[CONTRIBUTION FROM THE WALKER LABORATORY OF RENSSELAER POLYTECHNIC INSTITUTE]

The Action of Methylmagnesium Iodide on Substituted Pyrrolines and Related Substances[1]

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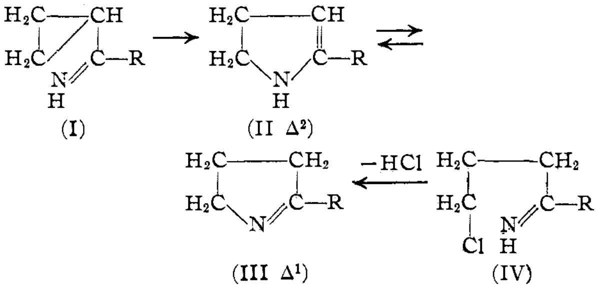
The work reported in the present paper was undertaken in order to throw more light on the structure of pyrrolines. A simple pyrroline, or dihydropyrrole, may conceivably exist in the isomeric Δ^1, Δ^2 and Δ^3 forms, depending upon the position of the double bond in the heterocyclic nucleus. The unsubstituted Δ^3 form[3,4] has been described, but derivatives have been reported of all three isomers. These compounds have been prepared by the cyclization of γ-aminoketones[5,6]; by the reduction of cyano ketones[7]; by the reduction of nitro ketones[8]; and by the action of Grignard reagents on 1-methyl-2-pyrrolidone.[9] The formation of 2-phenylpyrroline by the action of phenylmagnesium bromide on γ-chlorobutyronitrile was described by Cloke[10] and other illustrations of this synthesis are described in this paper.

The reaction between a Grignard reagent and γ-chlorobutyronitrile may follow several paths, as outlined by Cloke, Baer, Robbins and Smith[11] to give conceivably a Δ^1- or Δ^2-pyrroline, which may be tautomeric



It might be supposed that, by analogy with other amino compounds, the pyrrolines (III) formed from γ-chloropropyl ketimine (IV) would be the Δ^1 compounds, whereas those (II) formed as the result of the rearrangement of phenyl cyclopropyl ketimine (I) could be expected to possess the Δ^2 structure. Since in most cases a single compound is obtained, a change from one form to the other is indicated.

The Action of Methylmagnesium Iodide on Pyrrolines.—Since the Δ^1-pyrroline structure possesses an azomethine linkage and as the Δ^2 formation contains a secondary amine group, it appeared that the Zerevitinov method of Grignard analysis might offer a method for distinguishing between such Δ^1- and Δ^2-pyrroline isomers, as in similar work by Moureu and Mignonac.[12] The secondary amino group has been shown by Zerevitinov,[13] Moureu and Mignonac, and Oddo[14] to be active to methylmagnesium iodide, forming methane, while the tertiary amino nitrogen in the azomethine linkage should produce no methane under the same conditions.

In the work described in the present paper a quantitative study was made of the action of methylmagnesium iodide on pyrrolines substituted in the 2- and 3-positions in an apparatus designed to measure both the amount of methane formed and the total amount of Grignard reagent consumed in the reaction.[15] It was shown that the Grignard reagent reacted with 2-phenylpyrroline and other 2-substituted pyrrolines, as well as with 2,3-diphenylpyrroline and 2,3-diphenyl-3-ethyl-Δ^1-pyrroline, without the formation of gas, and that these compounds consumed an equivalent amount of the reagent.

Both 2-phenylpyrroline and 2,3-diphenylpyrroline behaved similarly toward methylmagnesium iodide when treated in the Zerevitinov apparatus, even when solutions of different concentrations, varying amounts of butyl ether solvent and Grignard reagents of different strengths were employed. 2-Phenylpyrroline gave 0.01 mole of active hydrogen and consumed 1.01 moles of reagent, while 2,3-diphenylpyrroline yielded 0.01 mole of active hydrogen and reacted with 1.03 moles of the reagent.

TABLE I

ACTION OF METHYLMAGNESIUM IODIDE ON PYRROLINES AND AZOMETHINES

Compound	Moles active hydrogen	Moles of Grignard reagent consumed
2-Methylpyrroline	0.00	0.92
2-Ethylpyrroline	.01	0.99
2-Propylpyrroline	.00	1.00
2-Amylpyrroline	.01	1.06
2-Benzylpyrroline	.00	0.92
2-Phenylpyrroline	.01	1.01
2-(1-Naphthyl)-pyrroline	.03	0.99
2,3-Diphenylpyrroline	.01	1.03
2,3-Diphenyl-3-ethylpyrroline	.03	1.00
Acetophenone anil[a]	.02	0.98
Benzalaniline[b]	.01	1.06
Benzophenone anil[a]	.05	0.94
Benzylideneëthylamine	.02	0.99

[a] Prepared by the method of Reddelien, *Ber.*, **46**, 2720 (1913); **43**, 2478 (1910). [b] Prepared as described in "Organic Syntheses," Col. Vol. I, 1941, p. 80.

