Chloroplatinate.—The chloroplatinate was made as was that of amylpyrroline; m.p. 166–168° (uncor.) with decomp.

Picrate.—The picrate, prepared in ethanol solution, melted at 176° (uncor.).

2,3-Diphenylpyrroline.—This pyrroline was prepared by the thermal rearrangement of phenylcyclopropyl phenyl ketimmonium chloride in an atmosphere of ether.[20] A sample of 3.0 g. of the ketimmonium chloride was mixed with 30 ml. of anhydrous ether in a Claisen–Vigreux flask connected to a condenser. The ether was distilled over, and the ketimine salt was then heated to 140° for 5 minutes in an oil-bath. The pinkish-colored residue was extracted with 20% hydrochloric acid, the pyrroline precipitated with sodium carbonate solution and collected on a filter.

Benzylideneëthylamine.—This compound was prepared according to the method of Zaunschirm.[21] A weight of 212 g. of benzaldehyde was mixed with 135 g. of 70% aqueous ethylamine and the mixture refluxed. Fractionation of the reaction mixture yielded 119 g. of a product b.p. 73–74° at 9–10 mm.

Anal. Calcd. for $C_9H_{11}N$: N, 10.54; mol. wt., 133. Found: N (Kjeldahl), 10.65; mol. wt. (ebullioscopic in $CHCl_3$) 129, unchanged after two years.

Measurement of Reaction between Methylmagnesium Iodide and Organic Compounds.—The reactions were measured in the apparatus previously mentioned.[15] The butyl ether solvent was purified by shaking with acidified ferrous sulfate to remove peroxides, drying with flake sodium hydroxide, and distillation. The distillate was stored over sodium for a few days, then was treated with sufficient methylmagnesium iodide, previously prepared, to destroy the last traces of compounds reactive to the Grignard reagent. Finally, the ether was again distilled, and stored over sodium ribbon in a glass stoppered bottle.[22]

During an analysis, the sample, dissolved in 5 ml. of the purified butyl ether, was treated with a measured volume of the methylmagnesium iodide solution (previously standardized) and when evolution of gas had ceased, the excess reagent was decomposed by the addition of a measured volume of water.

Isolation of Addition Compounds of Grignard Reagents and 2-Phenylpyrroline. (I) Methylmagnesium Iodide and 2-Phenylpyrroline.—A weight of 1.5 g. of 2-phenylpyrroline was treated with excess methylmagnesium iodide in ethyl ether. The resulting precipitate was washed several times with anhydrous ether by decantation, collected as rapidly as possible on a filter, and weighed. The substance, originally almost white, took on a yellow tinge after a short exposure to the atmosphere.

Anal. Calcd. for $C_{11}H_{14}NMgI$[23]: Mg, 7.81; I, 40.85. Found: Mg, 7.62, 7.83; I, 43.4.

(II) Isoamylmagnesium Bromide and 2-Phenylpyrroline.—One gram of 2-phenylpyrroline was treated with excess isoamylmagnesium bromide in ethyl ether. The white precipitate was collected as described above.

Anal. Calcd. for $C_{15}H_{22}NMgBr$: N, 4.37; Mg, 7.58; Br, 24.92. Found: N, 4.65; Mg, 6.69; Br, 25.95.

Recovery of Benzophenone Anil from Active Hydrogen Determinations.—A total of 1.1004 g. of benzophenone anil was used in the Grignard analyses of this compound. The combined butyl ether layers from the several runs were allowed to evaporate, giving about 1 g. of yellow crystals. Recrystallization from ethanol gave 0.9285 g. of pale yellow crystals, m.p. 116.5–117° (uncor.); m.p. of purified benzophenone anil, 117°; mixed m.p. with recovered solid, 116° (both uncor.).

Summary

1. A quantitative study of the action of methylmagnesium iodide on butyl ether solutions of 2-substituted pyrrolines prepared from γ-chlorobutyronitrile and Grignard reagents has shown that these compounds consume one mole of the reagent without the formation of methane, suggesting a Δ^1 structure.

2. This behavior is characteristic of other compounds containing the azomethine group, *e. g.*, benzalaniline, acetophenone anil and benzophenone anil.

3. Analysis of the precipitates resulting from the action of methylmagnesium iodide and isoamylmagnesium bromide on 2-phenylpyrroline indicates that an addition compound of the two components is formed in the reaction.

