] Huang-Minlon, *ibid.*, **68**, 2487 (1946).

[4] R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 51.

[5] C. D. Nenitzescu and J. Gavat (*Ber.*, **70**, 1883 (1937)) reported the synthesis of 4-phenylcyclohexaneacetic acid by the Friedel-Crafts reaction of cyclohexylideneacetic acid with benzene. The acid that was isolated melted at 112° and the amide at 195.5°. These workers degraded this acid to the known 4-phenylcyclohexane carboxylic acid. J. W. Cook and F. Goulden (*J. Chem. Soc.*, 1559 (1937)) independently carried out the same reaction as Nenitzescu and Gavat with essentially the same results. The English workers degraded the acid to 4-methylbiphenyl. Attempted cyclization of the acid yielded no ketone. L. F. Fieser, M. T. Leffler and co-workers (THIS JOURNAL, **70**, 3189 (1948)) have recently prepared and assigned structures to the two geometrical isomers of 4-phenylcyclohexaneacetic acid. The *trans* isomer of 4-phenylcyclohexaneacetic acid is reported to melt at 113–114° (amide 194–195.5°).

(V) was obtained.[6] This establishes the fact that the Friedel–Crafts reaction led not only to (IV) but also to 2-phenylcyclohexaneacetic acid (VI) in lesser amounts. The Friedel–Crafts reaction with the unsaturated acid was reported to yield none of the phenanthrone upon attempted cyclization.[5b]

1-Phenylcyclohexaneacetic acid readily undergoes cyclization in concentrated sulfuric acid to yield the spirocyclohexylindanone (VII).[7] As a further proof of structure, our sample of 1-phenylcyclohexaneacetic acid was converted to 1-phenylcyclohexaneethylamine *via* the acid chloride and the amide and the reduction of the amide with lithium aluminum hydride. The amine and its hydrochloride (m.p. 251–254°) had properties coinciding with those reported for these substances by Bachmann and Fornefeld.[1]

Experimental

Ethyl 1-Phenylcyclohexanepropionate.—Esterification of 10 g. of 1-phenylcyclohexanepropionic acid[1] dissolved in 275 ml. of dry benzene was accomplished by refluxing the solution with 50 ml. of absolute ethanol and 1.4 g. of *p*-toluenesulfonic acid monohydrate. When no water layer separated in the azeotrope trap (16 hours), refluxing was discontinued and the solution was concentrated by distillation under reduced pressure.

The residue was diluted with water, extracted twice with ether, and the ether extract washed with a saturated solution of sodium carbonate. The organic layer was dried, filtered and distilled. The ester (9.7 g., 86%) boiled at 145–149° (0.5–0.9 mm.).

Anal. Calcd. for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.43, 78.65; H, 9.12, 9.35.

Barbier–Wieland Degradation of Ethyl 1-Phenylcyclohexanepropionate.—A solution of 23 g. of ethyl 1-phenylcyclohexanepropionate in 150 ml. of ether was added to the Grignard reagent prepared from 32 ml. of bromobenzene and 7.1 g. of magnesium. The Grignard addition complex was decomposed with dilute sulfuric acid and the mixture subjected to steam distillation. The non-volatile residue was ether extracted and the extract dried. To the extract was added a trace of sulfuric acid, the ether removed, and the residue distilled under reduced pressure; yield 28 g. of the ethylene, b.p. 209–211° (0.2 mm.).

Anal. Calcd. for $C_{27}H_{28}$: C, 91.99; H, 8.01. Found: C, 91.63; H, 8.13.

A solution of 26 g. of the ethylene, 65 ml. of isoöctane and 225 ml. of acetic acid was treated in the usual manner with 28 g. of chromium trioxide. The excess oxidizing agent was destroyed with methanol and the reaction mixture was first concentrated under reduced pressure and then diluted with water. The mixture which contained some crude precipitate was extracted with ether. The ether layer was itself extracted several times with 10% aqueous potassium hydroxide. Upon acidification of the alkaline solution with hydrochloric acid and chilling, crude 1-phenylcyclohexaneacetic acid (9.3 g.) precipitated. Recrystallization from methanol–water yielded 1-phenylcyclohexaneacetic acid which melted at 85–86°.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.11; H, 8.21.

