[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

Synthesis of a Series of Alpha-Substituted N-Methylpyrrolines

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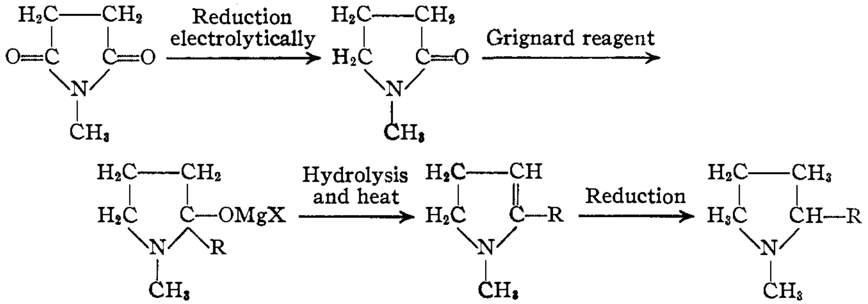
Introduction

As part of a systematic study of structure and physiological action in the nitrogen heterocyclics it seemed desirable to prepare and study a series of α-substituted N-methylpyrrolidines. Although several members of the series have previously been prepared a suitable general method of synthesis was lacking.

Löffler[2] prepared several of the aliphatic members of the series by ring closure of α-substituted butylmethylamines but LaForge[3] was not able to effect ring closure of 1-methylamino-1-phenylbutane by the same method. Methylation of the corresponding α-substituted pyrrolidine offers another possibility since a general method of synthesis of α-substituted pyrrolidines has been given[4] but methylation of heterocyclic nitrogen is usually a poor and oftentimes impossible procedure from a synthetic standpoint. The following synthesis was proposed in this Laboratory and proved satisfactory for the preparation of the compounds in the quantity desired.



The α-substituted N-methylpyrrolines are intermediates in the above synthesis. As these compounds have been little studied[5] it seemed well to report their synthesis and properties in a separate preliminary paper.

α-Methylpyrroline has been found by Marz[6] to react with hydroxylamine, semicarbazide and phenylhydrazine in aqueous solution. The following equilibrium has been postulated to account for the reaction.

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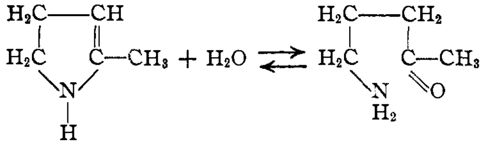
[2] Löffler, *Ber.*, **43**, 2046 (1910).

[3] LaForge, THIS JOURNAL, **50**, 2471 (1928).

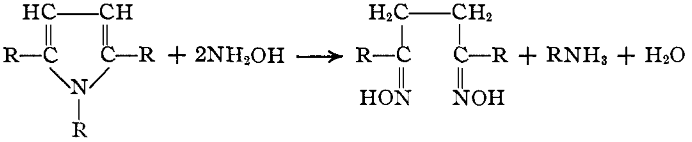
[4] Craig and Hixon, *ibid.*, **53**, 1831 (1931).

[5] While this work was under way the work of Lukes, *Collection Czechoslov. Chem. Comm.*, **2**, 531–44, who synthesized several α-substituted N-methylpyrrolines by a similar method, appeared.

[6] Marz, Diss. Techn. Hochsch., München, 1913.

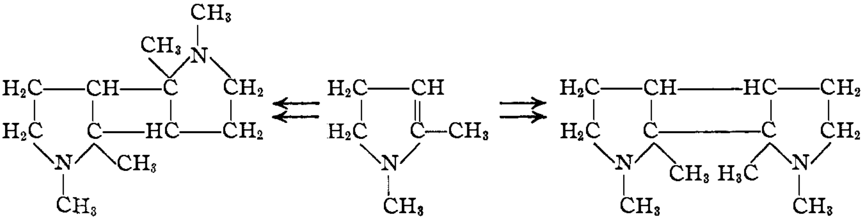


The same equilibrium has been found in the case of the analogous tetrahydropyridine series.[7] However, the compounds prepared in this Laboratory did not appear to exhibit the equilibrium. None of the series gave any indication of a reaction with semicarbazide or phenylhydrazine. When added to a solution containing equivalent quantities of hydroxylamine hydrochloride and potassium carbonate all of the derivatives readily dissolve but this fact cannot be taken as evidence for an equilibrium in the aqueous solution of the compound. A curious reaction of pyrrole derivatives with hydroxylamine according to the equation



has long been known.[8] It is only logical to expect that the half reduced pyrrole will act similarly with regard to the unreduced half of the ring. α-Methyl-N-methylpyrroline is the only member of the series that is soluble to any extent in water. All the other derivatives, when shaken with water and the layers separated, show little if any water to be present in the oily layer.

α-Methyl-N-methylpyrroline is the only member of the series which does not distil normally. Its behavior upon distillation can best be explained by a reversible polymerization to a dimer according to either or both of the following equations



This view is supported by the behavior of the compound upon reduction. The reduction products contain a 45% yield of α-methyl-N-methylpyrrolidine but also a 50% yield of a compound boiling at 132–134° (20 mm.). Analysis shows the compound to have the empirical formula $(C_8H_{12}N)_n$ which corresponds with that of the dipyrrolidine expected from either of

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(7) Lipp and Widmann, *Ann.*, **409**, 90 (1915).