CHESTNUT HILL, MASS. RECEIVED MAY 24, 1950

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[20] This method, based on the work of Drs. E. C. Knowles and J. V. Murray, was described by Dr. Saroff, in a thesis at Rensselaer Polytechnic Institute, 1940.

[21] Zaunschirm, *Ann.*, **245**, 279 (1888).

[22] It has been found that butyl ether, after standing several weeks, may develop a significant "blank" value. A second Grignard treatment and distillation are sufficient to purify it.

[23] A molecular compound from one mole of the pyrroline and one mole of methylmagnesium iodide.

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

Reactions of 2-Arylcyclohexanones. V. 1-Phenylcyclohexaneethylamine, 1-Methyl-9-phenyl-Δ^7-hexahydroindole and Related Compounds

BY W. E. BACHMANN AND E. J. FORNEFELD[1]

Reduction of the keto group of the readily available 2-oxo-1-phenylcyclohexanepropionic acid (I)[2] followed by a Curtius reaction on the reduced acid offered a simple approach to the preparation of 1-phenylcyclohexaneethylamine (II). Reduction of the keto acid presented some difficulty. The usual Clemmensen conditions left the keto group practically untouched, and extensive decomposition took place when the semicarbazone of I was heated with a solution prepared from sodium and diethylene glycol. However, application of the method of Huang-Minlon[3] in which the keto acid was heated with a mixture of potassium hydroxide, hydrazine and diethylene glycol gave the desired 1-phenylcyclohexanepropionic acid in 90% yield.

The azide of 1-phenylcyclohexanepropionic acid was prepared from an acetone solution of the acid chloride and aqueous sodium azide. Rearrangement of the azide in acetic acid followed by hydrolysis of the product with hydrochloric acid yielded the crystalline hydrochloride of 1-phenylcyclohexaneethylamine (II).

We next attempted the same type of Curtius reaction on 2-oxo-1-phenylcyclohexanepropionic acid (I). However, all of the methods which were used to prepare the acid chloride of I yielded a halogen-free, neutral compound, which could be hydrolyzed to the original acid. The compound must be the lactone of 2-hydroxy-1-phenyl-Δ^2-cyclohexenepro-

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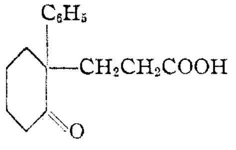
[1] From the Ph.D. dissertation of E. J. Fornefeld, 1950.

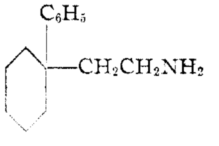
[2] Bachmann and Wick, THIS JOURNAL, **72**, 3388 (1950).

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

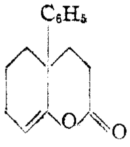
pionic acid (III), an α-hydropyrone with an angular phenyl group.



I



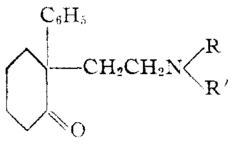
II



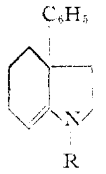
III

The keto group of the methyl ester of I was oximated and the oxime ester was converted into the oxime hydrazide. Treatment of the oxime hydrazide with nitrous acid in acid solution gave a crystalline compound which from the analysis appears to be a bimolecular derivative. The *o*-methyloxime hydrazide yielded an amine in the Curtius reaction but the reaction was not pursued further at the time in view of the successful results obtained on another derivative of the keto acid.

The Curtius degradation of the keto acid was accomplished through the hydrazone hydrazide, which was prepared from the keto ester and hydrazine. Apparently this is the first example of the Curtius degradation of a δ-keto acid. The hydrazone hydrazide reacted with three moles of nitrous acid as judged by a test with starch–potassium iodide paper; in the process apparently the azide of the keto acid was formed since the hydrazone group was also attacked by nitrous acid. According to Wieland and Horner[4] a hydrazone requires a mole of nitrous acid for conversion into the ketone, nitrous oxide and ammonia. In our experiments in which the acidity was high the ammonium ion was probably responsible for the consumption of the extra mole of nitrous acid. The azide was warmed with acetic acid and the product was hydrolyzed with hydrochloric acid. The analysis of the free amine (obtained in 68% yield from the keto ester) corresponded not to 2-oxo-2-phenylcyclohexaneethylamine (IVa) but to the cyclic amine 9-phenyl-Δ^7-hexahydroindole (Va),[5] which was formed by loss of the elements of water. The cyclization which takes place is similar to the formation of 2-methyl-4-phenyl-Δ^2-pyrroline by reduction of 4-phenyl-5-nitro-2-pentanone in acid solution.[6] That the cyclic amine was already present as its hydrochloride in the hydrolysis product and was not produced when the free amine was liberated from its salt was shown by the formation of the picrate of the cyclic amine from the hydrochloride without liberation of the free amine.



