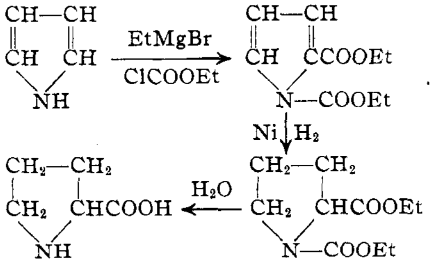
[A CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

A Synthesis of *dl*-Proline from Pyrrole[1]

BY FRANK K. SIGNAIGO AND HOMER ADKINS

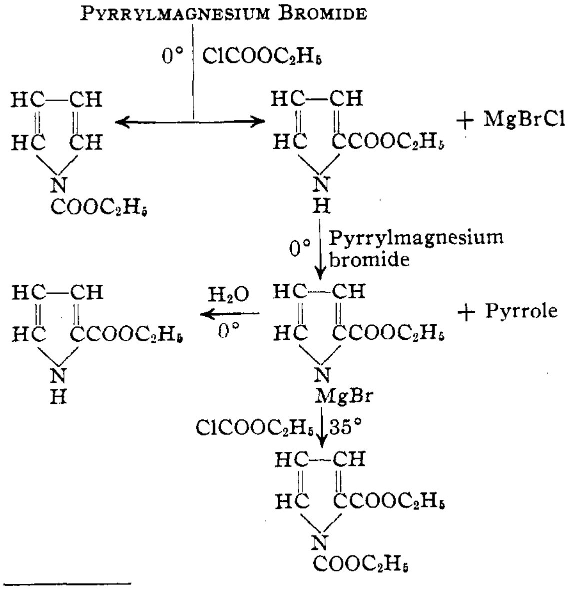
Several syntheses of *dl*-proline have been reported but none of them is very satisfactory from a preparational standpoint. The best methods are apparently those of Heymons,[2] who obtained the copper salt of *dl*-proline in three operations from piperidone-2, and that of Sørensen and Andersen,[3] who prepared the copper salt in five operations from malonic ester. The first method is said to give an over-all yield of 28%. The yield by the second method is not given, but is apparently somewhat greater. Several authors have suggested the desirability of developing a synthesis of proline from pyrrole through 2-carbethoxypyrrole as by Putokhin.[4] A difficulty in this process lies in the hydrogenation of the pyrrole ring in a carboxy- or carbethoxypyrrole. Putokhin used a high ratio of Adams platinum catalyst with 1 g. of pyrrole-2-carboxylic acid and as a result of repeated treatments with hydrogen and catalyst and change of solvent, obtained a 23% yield of the copper salt of *dl*-proline from the pyrrole acid.

While the hydrogenation of a 2-carboxy- or carbethoxypyrrole seems an impractical process with the catalysts now available, it appeared feasible to prepare *dl*-proline through the formation of 1,2-dicarbethoxypyrrole and the hydrogenation of the latter, *i. e.*



The hydrogenation may be carried out easily and almost quantitatively as a result of work recently reported.[5] The hydrolysis step is also a simple process but the preparation of the 1,2-dicarbethoxypyrrole in a good yield required study. However, by this process crystalline *dl*-proline has been obtained in an over-all yield of 57% from pyrrole.

Oddo[6] prepared 2-carbethoxypyrrole in over 90% yield from pyrrylmagnesium bromide and ethyl chlorocarbonate. In attempting to follow his method, but on a larger scale, we recovered 42% of the pyrrole and obtained 7% of 1-carbethoxypyrrole, 22% of 2-carbethoxypyrrole and 2% of 1,2-dicarbethoxypyrrole. When the conditions were modified by heating the reaction mixture for four hours at 35° before hydrolysis, instead of keeping it near 0°, then the yield of 1,2-dicarbethoxypyrrole was much greater, *i. e.*, 26%, accompanied by 13% of 1-carbethoxypyrrole and 3% of 2-carbethoxypyrrole. However, 50% of the pyrrole was recovered. These results suggested that pyrrylmagnesium bromide reacts with ethyl chlorocarbonate to give both 1- and 2-carbethoxypyrrole and that the latter but not the former reacts with pyrrylmagnesium bromide to give pyrrole and 2-carbethoxypyrrylmagnesium bromide. The last mentioned compound may then react, especially at higher temperatures, with ethyl chlorocarbonate to give 1,2-dicarbethoxypyrrole. These transformations are indicated below.



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[1] The Wisconsin Alumni Research Foundation allotted funds for a research assistantship held by F. K. S. in the period Sept., 1933 to Sept., 1935.

[2] Heymons, *Ber.*, **66**, 846 (1933).

[3] Sørensen and Andersen, *Z. physiol. Chem.*, **56**, 240 (1908).

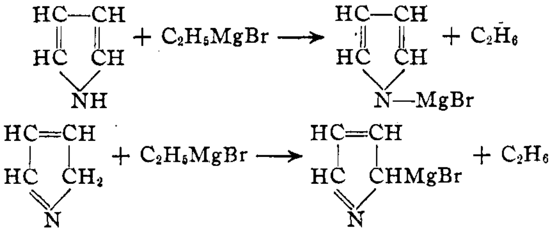
[4] N. Putokhin, *J. Russ. Phys.-Chem. Soc.*, **62**, 2216 (1930); *C. A.*, **25**, 3995 (1931).