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[1] This paper is taken partly from the second part of a thesis presented by Paul Morris Maginnity to the Rensselaer Polytechnic Institute, in partial fulfillment of the requirements for the degree of Doctor of Philosophy, February, 1946, and partly from theses submitted for the degrees of B.S. and M.S.

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[3] Ciamician and Dennstedt, *Ber.*, **16**, 1536 (1883).

[4] Treibs and Dinelli, *Ann.*, **517**, 170 (1935).

[5] Hielscher, *Ber.*, **31**, 277 (1898).

[6] Gabriel, *ibid.*, **41**, 513 (1908); **42**, 1238 (1909).

[7] Rupe and Gisiger, *Helv. Chim. Acta*, **8**, 338 (1925).

[8] Sonn, *Ber.*, **68**, 148 (1935); *ibid.*, **72**, 2150 (1939).

[9] Lukeš, *Coll. Czech. Chem. Comm.*, **4**, 181, 351 (1932).

[10] Cloke, THIS JOURNAL, **51**, 1174 (1929); Lipp and Seeles, *Ber.*, **62B**, 2456 (1929); Craig, Bulbrook and Hixon, THIS JOURNAL, **53**, 1831 (1931).

[11] Cloke, Baer, Robbins and Smith, *ibid.*, **67**, 2155 (1945).

[12] Moureu and Mignonac, *Compt. rend.*, **158**, 1395, 1624 (1914).

[13] Zerevitinov, *Ber.*, **41**, 2233 (1908).

[14] Oddo, *ibid.*, **44**, 2048 (1911).

[15] Maginnity with Cloke, *Anal. Chem.*, **20**, 978 (1948).

Moreover, when 2,3-diphenyl-3-ethylpyrroline, which would appear to possess the Δ^1 form,[16] was treated under the same conditions, a similar behavior was observed.

Table I summarizes the results of the action of methylmagnesium iodide on some pyrrolines and azomethines.

The above results indicate that when one mole of a pyrroline (or azomethine compound) reacts with one mole of methylmagnesium iodide, comparatively little methane is liberated. Analysis of the reaction mixture, in the case of 2-phenylpyrroline, demonstrated that a considerable portion of the original compound was recovered unchanged, while analysis of the addition complexes between 2-phenylpyrroline and both methylmagnesium iodide and isoamylmagnesium bromide indicate that a compound is formed from equimolar quantities of both reactants.

Failure to obtain methane cannot be attributed to slowness of the reaction, since a sample of 2-phenylpyrroline allowed to remain in contact with methylmagnesium iodide for 30 hours gave no gas, but consumed one mole of the reactant as before.

This behavior of pyrrolines was found to be similar to that of compounds known to contain the azomethine group when treated under similar conditions. Benzylideneëthylamine, benzalaniline and benzophenone anil all consumed one mole of methylmagnesium iodide. In the case of acetophenone anil, which may also exist in the enamine form,[17] no gas was evolved, and one mole of the reagent was consumed. When the mixture resulting from the action of methylmagnesium iodide on benzophenone anil was examined, a large part of the anil was recovered unchanged, a fact previously noted by Short and Watt.

The behavior of 2-substituted pyrrolines and azomethine compounds is also in harmony with the behavior of tertiary aliphatic amines toward the Grignard reagent under the same conditions.[18]

These results suggest a Δ^1 structure for pyrrolines prepared from γ-chlorobutyronitrile and Grignard reagents.

Acknowledgment.—The earlier research for this paper was done under the direction of Dr. James V. Murray, whose contribution to this work is gratefully acknowledged.

Experimental Part

Preparation of Pyrrolines.—2-Methyl-, 2-ethyl-, 2-propyl-, 2-benzyl- and 2-phenylpyrroline were prepared by the action of the appropriate Grignard reagent on γ-chlorobutyronitrile, followed by decomposition of the addition product in liquid ammonia and extraction of the product with ether, a modification of the original method of Cloke as developed by Lachmann.[19] A discussion is given of the preparation of 2-ethylpyrroline, which was very carefully carried out and its properties determined in order to make sure that work was being done on the simple pyrroline and not on another type of compound, which may be formed in the reaction. References to 2-amyl- and 2-(1-naphthyl)-pyrroline could not be found in the literature.