IVa, R = R′ = H
IVb, R = H, R′ = COC_6H_5
IVc, R = H, R′ = $COOC_2H_5$
IVd, R = CH_3, R′ = COC_6H_5



Va, R = H
Vb, R = $SO_2C_6H_5$
Vc, R = CH_3

9-Phenyl-Δ^7-hexahydroindole formed a benzenesulfonyl derivative with benzenesulfonyl chloride and alkali. The analysis and the insolubility of the derivative in aqueous sodium hydroxide indicated the cyclic structure Vb for the compound. The product of the reaction of the cyclic amine and benzoyl chloride and sodium hydroxide reacted immediately with 2,4-dinitrophenylhydrazine to give the 2,4-dinitrophenylhydrazone of the benzoyl derivative of the open structure (IVb). This reaction has a precedent in the formation of 6-benzoylamino-2-hexanone from 2-methyl-Δ^2-tetrahydropyridine under Schotten–Baumann conditions.[7] On this basis the benzoyl derivative formed from Va probably has the open structure before the reaction with 2,4-dinitrophenylhydrazine. The N-carbethoxy derivative (IVc) was obtained in the form of its 2,4-dinitrophenylhydrazone by rearrangement of the azide of 2-oxo-1-phenylcyclohexanepropionic acid in ethanol followed by treatment of the product with 2,4-dinitrophenylhydrazine.

The formation of the cyclic structure Va was a fortunate circumstance in that it furnished a solution to the problem of introducing a single methyl group on the nitrogen atom in the open structure IVa. Treatment of Va with dimethyl sulfate yielded 1-methyl-9-phenyl-Δ^7-hexahydroindole (Vc), which was converted under Schotten–Baumann conditions into the N-benzoyl derivative of N-methyl-2-oxo-1-phenylcyclohexaneethylamine (IVd). It is planned to use this compound in further syntheses. We have also prepared 2-methoxyethyl-2-phenylcyclohexanone by reaction of the sodio derivative of 2-phenylcyclohexanone with the benzenesulfonyl ester of methyl cellosolve.

Experimental

2-Oxo-1-phenylcyclohexanepropionic Acid (I).—A 75–77% yield of 2-oxo-1-phenylcyclohexanepropionitrile with b.p. 151–152° at 0.5 mm. was obtained by cyanoethylation of 20 g. of 2-phenylcyclohexanone by the procedure described[2] except that the cyanoethylation mixture was poured into a liter of water and the nitrile was extracted with ether. A mixture of 22.8 g. of the nitrile, 150 ml. of acetic acid, 50 ml. of concentrated hydrochloric acid and 50 ml. of water was refluxed under nitrogen for 15 hours, poured into 300 ml. of water and chilled. The crystalline acid was collected, purified through solution in dilute sodium hydroxide, and recrystallized from aqueous methanol; yield (98%), 22.3 g. with m.p. 114–114.5° and 1.85 g. with m.p. 113–114°.

The semicarbazone of the keto acid, which was produced in 80% yield by heating 1 g. of I with 1 g. of semicarbazide hydrochloride, 2.45 g. of sodium acetate trihydrate, 1 ml. of water and 5 ml. of methanol on a steam-bath for 15 minutes, crystallized from aqueous methanol in small colorless prisms; m.p. 202–203°.

Anal. Calcd. for $C_{16}H_{21}N_3O_3$: C, 63.4; H, 6.9; N, 13.9. Found: C, 63.6; H, 6.9; N, 13.9.

Reduction of the Keto Acid.—Following Huang-Minlon,[3] a solution of 1 g. of 2-oxo-1-phenylcyclohexanepropionic acid, 0.77 g. of potassium hydroxide and 2 ml. of 85% hydrazine hydrate solution was refluxed for 1.5 hours, heated without a reflux condenser until the solution reached a temperature of 195–200°, and then refluxed for 5 hours. Acidification of the cooled mixture with dilute hydrochloric acid precipitated the **1-phenylcyclohexanepropionic acid**, which crystallized from aqueous methanol in colorless glistening plates; yield (90%), 0.8 g. with m.p. 98.5–100° and 0.05 g.