[5] Signaigo and Adkins, THIS JOURNAL, **58**, 709 (1936).

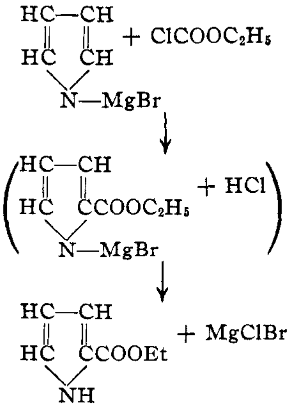
[6] Oddo, *Gazz. chim. ital.*, **39**, I, 649 (1909); **42**, II, 252 (1912).

Upon the basis of this scheme it seemed desirable to treat one mole of ethylmagnesium bromide with one mole of pyrrole and then to add *alternately* in *portions*, one mole each of ethyl chlorocarbonate and ethylmagnesium bromide and finally a second mole of ethyl chlorocarbonate. By such a process the reaction of all of the pyrrole was brought about and at the same time excessive reaction between the ethyl chlorocarbonate and the ethylmagnesium bromide was avoided. Such a procedure as described in the experimental part gave a 65% yield of 1,2-dicarbethoxypyrrole.

There seem to be two rather reasonable explanations of the fact that 1- and 2-carbethoxypyrroles are formed simultaneously. Tschelinzew and Karmanov[7] suggested that the isomerism of the pyrrole nucleus makes possible the formation of two "pyrrylmagnesium bromides," *i. e.*



The formation of a Grignard reagent in the second case would be analogous to the behavior of a methylene group in cyclopentadiene, indene and fluorene. The formulation is in accord with the fact that only pyrroles which may tautomerize form Grignard reagents.[8] If the above is accepted then the relative proportions of 1- and 2-carbethoxypyrroles formed are a function of the proportion of the tautomers and (or) of the relative rates of reaction of ethyl chlorocarbonate with the two Grignard reagents.



However, it is not necessary to assume the existence of tautomeric pyrroles in order to explain the formation of 2-carbethoxypyrrole, for the ethyl chlorocarbonate may condense with the hydrogen on the 2-carbon atom.

Such a scheme finds support in the fact that 1-methylpyrrole does not form a Grignard reagent yet condenses with acid chlorides in the presence of an alkylmagnesium halide to yield 1-methyl-2-acylpyrroles.[8] However 1-carbethoxypyrrole apparently did not react with ethyl chlorocarbonate in the presence of a Grignard reagent.

Experimental Part

The apparatus for the preparation of 1,2-dicarbethoxypyrrole consisted of a 1-liter, 4-necked flask fitted with a mercury-sealed stirrer, a reflux condenser, the upper end of which was connected to a drying tube containing calcium chloride, and two dropping funnels. One of these dropping funnels was of the usual type, and the other was a 500-cc. flask with a stopcock sealed on the bottom and so fitted that a Grignard reagent could be prepared in it. Both of the funnels were graduated.

Ethylmagnesium bromide (approximately 0.25 mole) was prepared in the reaction flask from 32.7 g. (0.30 mole) of ethyl bromide, 7.2 g. (0.30 mole) of magnesium turnings and 150 cc. of ether. A like amount also was prepared in the 500-cc. dropping funnel. The reaction flask was cooled with a mixture of ice and salt to below 0° and 17 g. (0.25 mole) of pyrrole in 35 cc. of ether was added dropwise through the smaller dropping funnel. The reaction mixture was stirred during this and subsequent operations.

Into the smaller dropping funnel was placed 75 cc. of an ether solution containing 28 g. (0.25 mole) of ethyl chlorocarbonate. The Grignard reagent in the larger dropping funnel was diluted with ether to a volume of 200 cc. These two reagents were then added to the reaction flask drop by drop in the following fashion. One-half of the ethyl chlorocarbonate solution (37 cc.) was first added. This was followed by one-half of the Grignard solution (100 cc.). Again half of the remaining ethyl chlorocarbonate solution (19 cc.) was added and followed by half of the remaining Grignard solution (50 cc.). This process was repeated, each time adding one-half of the solution remaining in the dropping funnel until only 5–10 cc. of each reagent remained. This last small amount of each solution was then added and 37 g. (0.35 mole) of ethyl chlorocarbonate was poured into the reaction mixture through the smaller dropping funnel. These addition processes were completed in two hours. The reaction mixture was allowed to warm up to room temperature and then refluxed on a steam-bath for four hours. The contents of the reaction flask were then poured onto ice and the mixture made slightly acid by the addition of dilute sulfuric acid. The ether layer was separated and the aqueous layer was extracted twice with ether. The combined ether solutions were then washed once with a small quantity of sodium bicarbonate solution and dried for eight hours over anhydrous sodium sulfate. The ether was distilled off and the liquid residue was fractionated at reduced pressure as indi-

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(7) (a) Tschelinzew and Karmanov, *J. Russ. Phys.-Chem. Soc.*, **47**, 161 (1915); (b) *cf.* Oddo, *Gazz. chim. ital.*, **64**, 584 (1934).

