

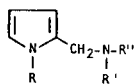
## A Study on the Condensation of Pyrroles, Formaldehyde and Primary Amine Hydrochlorides

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Most reported reactions employing pyrrole compounds, formaldehyde and primary amine hydrochlorides give rise to the expected products in significantly lower yields (1,2) than those utilizing secondary amine hydrochlorides (Table I). The amine free base has been successfully employed in place of the amine hydrochloride but is generally not preferred (3). This investigation provides a method with which good yields of Mannich products of pyrroles are obtained consistently from primary amine hydrochlorides.

TABLE I



R	R'	R''	Yield, %	R''	Yield, %
H	CH <sub>3</sub>	CH <sub>3</sub>	77 (1)	H	15 (1)
H	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	40 (1)	H	27 (1)
CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	73 (2)	H	26 (2)
CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	77 (2)	H	40 (2)

An examination of the reported (1-3) synthetic methods involving primary amine hydrochlorides in the Mannich reaction with pyrroles revealed only minor differences in procedure. Burke and Hammer (3), while preparing relatively high melting crystalline compounds, resorted to recrystallization techniques and obtained good yields. Herz *et.al.* (1) and Herz and Rogers (2), relying on distillation for purification of their lower melting or liquid products, obtained low yields of products and reported the formation of a considerable amount of polymeric material when using methylamine hydrochloride.

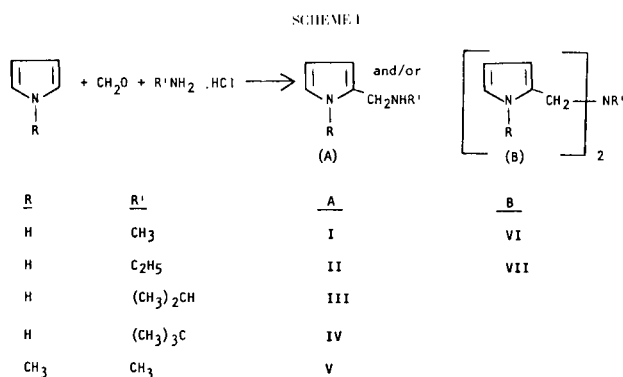
Treibs and Zinsmeister (4) treated 2-carbethoxy-3,5-dimethylpyrrole with ammonium acetate obtaining a 50 percent yield of di(2,4-dimethyl-5-carbethoxypyrrol-3-ylmethyl)amine, and no 3-aminomethyl-2,4-dimethyl-5-carbethoxypyrrole. The result of this reaction, utilizing ammonia in place of a primary amine, is not unexpected in

view of literature reports (5) on the course of the Mannich reaction with primary amine salts. It appears that the possibility of both polymerization and bis-alkylation of the amine could contribute to the poor yields of products obtained with primary amine hydrochlorides in the Mannich reaction.

The need in our laboratory for an efficient method for the preparation of the monoaminoalkylation products (A) from primary amine hydrochlorides and pyrrole compounds prompted a reinvestigation of portions of this earlier work. On repeating the procedure of Herz *et.al.* (1) for the preparation of 2-methylaminomethylpyrrole (I), there was obtained a second product which proved to be the bis reaction product, *N,N*-di(pyrrol-2-ylmethyl)-*N*-methylamine (VI). Chromatographic separation of the two products gave 4.0 parts of compound VI for every 2.5 parts of compound I obtained. Thus it seems probable that the reported (1) polymerization during distillation arose primarily from compound VI and not I.

Since the only significant difference between the starting materials used by Burke and Hammer (3) and by the earlier workers (1,2) was of a steric nature, it would appear that the bulk of the R' group was the determining factor in the yields obtained. A number of experiments were carried out to confirm this effect by varying the size of the R' group of the primary amine hydrochloride and determining the ratio of the formation of components A and B (see Scheme 1). Under similar reaction conditions using the general procedure of Herz *et.al.* (1), the hydrochlorides of methylamine, ethylamine, isopropylamine and tertiary-butylamine were treated with formaldehyde and pyrrole. Thin layer chromatography (6) was used to determine the relative ratios of compounds of the structure A to those of structure B present in the reaction residues. In the case of methylamine hydrochloride, the results of the column chromatography confirmed that the type B compound VI was formed to a greater extent than the type A compound I. With ethylamine hydrochloride, compound II and compound VII were present. Isopropyl and tertiary-butylamine hydrochloride formed only one com-

pound in each instance which proved to be the mono-aminoalkylation products III and IV, respectively.



It can be concluded that steric factors have a considerable effect on the ratio of products formed in a reaction that may lead to structures A and B but only in the case of the amine salt derived from ammonia, methylamine or a compound having a methylene group adjacent to the nitrogen atom. If the group possesses the bulk of an isopropyl group or greater, this conversion of A into B is suppressed to a point that only compounds of type A are isolated when using equimolar ratios of reactants. The low yields of Herz *et al.* (1) and Herz and Rogers (2) and the high yields of Burke and Hammer (3) are in agreement with this conclusion.