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(4) Wieland and Horner, *Ann.*, **528**, 95 (1937).

(5) The structure may also be written in the tautomeric form with the double bond to the nitrogen atom. The particular form in which the compound reacts will depend on the conditions and reagents involved.

(6) Treibs and Dinelli, *Ann.*, **517**, 170 (1935); Sonn, *Ber.*, **68**, 148 (1935).

(7) Lipp, *Ann.*, **289**, 173 (1896).

with m.p. 96.5–98°. After several recrystallizations an analytical sample melted at 99–100°.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.5; H, 8.6. Found: C, 77.3; H, 8.6.

The keto acid was recovered in 60% yield after 1 g. in 10 ml. of toluene had been heated for 35 hours with 20 g. of amalgamated zinc, 25 ml. of concentrated hydrochloric acid and 25 ml. of water with three further additions of 5 ml. each of hydrochloric acid.

1-Phenylcyclohexane-ethylamine Hydrochloride (II).—A chilled solution of the acid chloride, prepared from 200 mg. of 1-phenylcyclohexanepropionic acid and thionyl chloride, in 3 ml. of acetone was treated with a solution of 0.28 g. of sodium azide in 2 ml. of water. After 10 minutes, the mixture was diluted with water, the azide was extracted into ether and the ether extract was washed with aqueous sodium bicarbonate and dried. The azide remaining after removal of the ether under reduced pressure was warmed gently on a steam-bath with 3 ml. of acetic acid until nitrogen evolution ceased (several hours). After the addition of 5 ml. of concentrated hydrochloric acid, the mixture was refluxed for 12 hours. The cooled solution was diluted with water and extracted with ether, and the aqueous solution was made alkaline. The liberated amine was extracted into ether, the ethereal solution was washed with water and the amine was extracted with 6 *N* HCl. The amine hydrochloride obtained by evaporation of the solution crystallized from acetone–petroleum ether in colorless flocculent needles; yield 140 mg. (68%); m.p. 242–247° dec., raised to 253–254° dec. by further recrystallization.

Anal. Calcd. for $C_{14}H_{22}ClN$: C, 70.1; H, 9.2; Cl, 14.8; N, 5.8. Found: C, 69.6; H, 8.8; Cl, 15.0; N, 5.8.

Formation of the Lactone of 2-Hydroxy-1-phenyl-Δ^2-cyclohexenepropionic Acid (III).—A mixture of 1 g. of 2-oxo-1-phenylcyclohexanepropionic acid, 5 ml. of benzene and 5 ml. of thionyl chloride was refluxed for one hour, the volatile materials were removed under reduced pressure, a few ml. of benzene was added, and the evaporation was repeated. A solution of the product in a few ml. of acetone was treated with a solution of 1.3 g. of sodium azide (apparently unnecessary) in 3 ml. of water. Dilution with water yielded 0.9 g. (97%) of the lactone; m.p. 111–114°. The lactone crystallized from methanol in colorless cubes; m.p. 113.5–114.5°. A mixture of the lactone and the keto acid melted at 87–105°. The lactone is insoluble in cold dilute sodium hydroxide, but goes into warm alkali as the sodium salt of the keto acid.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.9; H, 7.0. Found: C, 78.6; H, 7.0.

Methyl 2-Oxo-1-phenylcyclohexanepropionate.—The ester obtained by treatment of 10 g. of the acid with excess ethereal diazomethane distilled at 146° and 0.05 mm.; yield 10.1 g. After a week the ester solidified; it crystallized from petroleum ether (60–75°) in small colorless prisms, m.p. 52–53°.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.9; H, 7.7. Found: C, 73.7; H, 7.8.

The oxime prepared by the method of Cheney and Piening[8] in 93% yield by refluxing a mixture of 1.57 g. of the keto ester, 2.1 g. of hydroxylamine hydrochloride and 3.58 g. of anhydrous barium carbonate in 15 ml. of absolute ethanol for 16 hours, crystallized from aqueous methanol in colorless prisms, m.p. 126–127°.

Anal. Calcd. for $C_{16}H_{21}O_3N$: C, 69.8; H, 7.6; N, 5.1. Found: C, 69.8; H, 7.7; N, 5.1.