(8) Oddo, *ibid.*, **44**, I, 706 (1914).

cated in the table. The recovery of ethyl chlorocarbonate as well as the amount of 1-carbethoxypyrrole obtained, indicate that 1.75 mole each of the Grignard reagent and the ethyl chlorocarbonate per mole of pyrrole would give as good a yield as did the proportion of reactants used above.

Table I

Products of Reaction

Fraction	Compound	Boiling range, °C.	Weight, g.	Yield, %
1	Ethyl chlorocarbonate	Up to 55° (65 mm.)	10	..
2	1-Carbethoxypyrrole	60– 65° (7 mm.)	9.2	26.4
3	2-Carbethoxypyrrole	100–110° (7 mm.)	0.5	1.5
4	1,2-Dicarbethoxypyrrole	125–135° (7 mm.)	34.2	65.0
	Residue		1.8	
			Total	92.9

The fourth fraction was found to be nearly pure 1,2-dicarbethoxypyrrole[6] since on refractionation 98% of the material distilled at 132–134° at 8 mm. The 1-carbethoxypyrrole had a b. p. of 57–58° at 7 mm., and 178–180° at 740 mm., and d^{25} 1.037, n^{25}_D 1.4698. The boiling point of this compound checks with that reported by other investigators. Only one author has reported the density and refractive index of this compound and these values do not check with those given above. However, the compound seems to be sufficiently characterized by the fact that it takes up 4 atoms of hydrogen to give a non-basic compound having the correct analysis for a carbethoxypyrrolidine, indicating that the carbethoxy group is on the nitrogen atom. The 1-carbethoxypyrrole is better prepared from potassium pyrrole and ethyl chlorocarbonate.[7a,9]

The 2-carbethoxypyrrole had a m. p. of 41–42° when crystallized from low-boiling petroleum ether and a b. p. of 102–104° at 7 mm.

The 1,2-dicarbethoxypyrrole so obtained was hydrogenated rapidly and quantitatively over Raney nickel.[5] In a typical experiment 1,2-dicarbethoxypyrrolidine b. p. 133–134° (8 mm.) was obtained in 98% yield by the hydrogenation of 0.2 mole of the pyrrole ester over 5 g. of Raney nickel under 100 to 200 atm. of hydrogen at 50 to 85° in less than one hour.

The 1,2-dicarbethoxypyrrolidine (10.6 g. or 0.05 mole), was refluxed with 25 cc. of concentrated hydrochloric acid for three hours; 10 cc. more of hydrochloric acid was then added and the refluxing continued for two hours. The mixture was then evaporated on a steam-bath. The partially crystallized residue was dissolved in 100 cc. of water and treated with 0.10 mole of freshly precipitated silver carbonate. After filtration, the filtrate was treated with hydrogen sulfide. The solution was heated with 1 g. of activated charcoal and this together with the silver sulfide was removed by filtration. Upon evaporation of the filtrate on a steam-bath, there was obtained 5.7 g. of a gummy crystalline mass. This was dissolved in 25 cc. of hot ethanol and 50 cc. of hot dioxane was added. After cooling the solution with ice, the crystalline proline was filtered off and dried in a desiccator. The yield was 5.2 g. (90%), m. p. 204°. The picrate was prepared by dissolving 1 g. of proline and 2 g. of picric acid in 2 cc. of hot acetic acid, followed by addition of 7 cc. of ether and cooling. The picrate was recrystallized from ethanol and showed a m. p. of 136°.

Summary

Crystalline *dl*-proline may be prepared in yields of 55 to 60% from pyrrole through the intermediate formation of 1,2-dicarbethoxypyrrole and 1,2-dicarbethoxypyrrolidine. A method for the synthesis of 1,2-dicarbethoxypyrrole has been devised and developed.

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[9] Ciamician and Dennstedt, *Ber.*, **15**, 2579 (1882); *Ber.*, **60**, 196 (1927).

[Contribution from the Converse Memorial Laboratory of Harvard University]

A Further Study of Extremely Weak Acids

By W. K. McEwen

The purpose of this paper is to report the new methods used and the results obtained in the study of extremely weak acids.

It has been shown by Conant and Wheland[1] that reactions of the type

$$R_1H + R_2^- \rightleftarrows R_1^- + R_2H$$

may be used to determine the relative acid strength of very weak acids such as the aromatic and aliphatic derivatives of water, ammonia and methane. The determination of the relative amounts of the different substances present at the point of equilibrium is a measure of the relative strength of the two acids. This can be determined in either of two ways.

The first method used was to observe the change in color. Since many compounds of the type R^- are colored, it is only necessary to mix the reactants and observe whether or not a change in color results. As a check the products of the reaction are also mixed. From such observations the compounds can be arranged in a series of de-

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[1] Conant and Wheland, This Journal, **54**, 1212 (1932).