

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

## A GENERAL METHOD OF SYNTHESIS FOR ALPHA-SUBSTITUTED PYRROLINES AND PYRROLIDINES

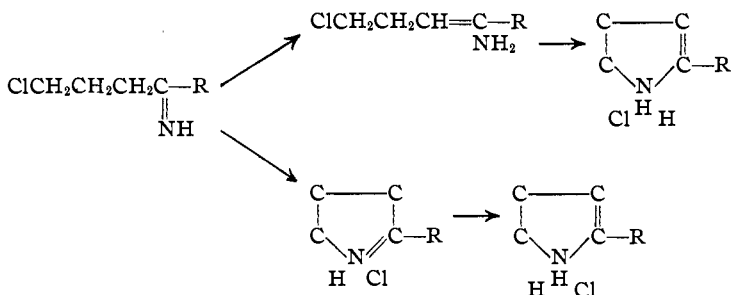
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In extending the series of pyrrole and pyrrolidine compounds for the contemplated study of insecticidal action and physical properties<sup>1</sup> several  $\alpha$ -substituted pyrrolidine derivatives were desired. The methods of synthesis reported in the literature<sup>2</sup> are, in general, difficult and inadequate for the preparation of larger amounts of these compounds. Cloke<sup>3</sup> described a rearrangement of  $\gamma$ -chloropropylketimines to pyrroline derivatives and proposed this as a convenient synthesis of  $\alpha$ -substituted pyrrolines. His work was devoted chiefly to a study of the mechanism of the reaction, the yields of pyrroline compounds formed being particularly disappointing for the preparation of the aliphatic substituted pyrrolines. If satisfactory yields of  $\alpha$ -substituted pyrroline derivatives could be obtained by this reaction, reduction would offer a convenient method of synthesis for  $\alpha$ -substituted pyrrolidine derivatives. The reaction has been studied for this particular purpose.

If we accept the mechanism given by Cloke for the formation of the  $\alpha$ -substituted pyrrolines as indicated by either one or both of the equations

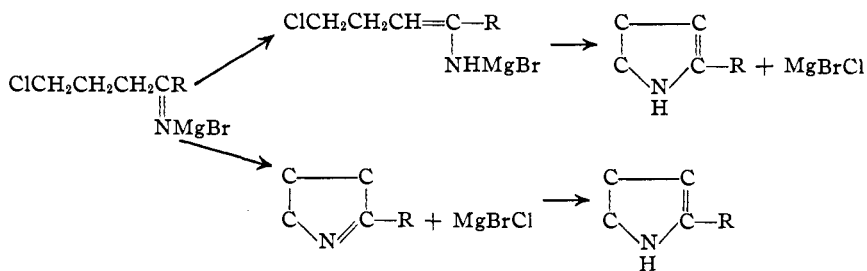


then it would seem possible that ring closure could be effected by raising the temperature of the reaction mixture containing the addition product of the  $\gamma$ -chlorobutyronitrile without going through the steps of forming the ketimine itself. The reaction would then go according to either or both of the equations

<sup>1</sup> Craig and Hixon, *THIS JOURNAL*, **52**, 804 (1930).

<sup>2</sup> Fenner and Tafel, *Ber.*, **31**, 906 (1898); Hielscher, *ibid.*, **31**, 277 (1898); Braun, *ibid.*, **43**, 2864 (1910); Gabriel and Colman, *ibid.*, **41**, 517 (1908); Müller and Wachs, *Monatsh.*, **53**, 420 (1929).

<sup>3</sup> Cloke, *THIS JOURNAL*, **51**, 1174 (1929).



Accordingly an experiment was performed in which the ether was removed from the phenylmagnesium bromide-nitrile addition product and dry xylene added, keeping the volume constant. When the temperature approached that of boiling xylene, the mixture suddenly reacted to give a viscous semi-crystalline material which was probably a mixture of  $\text{MgClBr}$  and  $\alpha$ -phenylpyrroline-N-magnesium bromide, the latter compound being formed by reaction of the  $\alpha$ -substituted pyrroline with the excess phenylmagnesium bromide. This method of ring closure gives much better yields than are obtained by passing through the ketimines since there is partial hydrolysis of the ketimine to the corresponding ketone. The procedure is also shorter as the pyrroline can easily be recovered from the mixture by either steam distillation or extraction with ether, according to solubility in water. The yields of  $\alpha$ -phenyl,  $\alpha$ -ethyl and  $\alpha$ -benzylpyrroline are, respectively, 55, 46 and 13% of the theoretical. The order of reactivity of the Grignard compounds from which they are derived is the reverse of this.