Oxime Hydrazide of 2-Oxo-1-phenylcyclohexanepropionic Acid.—A quantitative yield of the oxime hydrazide with m.p. 192.5–193.5° was obtained by refluxing 1.54 g. of the oxime ester with 5 ml. of 85% hydrazine hydrate solution and 3 ml. of ethanol for one hour. The oxime hydrazide crystallized from methanol in colorless cubes; m.p. 194°.

Anal. Calcd. for $C_{15}H_{21}O_2N_3$: C, 65.5; H, 7.6; N, 15.3. Found: C, 65.5; H, 7.8; N, 15.5.

The O-methyloxime hydrazide, which was prepared from 1.18 g. of the methyl ester of the keto acid by the same procedures used for the oxime hydrazide, crystallized from benzene–petroleum ether in small colorless prisms; yield 0.76 g. with m.p. 129–130° (not raised by further recrystallization) and 0.12 g. with m.p. 126–130°.

Anal. Calcd. for $C_{16}H_{23}N_3O_2$: C, 66.5; H, 7.9; N, 14.6. Found: C, 66.6; H, 7.8; N, 14.9.

Reaction of the Oxime Hydrazide with Nitrous Acid.—An ice-cold solution of 100 mg. of the oxime hydrazide in 10 ml. of 3 *N* HCl was stirred vigorously during the slow addition of a solution of sodium nitrite (0.09 g. in 10 ml. of water). A positive starch–iodide test was obtained after 7 ml. of the solution (2.4 equivalents of nitrite) had been added. The chalky solid which precipitated was dried *in vacuo;* yield 75 mg.; m.p. 204–210° with previous darkening. The compound crystallized from methanol in colorless prisms; m.p. 217–218°. It was recovered unchanged after solution in warm dilute alkali and reprecipitation with the acid. Its analysis agrees fairly well with that of the lactam of N-(2′-hydroximino-1′-phenylcyclohexenepropionamido)-2-amino-1-phenyl-Δ^2-cyclohexanepropionic acid.

Anal. Calcd. for $C_{30}H_{35}O_3N_3$: C, 74.2; H, 7.2; N, 8.7. Found: C, 74.8; H, 7.4; N, 8.5.

Curtius Degradation of 2-Oxo-1-phenylcyclohexanepropionic Acid.—A mixture of 5 g. of the methyl ester of I, 7.5 ml. of 85% hydrazine hydrate solution and 25 ml. of ethanol was refluxed for 3 hours. The volatile materials were removed under reduced pressure on a steam-bath and the glassy residue was dissolved in 100 ml. of 3 *N* HCl; extraction with ether served to remove a slight turbidity. The hydrazide solution was stirred in an ice-bath during the addition of a solution of sodium nitrite (6.85 g. in 50 ml. of water); a test for nitrous acid with starch–iodide test was obtained after 30 ml. (3 equivalents) had been added. The viscous azide, which was isolated with ether (solution washed with bicarbonate, dried and evaporated at room temperature), was warmed gently in 10 ml. of acetic acid on a steam bath and then more strongly for one hour after the initial gas evolution had ceased. After the addition of 10 ml. of concentrated hydrochloric acid and 5 ml. of water, the mixture was refluxed for 1.5 hours. After the removal of the solvents under reduced pressure, a solution of the hydrochloride in water was freed from non-basic material by extraction with ether. Addition of solid sodium hydroxide to the aqueous phase liberated the amine, which was extracted into ether, washed with water and dried. By distillation the **9-phenyl-Δ^7-hexahydroindole (Va)** was obtained as a colorless rather mobile liquid; b.p. 98–100° at 0.1 mm.; yield 2.6 g. (68%).

Anal. Calcd. for $C_{14}H_{17}N$: C, 84.4; H, 8.5; N, 7.0. Found: C, 83.7; H, 8.6; N, 6.9.

The picrate crystallized from methanol in yellow prismatic plates; m.p. 147.5–148.5°.

Anal. Calcd. for $C_{20}H_{20}O_7N_4$: C, 56.1; H, 4.7; N, 13.1. Found: C, 56.7; H, 4.7; N, 12.9.

The benzenesulfonamide (Vb), prepared by the Schotten–Baumann method, after purification by adsorption on alumina from benzene–petroleum ether solution and elution with the same mixture crystallized from aqueous methanol in colorless plates; m.p. 127–128°.

