[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD RESEARCH INSTITUTE]

IMPROVED SYNTHESIS OF 2-PYRROLEALDEHYDE AND OF N-METHYL-2-PYRROLEALDEHYDE. FURTHER STUDIES OF PYRROLE ALCOHOLS

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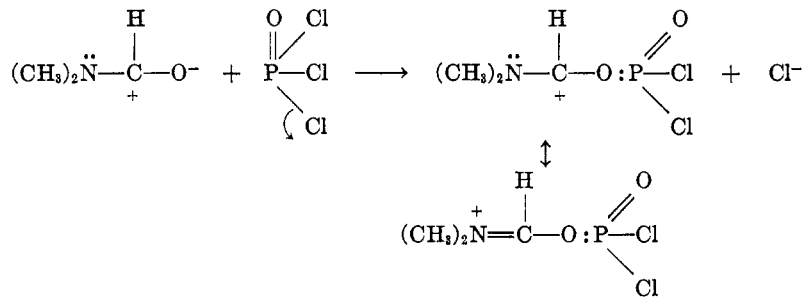
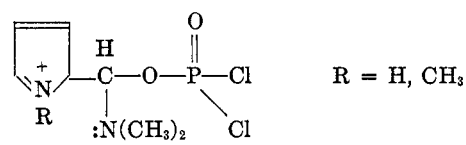
Recently (1, 2) we reported the synthesis of 2-pyrrolealdehyde by direct formylation of pyrrole in 59% yield, and the synthesis of N-methyl-2-pyrrolealdehyde by direct formylation of N-methylpyrrole in 48% yield. The present paper records an improved formylation procedure whereby 2-pyrrolealdehyde was obtained in 89% yield, and N-methyl-2-pyrrolealdehyde in 79–90% yield. The formylating agent was an equimolar mixture of phosphorus oxychloride and dimethylformamide. A decrease in the ratio of the former to the latter resulted in a decreased yield of the aldehydes. We suggest that a 1:1 complex is formed with the phosphorus oxychloride functioning as a Lewis acid:



The reaction of this resonance-stabilized cation at the 2-position of the pyrrole nucleus forms

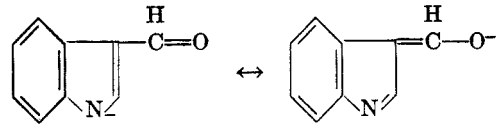


which on hydrolysis yields the aldehydes.[1]

[1] On completion of this phase of our work, we submitted the procedure for the preparation of 2-pyrrolealdehyde to *Organic Syntheses* in August 1954. A paper has since appeared [G. F. Smith, *J. Chem. Soc.*, 3842 (1954, November)] which describes a rather similar procedure for the preparation of 2-pyrrolealdehyde in 83% yield, and proposes an essentially identical mechanism. Smith confirmed the mechanism by the elegantly simple expedient of isolating the intermediate compound  involved in the formylation of indole.

We also described (1) a compound obtained by sodium borohydride and lithium aluminum hydride reductions of 2-pyrrolealdehyde. The elemental analyses, molar refractivity, molecular weight, and infrared spectrum were in accord with those expected for 2-hydroxymethylpyrrole. However, it was not possible to prepare a derivative of this compound by any of the usual procedures. Subsequently (2) we described the compound obtained by sodium borohydride reduction of N-methyl-2-pyrrolealdehyde. Again, attempted characterization by means of a derivative was unsuccessful although the analytical evidence for the postulated structure, N-methyl-2-hydroxymethylpyrrole, was satisfactory. In this case, unequivocal identification was forthcoming by obtaining the same compound from a crossed-Cannizzaro reaction of N-methyl-2-pyrrolealdehyde, and by the alkaline hydrolysis of the methiodide of N-methyl-2-dimethylaminomethylpyrrole.