Since the yield of the pyrroline compound as obtained by the ketimine reaction is reduced through unavoidable hydrolysis to the ketone, it seemed probable that this loss could be eliminated by reducing the ketimine acetate of the substituted  $\gamma$ -chloropropylketimine to the corresponding amine. These compounds on heating split out hydrochloric acid to give  $\alpha$ -substituted pyrrolidines.  $\alpha$ -Phenylpyrrolidine was prepared by this method but the yield was not as high as that obtained by passing through  $\alpha$ -phenylpyrroline as an intermediate. No attempt was made to extend the method of synthesis to the  $\alpha$ -alkylpyrrolidines.

Aliphatic  $\alpha$ -substituted pyrrolidines can be obtained easily by catalytic reduction<sup>4</sup> of  $\alpha$ -substituted pyrrolines. With aromatic  $\alpha$ -substituted pyrrolines, reduction of the benzene ring also takes place. Catalytic reduction of  $\alpha$ -phenylpyrroline gave a mixture of reduction products that could not be separated. The literature is conflicting regarding chemical reduction of  $\alpha$ -phenylpyrroline. Gabriel and Colman<sup>2</sup> obtained a quantitative reduction to  $\alpha$ -phenylpyrrolidine using tin and concentrated hydrochloric acid, while LaForge<sup>5</sup> was not able to reduce  $\alpha$ -phenylpyrroline. In this Laboratory the results of Gabriel and Colman were confirmed.

<sup>4</sup> Wibaut, *Rec. trav. chim.*, **49**, 237 (1930).

<sup>5</sup> LaForge, *THIS JOURNAL*, **50**, 2471 (1928).

### Experimental

**$\alpha$ -Phenylpyrroline.**—A solution of phenylmagnesium bromide was prepared using 150 cc. of anhydrous ether, 8.6 g. of magnesium and 56 g. of bromobenzene. To this 15 g. of  $\gamma$ -chlorobutyronitrile in an equal volume of ether was added. The Grignard addition product precipitated when most of the nitrile had been added. The mixture was refluxed for two hours; the reflux condenser was then reversed and the ether allowed to distil off, keeping the volume constant by addition of xylene dried over sodium. When the ether had practically all distilled over, the mixture suddenly reacted to give a solid semi-crystalline mass. The mixture was then treated with a solution of ammonium chloride and the xylene layer removed. The aqueous layer was extracted once with ether and the ether extract added to the xylene solution. The  $\alpha$ -phenylpyrrolidine was extracted from the organic solvents with a small volume of hydrochloric acid, the hydrochloric acid layer washed once with ether to remove xylene and heated to remove the ether. It was then treated with excess strong caustic solution, the oily layer dried over solid potassium hydroxide and distilled, 11 g. coming over at 120–130° under 18 mm. The yield was 55% of the theoretical. Several grams of a high-boiling residue was left. The picrate melted at 198° as reported by Gabriel and Colman.<sup>2</sup> The identity of this compound was further proved by reduction to  $\alpha$ -phenylpyrrolidine.

**Reduction of  $\alpha$ -Phenylpyrroline.**— $\alpha$ -Phenylpyrroline was reduced with tin and hydrochloric acid according to the method of Gabriel and Colman.<sup>2</sup> The reduction product showed a constant boiling point of 120° under 20 mm. and gave a picrate that melted at 148° as previously reported. Catalytic reduction using absolute alcohol acidified with hydrochloric acid as a solvent did not go quantitatively but gave an indefinite mixture from which a picrate melting at 148° was isolated.