Anal. Calcd. for $C_{20}H_{21}O_2NS$: C, 70.8; H, 6.2; N, 4.1, S, 9.4. Found: C, 70.8; H, 6.3; N, 4.1; S, 9.4.

2-Oxo-1-phenylcyclohexane-ethylbenzamide (IVb).—The product formed by treatment of 9-phenyl-Δ^7-hexahydroindole with benzoyl chloride and alkali readily yielded a crystalline **2,4-dinitrophenylhydrazone** in methanol. After several recrystallizations from acetic acid–methanol, the derivative formed yellow elongated prisms; m.p. 218.5–219°.

Anal. Calcd. for $C_{27}H_{27}O_5N_5$: C, 64.5; H, 5.4; N, 14.0. Found: C, 64.6; H, 5.4; N, 13.7.

N-Carbethoxy-2-oxo-1-phenylcyclohexane-ethylamine (IVc).—The urethan which was prepared by heating the azide in absolute ethanol was evaporatively distilled at 150–155° and 0.1 mm. From 1 g. of the methyl ester of I, 0.94 g. (84%) of the liquid urethan was obtained. When the product was subjected to distillation under reduced pressure (0.05 mm.), decomposition occurred and the yield was reduced to 55%. The **2,4-dinitrophenylhydrazone** crystallized from methanol in orange-yellow micro-prisms, m.p. 138–138.5°.

Anal. Calcd. for $C_{23}H_{27}O_6N_5$: C, 58.9; H, 5.8; N, 14.9. Found: C, 59.3; H, 5.7; N, 14.9.

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[8] Cheney and Piening, THIS JOURNAL, **67**, 734 (1945).

1-Methyl-9-phenyl-Δ^7-hexahydroindole (Vc).—A chilled solution of 1.42 g. of 9-phenyl-Δ^7-hexahydroindole in 3 ml. of methyl ethyl ketone was treated with 0.9 g. of dimethyl sulfate. After 16 hours at room temperature, the mixture was refluxed for 1 hour, treated with 5 ml. of water, and refluxed for 3 hours more. Dilution with water and addition of alkali gave the amine which was extracted into ether and evaporatively distilled at 75–80° and 0.05–0.01 mm.; yield of colorless liquid, 1.35 g. (88%). In air the base quickly assumed a red color. The **picrate**, which was prepared in ether, formed yellow prismatic plates after several recrystallizations from methanol; m.p. 142–143°, depressed to 117–128° by admixture with the picrate of the starting amine.

Anal. Calcd. for $C_{21}H_{22}O_7N_4$: C, 57.0; H, 5.0; N, 12.7. Found: C, 57.3; H, 5.2; N, 12.4.

2-Oxo-1-phenylcyclohexane-ethylmethylbenzamide (IVd).—The benzamide obtained as a viscous liquid by a Schotten–Baumann reaction of Vc was converted into its **2,4-dinitrophenylhydrazone**, which after one recrystallization from acetic acid–methanol and three recrystallizations from benzene–petroleum ether formed rosettes of fine orange-yellow needles, m.p. 172–174°.

Anal. Calcd. for $C_{28}H_{29}O_5N_5$: C, 65.3; H, 5.6; N, 13.6. Found: C, 65.6; H, 5.7; N, 13.5.

2-Methoxyethyl-2-phenylcyclohexanone.—A solution of 20 g. of methyl cellosolve and 50 ml. of pyridine in 50 ml. of benzene was treated at 0° with 56 g. of benzenesulfonyl chloride. After 1.5 hours 100 ml. of ice-cold 6 *N* HCl was added to the cold mixture. The methoxyethylbenzenesulfonate was collected at 136–141° and 0.2 mm.; weight 35 g.

After the slow addition of a solution of 29.5 g. of 2-phenylcyclohexanone in 110 ml. of benzene to a stirred, refluxing suspension of 7.25 g. of finely divided sodamide in 100 ml. of benzene, the mixture was refluxed for 2.5 hours and then treated with 44 g. of methoxyethyl benzenesulfonate. After 12 hours of refluxing, 200 ml. of water was added, and the product which was isolated from the organic layer was refluxed with 100 ml. of acetic acid, 20 ml. of concentrated hydrochloric acid and 20 ml. of water for one-half hour in order to hydrolyze the excess alkylating agent. This procedure circumvented the difficulty which Newman and Magerlein[9] experienced in separating the product from the excess reagent (tosyl ester of ethyl cellosolve). The 2-methoxyethyl-2-phenylcyclohexanone was collected as a colorless viscous liquid at 138–140° and 0.5 mm.; weight 25.5 g. (65%). The **semicarbazone** crystallized from aqueous methanol in small colorless prisms; m.p. 185.5–186°.