Wolff–Kishner Reduction of 2-Oxo-1-phenylcyclohexaneacetonitrile.—Recrystallized ketonitrile[2] (19 g.), potassium hydroxide pellets (15.6 g.), 85% hydrazine (40 ml.) and diethylene glycol (100 ml.) were refluxed for one hour over an open flame according to the Huang-Minlon modification of the Wolff–Kishner reduction as described by Bachmann.[1]

The condenser was set for distillation and the temperature raised to 195–200°. As the temperature rose, a yellow oil distilled along with the water and diethylene glycol. This was extracted three times with 50 ml. of ether and dried over anhydrous magnesium sulfate after which the ether was removed and the residue distilled, 3.6 g., b.p. 55–65° (0.4–0.7 mm.). This was subsequently combined with the material collected as described below.

When the temperature of the reaction mixture reached 200°, distillation was discontinued and the residue was refluxed for five hours and then decomposed by ice.

The decomposed mixture was extracted twice with ether, and the ethereal solution dried over anhydrous magnesium sulfate, filtered, concentrated, and finally fractionally distilled under reduced pressure. Impure phenylcyclohexane (7.3 g.) was collected which boiled at 50–60° (0.2–0.5 mm.).

The above two fractions were combined and redistilled to yield a sample of phenylcyclohexane, b.p. 57–60° (0.6–0.7 mm.), 237° (atm.), m.p. 5°; n^{20}_D 1.526.[8]

Anal. Calcd. for $C_{12}H_{16}$: C, 89.93; H, 10.07. Found: C, 90.28; H, 10.29.

Wolff–Kishner Reduction of 2-Phenylcyclohexanone.—The reduction was accomplished as above. From 22 g. of the ketone 14.7 g. of phenylcyclohexane was obtained.

The above two samples (4 g. each) of phenylcyclohexane were nitrated with fuming nitric acid (22 ml.).[9] The nitration product was extracted with ether from water and after drying was distilled; 3.5 g., b.p. 185–192° (17 mm.). After two sublimations and several recrystallizations from ethanol–water pale yellow platelets, m.p. 55–57° (literature, 57°[9]), of 2,4-dinitrophenylcyclohexane were obtained.

Anal. Calcd. for $C_{12}H_{14}O_4N_2$: C, 57.69; H, 6.40; N, 11.20. Found: C, 57.58; H, 5.57; N, 11.14.

Wolff–Kishner Reduction of 2-Oxo-1-phenylcyclohexaneacetic Acid.—A mixture containing 14.2 g. of the ketoacid,[2] 12 g. of potassium hydroxide, 30 ml. of 85% hydrazine and 150 ml. of diethylene glycol was refluxed over an open flame for two hours.

The reflux condenser was removed, set for distillation and the temperature raised to 195–200°. A small amount of yellow oil steam distilled during the temperature elevation indicating a partial cleavage of the side chain.

When the temperature reached 200°, distillation was discontinued. The mixture was refluxed for 6 more hours, and then the hot solution was decomposed by pouring it over ice.

A white crystalline precipitate separated from the basic media as it was decomposed. This was isolated by filtration.

The white crystalline precipitate was found to be insoluble in water, ether, dilute hydrochloric acid and 10% sodium hydroxide. Recrystallization was accomplished by dissolving in hot concentrated acetic acid and diluting with water to the cloud point. White crystals were obtained which melted sharply at 234–235° and which are believed to be pyridazone (III).

Anal. Calcd. for $C_{14}H_{16}ON_2$: C, 73.65; H, 7.07; N, 12.27. Found: C, 73.49; H, 7.15; N, 12.25.

4-Phenylcyclohexaneacetic Acid (IV).—To a stirred mixture of 260 ml. of benzene and 160 g. of aluminum chloride which was chilled in an ice-bath 94 g. of ethyl-1-hydroxycyclohexaneacetate was added over a period of three hours. The ice-bath was removed[10] and the solution allowed to warm to room temperature. Stirring was continued for a further six hours after which time it was allowed to stand for an additional 12 hours. Upon isolation of the product 75 g. of ethyl 4-phenylcyclohexaneacetate (b.p. 171–172° (5.3 mm.); literature,[5] 168° (5 mm.)) was obtained.

Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.00; H, 9.00. Found: C, 77.98; H, 8.98.

The above ester (41 g.) was saponified with 25% aqueous sodium hydroxide. The resulting solution was chilled and acidified with hydrochloric acid. The crude solid acid (36 g.) was isolated by suction filtration. After several recrystallizations from petroleum ether *trans*-4-phenylcyclohexaneacetic acid was obtained melting at 112–114°.[5] The amide melted at 197–199°.[5]

The reduction of 12 g. of the amide with lithium aluminum hydride in ether was accomplished in the usual manner, after decomposing the solution with water, the ether layer was dried and hydrogen chloride slowly added. β-(4-Phenylcyclohexane)-ethylamine hydrochloride (6.9 g.) pre-

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(6) W. E. Bachmann and E. J. Fornefeld, THIS JOURNAL, **72**, 5530 (1950).

(7) L. H. Schwartzman, *J. Org. Chem.*, **15**, 517 (1949).

(8) N. Kursanoff, *Ann.*, **318**, 313 (1901), reports b.p. 239°, m.p. 7°.

(9) H. A. Mayes and E. E. Turner, *J. Chem. Soc.*, 503 (1929).

(10) S. Natelson and S. P. Gottfried, THIS JOURNAL, **61**, 970 (1939).

cipitated, which after several recrystallizations from ethanol–ether, melted at 174–177°.

Anal. Calcd. for $C_{14}H_{22}NCl$: C, 70.12; H, 9.25. Found: C, 70.06; H, 9.33.

***trans*-9-Keto-1,2,3,4,4a,9,10,10a-octahydrophenanthrene** (V).—The crude acid products isolated from the hydrolysis of the ester obtained in the above described Friedel–Crafts reaction (9.5 g.) were dissolved in 48 ml. of concentrated sulfuric acid, and heated on the steam-bath for 15 minutes. The cooled mixture was poured onto ice, and extracted with ether. The ether extract was washed with water, dilute alkali, dried, and concentrated. A small amount of the ketone was obtained, the quantity depending on the conditions of the Friedel–Crafts reaction from which the acid material was derived. If the Friedel–Crafts reaction was carried out at room temperature for 24–36 hours about 5% of the ketone was obtained; if refluxing temperature conditions were employed approximately 10% of the ketone was obtained. On the assumption that higher temperatures increased the yield of the 2-phenylcyclohexaneacetic acid, the Friedel–Crafts reaction was carried out in refluxing benzene–nitrobenzene. The yield of ketone upon cyclization of this acid product led to 1% or less of the ketone.

The ketone, twice recrystallized, and once sublimed, melted at 95.5–97.5°. This sample gave no melting point depression with an authentic sample which had been kindly supplied by Dr. W. E. Bachmann.

A 2,4-dinitrophenylhydrazone was prepared in the usual manner and recrystallized several times from toluene–methanol mixtures. It melted at 267–269° (no depression in mixed melting point with authentic sample).

Anal. Calcd. for $C_{20}H_{20}O_4N_4$: C, 63.15; H, 5.30. Found: C, 63.21; H, 5.35.

The Preparation of Spirocyclohexane-1,1-indanone-3 (VII).—Unrecrystallized 1-phenylcyclohexaneacetic acid (6 g.) was dissolved in 157 ml. of concentrated sulfuric acid and heated on a steam-bath. The temperature was maintained at about 85° for 25 minutes, after which the mixture was cooled and poured slowly with stirring over ice.

The product was extracted with ether; the ethereal solution was washed with 10% potassium hydroxide, and dried over anhydrous magnesium sulfate. After filtering, the ether was removed and the residue seeded with an authentic crystal of the indanone.

The white solid, obtained by cooling the seeded concentrate in an ice-bath, was dissolved in 30–60° petroleum ether and decolorized with Norite. Recrystallization was effected by chilling the filtrate in an acetone–Dry Ice-bath; yield 3.8 g. (69.1%).