**$\alpha$ -Phenyl-N-methylpyrrolidine.**—In attempting to prepare the  $\alpha$ -phenyl-N-methylpyrrolidine by methylation of  $\alpha$ -phenylpyrrolidine according to the directions of LaForge,<sup>5</sup> it was found that large quantities of the quaternary derivative were formed and purification by the Hinsburg secondary-tertiary amine separation gave a few drops only of a tertiary amine when 5 g. of starting material was used. A picrate prepared from the tertiary amine melted at 196°. This tertiary amine in ether solution reacted with benzoyl chloride, which indicated ring rupture in analogy to nicotine. Purification of  $\alpha$ -phenyl-N-methylpyrrolidine is for this reason difficult and analysis is not sufficiently sensitive to show the absence of large amounts of  $\alpha$ -phenylpyrrolidine in the  $\alpha$ -phenyl-N-methylpyrrolidine fraction.

**Reduction of Phenyl- $\gamma$ -chloropropyl Ketimine.**—The phenylmagnesium bromide addition product of  $\gamma$ -chlorobutyronitrile was prepared as in the synthesis of  $\alpha$ -phenylpyrroline using the same quantities throughout. Glacial acetic acid was then slowly added until all the Grignard reagent was destroyed, the ether decanted and the residue dissolved in as little glacial acetic acid as possible. After adding 0.3 g. of platinum oxide-platinum black catalyst the solution was shaken in an atmosphere of hydrogen. In two hours reduction was complete and the catalyst was filtered off. Most of the acetic acid was removed by distillation using a water-bath and reduced pressure. The residue was then made strongly alkaline and steam distilled. Recovery of the base by making the distillate strongly acid with hydrochloric acid, evaporating to a small volume, treating with excess of strong caustic and drying over solid potassium hydroxide gave 5 g. of base boiling at 120° under 20 mm. pressure. A picrate melted at 148° as reported by Gabriel and Colman<sup>2</sup> for  $\alpha$ -phenylpyrrolidine and a mixed melting point confirmed its identity. It is interesting to note that in this case the benzene ring was not reduced.

**$\alpha$ -Ethylpyrroline.**—A Grignard reagent was prepared using 8.6 g. of magnesium, 38 g. of ethyl bromide and 150 cc. of anhydrous ether. To this was added 15 g. of  $\gamma$ -

chlorobutyronitrile in an equal volume of ether. The mixture was refluxed for two hours, then the ether removed by distillation, replacing it as a solvent with anhydrous xylene. After the mixture had reacted it was treated with 50 cc. of water and the xylene decanted. The residue was treated with caustic solution and steam distilled. After adding 15 cc. of concentrated hydrochloric acid to the distillate it was shaken in a separatory funnel with the xylene layer. The acid layer was washed once with ether and concentrated to a volume of approximately 50 cc. It was then treated with strong caustic, the oily layer drawn off and dried over solid potassium hydroxide. The oil, amounting to 11 cc., was distilled, 6.5 g. of distillate coming over under a temperature of 140°. The yield was 46% of the theoretical. It gave a picrate melting at 87° when crystallized from absolute alcohol. The gold chloride could be crystallized from water strongly acidified with hydrochloric acid and melted at 122°. A sample for analysis was dried in a vacuum desiccator at room temperature.  $\alpha$ -Ethylpyrrolidine was first prepared by Dennstedt<sup>6</sup> but the only derivative reported was the chloroplatinate.

*Anal.* Calcd. for  $C_6H_{11}NHAuCl_4$ : Au, 45.20. Found: Au, 45.25, 45.30.

As a further confirmation of the identity of this compound it was reduced catalytically with Adams and Shriner platinum oxide platinum black catalyst to  $\alpha$ -ethylpyrrolidine. The reduction was quantitative. A picrate of  $\alpha$ -ethylpyrrolidine melted at 85° as reported by Muller and Wacks.<sup>2</sup> A sample of the free oil with a constant boiling point was obtained by recrystallizing the picrate and regenerating; 12 g. of distillate and 28 g. of picric acid were added to 300 cc. of absolute alcohol. The alcohol was heated to effect solution and slowly cooled to the temperature of ice water; 24 g. of crystalline picrate, melting at 85–86°, was filtered off. The whole was treated with 50 cc. of water containing 15 cc. of concentrated hydrochloric acid, heated to boiling, cooled, then filtered and the picric acid washed with a small volume of water. The filtrate was then treated with strong caustic, the oil separating dried over solid potassium hydroxide and distilled. It distilled entirely at 125–126° and weighed 5.5 g. It was a colorless oil with a foul musty odor and did not color on standing. It is interesting to note that Hielscher<sup>2</sup> reports that he was not able to distil pure  $\alpha$ -methylpyrrolidine or  $\alpha$ -methyl-N-methylpyrrolidine without decomposition. There was no sign of decomposition during the distillation of pure  $\alpha$ -ethylpyrrolidine.