In order to obtain conclusive confirmation of the identity of 2-hydroxymethylpyrrole, the Cannizzaro and the crossed-Cannizzaro reactions were applied to 2-pyrrolealdehyde; all efforts resulted only in good recovery of the starting material. This is in accord with the observation by Van Order and Lindwall (3) that 3-indolealdehyde did not undergo the Cannizzaro reaction although the reaction was successful with 1-methyl-3-indolealdehyde. Thesing (4) postulated that the failure of 3-indolealdehyde to undergo the Cannizzaro reaction or the benzoin condensations was a consequence of the preponderance of the following in strongly alkaline solution:



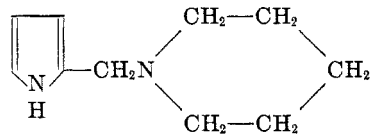
Presumably the same considerations apply to 2-pyrrolealdehyde. We were also unsuccessful in attempting to carry out a benzoin condensation with 2-pyrrolealdehyde in a further effort to establish the structure of the compound which Taggart and Richter (5) thought to be 2-hydroxymethylpyrrole, but which we suggested (1) was probably the pinacol.

Conclusive confirmation of the identity of 2-hydroxymethylpyrrole was finally obtained by alkaline hydrolysis of the methiodide of 2-dimethylaminomethylpyrrole, and satisfactory agreement of the boiling point, refractive index, and infrared spectrum of the product of this reaction with those properties of the product of the sodium borohydride reduction of 2-pyrrolealdehyde. It is of interest to note that the mild conditions used by Leete and Marion (6) for the hydrolysis of gramine methiodide were adequate for the hydrolysis of the methiodide of the pyrrole Mannich base, whereas the N-methyl homolog required more drastic conditions and gave a poorer yield (2).

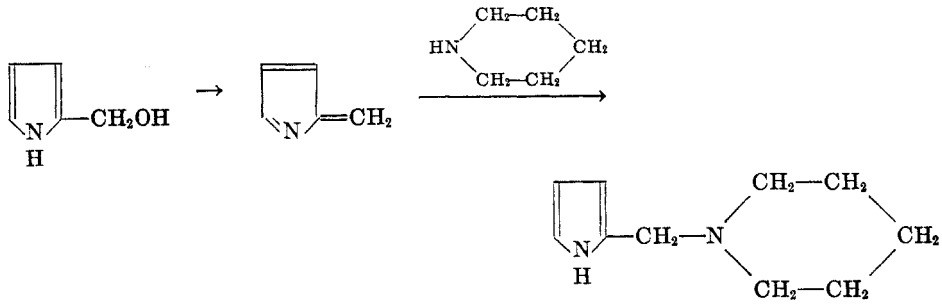
Following the publication of our first Note, in which we also described the synthesis and properties of 3-hydroxymethylindole, Professor Carlo Runti brought to our attention his work on this compound (7, 8). Runti pointed out that 3-hydroxymethylindole may be considered as an intermediate in a Mannich reaction, and as such, should react with amines. He successfully carried out this

reaction with morpholine and with piperidine, and then generalized the concept to include reactions with other nucleophilic reagents.

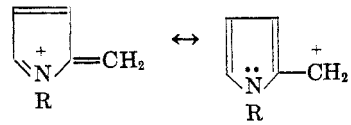
We were able to obtain the Mannich base



by refluxing 2-hydroxymethylpyrrole with piperidine and sodium in absolute ethanol for one hour. Although an attempt was made to force the reaction of N-methyl-2-hydroxymethylpyrrole with piperidine by refluxing for 24 hours, most of the alcohol was recovered unchanged. These results are in accord with observations made on the relative reactivities of gramine and 1-methylgramine toward nucleophilic reagents (9). Although, the path by which alkylation with tertiary amines occurs has not been definitely established, it has been postulated (9) that gramine may suffer amine elimination followed by a Michael type addition of the nucleophilic reagent (*e.g.* sodium cyanide). 1-Methylgramine cannot undergo this type of base-catalyzed amine elimination. In the same manner, it may be argued that the reaction of 2-hydroxymethylpyrrole proceeds by the following mechanism which is not permitted to N-methyl-2-hydroxymethylpyrrole:



The failure of both of these pyrrole alcohols to behave as primary alcohols may be accounted for by the ready formation of resonance-stabilized cations:



R = H, CH_3

EXPERIMENTAL

2-Pyrrolealdehyde. In a 3-l. flask fitted with a stirrer, reflux condenser, and dropping-funnel was placed 80 g. (1.1 moles) of dimethylformamide. The flask was immersed in an ice-bath, the stirrer started, and 169 g. (1.1 moles) of phosphorus oxychloride was added over a period of five minutes. The ice-bath was removed, and the mixture was allowed to stir for 15 minutes.