Anal. Calcd. for $C_{16}H_{23}N_3O_2$: C, 66.4; H, 7.9; N, 14.5. Found: C, 66.6; H, 7.9; N, 14.1.

The 2,4-dinitrophenylhydrazone formed yellow needles after several recrystallizations from methanol; m.p. 133–134°.

Anal. Calcd. for $C_{21}H_{24}N_4O_5$: C, 61.2; H, 5.8. Found: C, 61.8; H, 5.4.

Summary

1-Phenylcyclohexane-ethylamine was prepared from 1-phenylcyclohexanepropionic acid by the Curtius reaction.

The Curtius reaction has been applied to the δ-keto acid, 2-oxo-1-phenylcyclohexanepropionic acid *via* the hydrazone hydrazide. The product of hydrolysis of the rearranged azide in acid solution was the cyclic amine 9-phenyl-Δ^7-hexahydroindole. Various derivatives of the cyclic amine, of its N-methyl derivative, and of the aminoketones obtained by hydrolytic cleavage were prepared.

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(9) Newman and Magerlein, THIS JOURNAL, **69**, 942 (1947).

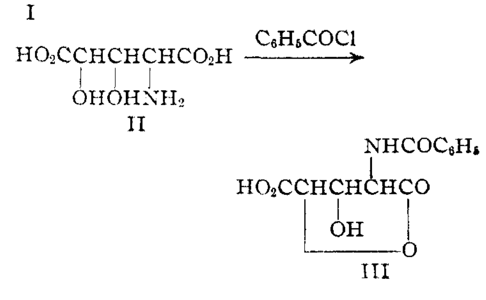
ANN ARBOR, MICHIGAN RECEIVED MAY 26, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY OF VANDERBILT UNIVERSITY SCHOOL OF MEDICINE AND THE DIVISION OF BIOCHEMISTRY OF THE UNIVERSITY OF ILLINOIS]

The Synthesis of β,γ-Dihydroxyglutamic Acid[1]

BY OSCAR TOUSTER AND H. E. CARTER

In recent years there has been considerable interest in the preparation of various derivatives of natural amino acids for possible use in antimetabolite studies. β-Hydroxyglutamic acid has been reported to be a potent competitor of glutamic acid in the nutrition of *Lactobacillus arabinosus*.[2] In connection with another problem, we prepared 3,5-dicarbethoxy-4-hydroxyisoxazole (I) from ethyl acetonedicarboxylate and amyl nitrite[3] and found that high pressure hydrogenation of the isoxazole and hydrolysis of the reduction product with hydrochloric acid yielded β,γ-dihydroxyglutamic acid (II). This is apparently the first report of the catalytic reduction of an isoxazole to a β-aminoalcohol, although Claisen[4] obtained β-imino- and β-aminoketones by the reductive cleavage of 3,5-dimethylisoxazole with sodium. The amino acid was isolated as the monoammonium salt and as the hydrochloride. The ammonium salt was characterized by elementary analyses, ammonium determination, and by quantitative study of its reaction with sodium metaperiodate. The structure of the amino acid was further established by its conversion to the N-benzoyl derivative (III), which existed in the expected lactone form, as indicated by elementary analyses, failure to react with sodium metaperiodate, and neutral equivalent. The lactone ring was opened readily by



I

II

III

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[1] The authors wish to express their appreciation to the Abbott Laboratories, Eli Lilly and Company, Parke, Davis and Company, and the Upjohn Company for a generous grant in support of this work. Part of the material presented in this paper was taken from the thesis submitted by Oscar Touster to the Graduate College of the University of Illinois in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry, 1947. The work carried out at Vanderbilt University was supported in part by The Rockefeller Foundation and Nutrition Foundation through grants to the Division of Nutrition.

(2) Borek and Waelsch, *J. Biol. Chem.*, **177**, 135 (1949).

(3) Pechmann, *Ber.*, **24**, 857 (1891).

(4) Claisen, *ibid.*, **24**, 3900 (1891).