In the literature<sup>7</sup> it is reported that  $\alpha$ -methylpyrrolidine and compounds of like structure exist in water solution in a state of equilibrium, a molecule of  $\alpha$ -substituted pyrrolidine reacting with one of water to form  $\gamma$ -aminopropyl substituted ketones. Pure  $\alpha$ -ethylpyrrolidine dissolved in a small volume of water did not react with either phenylhydrazine or phenylsemicarbazide in the cold. However, upon warming in a small volume of water for one hour on the water-bath equivalent quantities of  $\alpha$ -ethylpyrrolidine and phenylsemicarbazide hydrochloride, a white solid insoluble in water and alcohol and melting at 244° was formed.

**$\alpha$ -Benzylpyrrolidine.**—A Grignard reagent was prepared using 8.6 g. of magnesium, 45 g. of benzyl chloride and 220 cc. of anhydrous ether; 15 g. of  $\gamma$ -chlorobutyronitrile was slowly added and the mixture refluxed for two hours. The ether was then removed by distillation, replacing it as solvent by xylene. As was the case with the other two derivatives prepared there was no sudden separation of solid material. When all of the ether had volatilized, the mixture was heated for one-half hour and the  $\alpha$ -benzylpyrrolidine recovered in the same manner as was  $\alpha$ -phenylpyrrolidine; 3 g. of distillate boiling at 126–128° under 15 mm. pressure was obtained. The yield was 13% of the theoretical. It was a colorless oil which rapidly colored in air, and was soluble in all organic

<sup>6</sup> Dennstedt, German Patent 137,086, *Chem. Centr.*, I, 73, 338 (1902).

<sup>7</sup> Lipp and Widmann, *Ann.*, 409, 79 (1915).

solvents and insoluble in water. A picrate crystallized from alcohol melted at 89°. A gold chloride crystallized from an alcohol-water mixture, strongly acidified with hydrochloric acid, melted with decomposition at 125°. A sample was dried in a vacuum desiccator at room temperature and immediately analyzed as it showed some signs of decomposition. The following analyses were run on the gold chloride and free base, respectively.

*Anal.* Calcd. for  $C_{11}H_{13}NHAuCl_4$ : Au, 39.50. Found: Au, 39.45, 39.43. Calcd. for  $C_{11}H_{13}N$ : C, 82.80; H, 8.23. Found: C, 82.70; H, 8.61.

A reference to this compound could not be found in the literature.

### Summary

A study has been made of the synthesis reported by Cloke for the preparation of  $\alpha$ -substituted pyrrolines from  $\gamma$ -chlorobutyronitrile. The yields have been increased and the procedure shortened by elimination of magnesium chlorobromide from the addition product of the Grignard reagent with  $\gamma$ -chlorobutyronitrile, closing the ring without passing through the intermediate ketimine.

$\alpha$ -Ethylpyrroline has been obtained pure for the first time and its boiling point reported.

The work of Gabriel and Colman on the reduction of  $\alpha$ -phenylpyrroline with tin and hydrochloric acid has been confirmed. The catalytic reduction of this compound yields an indefinite mixture.

$\gamma$ -Chloropropylphenyl ketimine acetate has been reduced catalytically to 1-phenyl-1-amino-4-chlorobutane although the latter compound was not isolated due to the ease with which it splits out hydrochloric acid to form  $\alpha$ -phenylpyrrolidine.

$\alpha$ -Benzylpyrroline has been synthesized for the first time and suitable derivatives of it are reported.

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