(8) Ciamician and Zanetti, *Ber.*, **22**, 1968 (1889); **23**, 1787 (1890); Fischer and Zimmermann, *Z. physiol. Chem.*, **89**, 163 (1924).

the two postulated dimers if the unstable cyclobutane ring is ruptured. It has been shown by Lipp[9] that the analogous compound N-methyltetrahydropicoline polymerizes to a dimer which dissociates again quite easily.

As a class the α-substituted N-methylpyrrolines are all unstable and quickly develop a deep red color after distillation when exposed to the atmosphere. However, they may be preserved colorless indefinitely if carefully sealed in ampoules with the exclusion of air. They are soluble in all organic solvents but insoluble in water with the exception of α-methyl-N-methylpyrroline, which is soluble in almost all proportions. They have a characteristic unpleasant odor.

Reduction of the series of α-substituted N-methylpyrrolines will be reported in a later paper.

The writer wishes to thank Professor E. Emmet Reid for his encouragement and advice during this work.

Experimental

Synthesis of N-Methyl-α-pyrrolidone.—This compound was first synthesized by Tafel and Wassmuth;[10] later by Späth and Bretschneider.[11] They reduced succinimide electrolytically at a lead cathode using a high current density. The resulting pyrrolidone was converted to the sodium derivative and methylated with methyl iodide or sulfate. A much more convenient synthesis is the electrolytic reduction[5] of N-methylsuccinimide[12] by the method of Tafel and Stern.[13] The reduction product is isolated from the 50% sulfuric acid solution by a continuous extractor which is a modification of the Soxhlet extractor designed to extract aqueous solutions by chloroform. This method of isolation almost doubles the yield obtained by the method of Lukes.[5] Fractionation of the chloroform extract gives a yield of 80% of the theoretical amount of N-methyl-α-pyrrolidone boiling at 94–96° (20 mm.) and a small amount of unreduced succinimide.

Synthesis of α-Substituted N-Methylpyrrolines.—The Grignard reagent is prepared in the usual way using 2 moles of RX. One mole of pyrrolidone in an equal volume of ether is added dropwise. The mixture is allowed to stand overnight and hydrolyzed with an equivalent of hydrochloric acid. The aqueous layer is treated with excess sodium hydroxide solution and steam distilled. The base recovered from the distillate is dried over solid potassium hydroxide.

Table I

		Analysis, %			
		Calculated		Found	
Compounds		C	H	C	H
α-Phenyl-N-methylpyrroline	$C_{11}H_{13}N$	82.4	8.24	82.7	8.5
α-*n*-Butyl-N-methylpyrroline	$C_9H_{17}N$	77.5	12.3	77.3	12.2
α-*n*-Propyl-N-methylpyrroline	$C_8H_{15}N$	76.7	12.0	76.4	12.0
α-Ethyl-N-methylpyrroline	$C_7H_{13}N$	75.7	11.8	75.5	12.5
α-Methyl-N-methylpyrroline	$C_6H_{11}N$	74.3	11.4	74.2	11.1

In the following table which describes some properties of the series the percentage yield is calculated on the weight of N-methyl-α-pyrrolidone used.

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(9) Lipp, *Ann.*, **289**, 218 (1896).

(10) Tafel and Wassmuth, *Ber.*, **40**, 2839 (1907).

(11) Späth and Bretschneider, *ibid.*, **61**, 330 (1929).

(12) Menschutkin, *Ann.*, **182**, 90 (1876).

(13) Tafel and Stern, *Ber.*, **33**, 2224 (1900).

TABLE II

Compounds	Yield, %	B. p., °C.	Picrate	Oxalate
α-Phenyl-N-methylpyrroline	70	105–109 (11 mm.)	M. p., 139°	M. p., 138°
α-*n*-Butyl-N-methylpyrroline	54	86–87 (30 mm.)	M. p., 66°	Oil
α-*n*-Propyl-N-methylpyrroline	50	176–177	Oil	Oil
α-Ethyl-N-methylpyrroline	53	148–149	M. p., 114°	Oil
α-Methyl-N-methylpyrroline	50	130–131	Decd. upon heating	Oil

The measurement of other physical properties of the series is impracticable due to the speed with which the colorless freshly distilled base decomposes or reacts with the atmosphere. α-Methyl-N-methylpyrroline does not always distil in the same way in separate preparations. While in one run it distils completely at 130°, in another it cannot be distilled at atmospheric pressure. This run, at 30 mm. pressure does not give a well-defined distillation but the entire lot distils over, the temperature reaching as high as 140° (30 mm.) depending on the rate of distillation. The entire distillate comes over at 125–130° at atmospheric pressure when immediately redistilled.

Hielscher[14] first prepared α-methyl-N-methylpyrroline by ring closure of $CH_3COCH_2CH_2CH_2NHCH_3$. He reported that the compound could not be distilled under atmospheric pressure but gave no explanation of its instability. LaForge[3] reported the preparation of α-phenyl-N-methylpyrroline. The properties of α-*n*-propyl- and α-ethyl-N-methylpyrroline correspond substantially with those reported by Lukes.[5] α-*n*-Butyl-N-methylpyrroline could not be found in the literature.

Summary

N-methylsuccinimide was reduced electrolytically and N-methyl-α-pyrrolidone recovered in a yield of 80% of the theoretical.

A series of α-substituted N-methylpyrrolines have been prepared and their properties discussed. α-Substituted N-methylpyrrolines were not found to react with water in aqueous solution to give amino ketones and an explanation of the reaction with hydroxylamine in aqueous solution has been given.

α-Methyl-N-methylpyrroline has been shown to polymerize to a dimer which dissociates again quite easily.

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