An analytical sample, prepared by sublimation at 60–75° (0.1 mm.) melted at 58–59° (literature 58–59°[7] no depression on mixed m.p. with an authentic sample).

The oxime and semicarbazone derivatives were prepared in the usual manner and melted at 138–139° and 210–213°, respectively, and mixed m.p. with authentic sample gave no depressions.

β-(1-Phenylcyclohexane)-ethylamine.—1-Phenylcyclohexaneacetic acid was dissolved in 30 ml. of dry benzene and 3.5 ml. of thionyl chloride added. The solution was heated on a steam-bath for 2 hours and then concentrated under reduced pressure. The oily residue was added dropwise with stirring to a cold solution of 250 ml. of concentrated ammonium hydroxide. The stirring was continued overnight. Since the product was an oil, it was extracted with benzene, washed and dried over anhydrous magnesium sulfate. The benzene solution was added to 50 ml. of 1 molar lithium aluminum hydride in ether and refluxed for 18 hours, cooled and decomposed with water. The benzene–ether layer was separated, dried and hydrogen chloride gas passed into the solution. The amine hydrochloride (1.5 g.) was obtained, which after recrystallization from absolute alcohol–ether melted at 250–254° (dec.). Bachmann and Fornefeld[1] report m.p. 253–254° (dec.).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Open-chain Acylals, Formals and Ethers Containing Terminal Double Bonds

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Allyl chloromethyl ether, a hemiacetal chloride, was used in the synthesis of several new acylals, formals and ethers. Reactions were with carboxylic salts, with alcohols in the presence of pyridine, and with butadiene in the presence of zinc chloride. The reaction of allyl chloroformate and 2-allyloxy-1-ethanol was studied.

Relatively few simple hemiacetal chlorides, $ROCH_2Cl$, have been reported (R = methyl, ethyl, isopropyl, *s*-butyl, cyclohexyl, 2-chloroethyl), the general synthesis being the interaction of formaldehyde, an alcohol and hydrogen chloride. The allyl analog was prepared in the present work. Distillation gave rise to a product (b.p. 107°) analyzing 1.5% low in chlorine, probably because of entrained allyl alcohol. However, most of the latter was removable by benzoylation to yield a product containing 0.8% less chlorine than the theoretical. Its derivatives were generally of acceptable purity.

Acylals were prepared by metathesis of allyl chloromethyl ether with sodium salts

$$CH_2{=}CHCH_2OCH_2Cl + RCOONa \longrightarrow CH_2{=}CHCH_2OCH_2OCOR + NaCl$$

The salts included the acetate, acrylate, oxalate, α-acetoxypropionate and phthalate. Details followed the general procedure of Hurd and Green.[2] Similar treatment of the formate gave a product which resisted purification, perhaps owing to the presence of allyl formal, $CH_2(OC_3H_5)_2$.

Several other formals were prepared by interaction of the chloride with various alcohols in the presence of a base such as pyridine

$$CH_2{=}CHCH_2OCH_2Cl + ROH + C_5H_5N \longrightarrow CH_2{=}CHCH_2OCH_2OR + C_5H_5NHCl$$

The alcohols investigated were 2-ethoxy-1-ethanol, 2-allyloxy-1-ethanol, ethyl lactate and allyl lactate.

The reaction of allyl chloromethyl ether with 1,3-butadiene in the presence of zinc chloride presumably involved a 1,4-addition, but this point is unsettled. The expected product would be 5-allyloxy-1-chloro-2-pentene

$$CH_2{=}CHCH_2OCH_2Cl + CH_2{=}CH{-}CH{=}CH_2 \longrightarrow CH_2{=}CHCH_2OCH_2{-}CH_2CH{=}CHCH_2{-}Cl$$

This reaction is analogous to the one reported by Straus and Thiel,[3] namely, the addition of methyl α-chlorobenzyl ether to butadiene to form 5-

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(1) Pittsburgh Plate Glass Company research associates: (a) 1944, (b) 1943–1944.

(2) C. D. Hurd and F. O. Green, THIS JOURNAL, **63**, 2201 (1941).

(3) Straus and Thiel, *Ann.*, **525**, 151 (1936).