2-Ethylpyrroline.—Ethylmagnesium bromide was prepared from 273 g. (2.5 moles) of ethyl bromide, 61 g. (2.5 moles) of magnesium and 1200 ml. of ethyl ether. When the Grignard solution had refluxed for 3.5 hours, the ethyl ether was replaced by isoamyl ether, and the mixture distilled until a temperature of 54° was reached. By this procedure, it was expected that all the excess ethyl bromide (b.p. 38°) would have been removed. Treatment of this solution with 103.5 g. (1 mole) of γ-chlorobutyronitrile, decomposition in 1500 ml. of liquid ammonia, and fractionation of the purified ether extract yielded 29 g. of a liquid b.p. 127.5–128.3° (cor.), at 765 mm.; $n^{25}\text{D}$ 1.4732; d^{25} 0.8540; mol. refraction, 29.77.

Anal. Calcd. for $C_6H_{11}N$: N, 14.42; neut. equiv., 97.1. Found: N, 14.46 (Dumas), 14.46 (Kjeldahl); neut. equiv., 98.5.

Chloroplatinate.—The chloroplatinate was made by adding 10% chloroplatinic acid to a solution of 2-ethylpyrroline in ethanol. The solid was recrystallized twice from ethanol; m.p. 177–178° (cor.).

Anal. Calcd. for $C_{12}H_{24}N_2PtCl_6$: Pt, 32.20. Found: Pt, 32.45, 32.39.

Picrate.—A saturated solution of picric acid in benzene was added to a solution of 2-ethylpyrroline in benzene. The resulting precipitate was recrystallized from glacial acetic acid; m.p. 86–87° (cor.).

Anal. Calcd. for $C_{12}H_{14}N_4O_7$: N, 17.19. Found: N, 17.13 (Dumas).

2-Amylpyrroline.—Amylmagnesium iodide was prepared from 247 g. (1.25 moles) of amyl iodide, 37 g. (1.5 moles) of magnesium and 500 ml. of anhydrous ethyl ether. The solution was refluxed for 2.5 hours, when 52 g. (0.5 mole) of γ-chlorobutyronitrile was added over a period of one hour. Refluxing was continued 2.5 hours longer. The mixture was then decomposed in 600 ml. of liquid ammonia and purified by extraction with hydrochloric acid, neutralization with sodium hydroxide, extraction with ether and distillation, giving 14 g. of a liquid of b.p. 88–91° at 22.5 mm., mainly at 89°.

Anal. Calcd. for $C_9H_{17}N$: N, 10.07; neut. equiv., 139.2. Found: N, 9.92, 9.60 (Kjeldahl); neut. equiv., 141.5.

Chloroplatinate.—The compound was prepared as was the chloroplatinate of 2-ethylpyrroline; m.p. 170–170.5° (cor.) with dec.

Picrate.—To 0.5 g. of the pyrroline dissolved in about 1 ml. of benzene was added a few ml. of a saturated solution of picric acid in benzene. After standing several days, crystals were obtained, which were then recrystallized from 95% ethanol; m.p. 82–82.5°.

Anal. Calcd. for $C_{15}H_{20}N_4O_7$: N, 15.22. Found: N, 15.13 (Dumas).

2-(1-Naphthyl)-pyrroline.—1-Naphthylmagnesium bromide was prepared from 126.8 g. (0.61 mole) of 1-bromonaphthalene, 14.9 g. (0.61 mole) of magnesium and 300 ml. of anhydrous ether, using a small crystal of iodine as a catalyst. The Grignard solution was refluxed for one hour, and 25.9 g. (0.25 mole) of γ-chlorobutyronitrile in 22 ml. of ether was added slowly at such a rate as to cause refluxing of the ether. The mixture was decomposed in 500 ml. of liquid ammonia and purified as in the case of amylpyrroline. At this point, the crystals were light brown in color. An attempt was made to purify the compound further as follows: The pyrroline was dissolved in ether and extracted with 20% hydrochloric acid. The hydrochloride solution was washed three times with carbon tetrachloride, until the washings were no longer colored, and with ethyl ether until the ether remained colorless. Finally the hydrochloride solution was further decolorized by heating for half an hour with Norit charcoal. The free base was precipitated by the addition of 10% sodium hydroxide solution and the solid material collected on a filter. The solid was recrystallized by dissolving it in 125 ml. of 95% ethanol and adding ice while stirring vigorously. When sufficient water had been added, the free base separated out in the form of pale brown crystals; m.p. 37° (uncor.).

Anal. Calcd. for $C_{14}H_{13}N$: N, 7.18. Found: N, 7.30 (Dumas).

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[16] Murray and Cloke, THIS JOURNAL, **68**, 126 (1946).

[17] Short and Watt, *J. Chem. Soc.*, 2293 (1930), reported that this compound condenses in the presence of Grignard reagents to dypnone anil, asserting that the Grignard reagent takes part in the reaction. The above results show that one mole of the reagent is consumed for one mole of the anil.

[18] A study of the action of methylmagnesium iodide on aliphatic amines is currently in progress.

[19] Lachmann, Thesis, Rensselaer Polytechnic Institute, 1931.

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.

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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.

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[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

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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).