The ice-bath was replaced, and 250 ml. of ethylene dichloride was added to the mixture.

When the solution cooled to 5°, 67.0 g. (1.0 mole) of freshly distilled pyrrole in 250 ml. of ethylene dichloride was added through a clean dropping-funnel to the stirred, cooled mixture over a period of one hour. The stirred mixture was then refluxed for 15 minutes, and cooled to room temperature.

A solution of 750 g. (5.5 moles) of sodium acetate trihydrate in about 1000 ml. of water was added to the stirred mixture, cautiously at first, then as rapidly as possible. The mixture was refluxed for 15 minutes with stirring and cooled to room temperature. The layers were separated. The aqueous phase was extracted three times with a total of about 500 ml. of ether. The ether and ethylene chloride solutions were combined and washed with a saturated sodium carbonate solution. The solution was dried over sodium carbonate, the solvents were removed, and the residue was distilled at 78° at 2 mm. The yield was 85 g. (89%) of a colorless distillate which crystallized on standing a short time. The melting point of the distillate was 35–40°. One recrystallization from petroleum ether (30–65°) raised the m.p. to 44–45°.

N-Methyl-2-pyrrolealdehyde. This synthesis was carried out in the same manner and using the same molar proportions as described above for the synthesis of 2-pyrrolealdehyde. The product was distilled at 72–75° at 11 mm., n_D^{22} 1.5589. Yield 79%. A second cut was taken at 75–76°; n_D^{22} 1.5612. The combined yield was 90%.

2-Hydroxymethylpyrrole. To a stirred mixture of 250 ml. of 10% sodium hydroxide and 250 ml. of peroxide-free ether, was added dropwise 13.3 g. (0.05 mole) of 2-dimethylaminomethylpyrrole methiodide (10) in 150 ml. of water over a period of 20 minutes. Stirring was continued for an additional 20 minutes. The ether solution was separated, and the aqueous phase was extracted with several portions of ether. The aqueous phase was saturated with sodium carbonate, and again extracted. The combined ether extracts were dried, the ether removed, and the residue was distilled at 72–74° at 2 mm. The distillate was a moderately viscous, colorless oil; yield 21.6%, n_D^{20} 1.5438. The infrared spectrum was identical with that of the product obtained by reduction of 2-pyrrolealdehyde (1).

2-Piperidinomethylpyrrole. To a stirred mixture of 3.5 g. of 2-hydroxymethylpyrrole and 3.1 g. of piperidine was added 0.8 g. of sodium in 43 ml. of absolute ethanol. The mixture was refluxed for one hour and, after standing overnight at room temperature, was diluted with approximately 20 ml. of water, saturated with potassium carbonate, and extracted with ether. The ether solution was dried and evaporated. The residue was recrystallized twice from ethanol-water. The product weighed 2.3 g, m.p. 75–77°.

Anal. Calc'd for $C_{10}H_{16}N_2$: C, 73.2; H, 9.76.
Found: C, 72.8; H, 9.76.

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SUMMARY

An improved procedure for the formylation of pyrrole and of N-methylpyrrole is presented, and a mechanism is proposed. Confirmation of the identity of 2-hydroxymethylpyrrole is obtained by an independent synthesis from a Mannich base, and by treatment of the alcohol with piperidine to form a Mannich base. The failure of N-methyl-2-hydroxymethylpyrrole to react with piperidine is explained. The concept of a resonance-stabilized cation is invoked to account for the failure of these pyrrole alcohols to behave as primary alcohols.

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