The undesirable formation of tertiary amines is readily controlled in Mannich Reactions by changing the ratio of reactants to favor the primary amine hydrochloride and this approach has been found to be successful in raising the yields of type A structures (see Table II). It follows that when the desired product is of type B, the ratio of reactants should favor the pyrrole and formaldehyde. When a 2:2:1 molar ratio was employed with ethylamine hydrochloride representing the lowest number in the ratio, *N,N*-di(pyrrol-2-ylmethyl)-*N*-ethylamine (VII) was formed in 98% yield.

## EXPERIMENTAL

The Chromatographic Separation of 2-Methylaminomethylpyrrole (I) and *N,N*-Di(pyrrol-2-ylmethyl)-*N*-methylamine (VI).

The crude mixture of products (6.5 g.), obtained by carrying out the reaction between pyrrole (6.7 g.), methylamine hydrochloride (7.4 g.) and formalin (7.9 g.) according to the published (1) procedure for the preparation of 2-methylaminomethylpyrrole (I), was placed on a silica gel column (30 cm.) (distillation stage). The column was slowly eluted with ethanol 2B and 12 fractions (200 ml. each) were collected and the solvent removed. Compound VI (4.0 g.) (fractions 2-5), a viscous oil, was first obtained followed by compound I (2.5 g.) (fractions 8-12). Compound VI crystallized on standing and was further recrystallized from benzene-*n*-hexane (m.p. 74-76°).

*Anal.* Calcd. for C<sub>11</sub>H<sub>15</sub>N<sub>3</sub>: C, 69.81; H, 7.99; N, 22.20. Found: C, 70.29; H, 8.05; N, 22.16.

General Procedure for the Preparation of 2-Alkylaminomethylpyrrole Compounds (I, II and V).

The yields, physical constants and analytical data are reported in Table II. The alkylamine hydrochloride (2 mole) dissolved in formalin (150 ml.) was added in a dropwise manner over a 4 hour period to a stirred mixture of pyrrole (in the preparation of V, *N*-methylpyrrole was used) (2 mole) and alkylamine hydrochloride (4 mole) in water (500 ml.) which was cooled by an ice bath. The reaction mixture was stirred for 24 hours at room temperature, after which 25% aqueous sodium hydroxide solution (500 ml.) was added. After 3 ether extractions (500 ml. each), the extracts were combined, dried over anhydrous sodium sulfate, filtered, and the solvent removed on a rotary evaporator. The resulting residue was distilled.

General Procedure for the Preparation of 2-Alkylaminomethylpyrrole Compounds III and IV.

The yields, physical constants and analytical data are reported in Table II. The alkylamine hydrochloride (0.1 mole) dissolved in a solution containing formalin (7.5 ml.) and water (30 ml.) was added in a dropwise manner over approximately 30 minutes to stirred pyrrole (0.1 mole, 6.7 g.) not permitting the temperature to exceed 60°. After stirring for 1.5 hours the reaction mixture was permitted to stand for 24 hours and worked up in the same way as compounds I, II and V.

Preparation of *N,N*-Di(pyrrol-2-ylmethyl)-*N*-ethylamine (VII).

Ethylamine hydrochloride (0.1 mole, 8.2 g.) dissolved in for-

TABLE II

Compound	Literature Yield %	Yield, %	Bp (m.p., °C)	Ratio of Reactants R'NH <sub>2</sub> ·HCl:H <sub>2</sub> CO:C <sub>4</sub> H <sub>4</sub> NR
I	15 (1)	51 (a)	45-65/0.1-1mm	3:1:1
II	27 (1)	61	78-80/2mm (34-36)	3:1:1
III	---	44 (b)	98/7mm	1:1:1
IV	---	61 (c)	92-94/5mm (55-57)	1:1:1
V	26 (2)	82	72-74/7mm	3:1:1

(a) *Anal.* Calcd. for C<sub>6</sub>H<sub>10</sub>N<sub>2</sub>: C, 65.42; H, 9.15; N, 25.43. Found: C, 65.57; H, 9.50; N, 24.45. (b) *Anal.* Calcd. for C<sub>8</sub>H<sub>14</sub>N<sub>2</sub>: C, 69.52; H, 10.21; N, 20.27. Found: C, 68.89; H, 10.61; N, 20.17. (c) *Anal.* Calcd. for C<sub>9</sub>H<sub>16</sub>N<sub>2</sub>: C, 71.00; H, 10.59; N, 18.40. Found: C, 70.93; H, 10.63; N, 18.35.

malin (15 ml.) was added in a dropwise manner over an approximately 30 minute period to stirred pyrrole (0.2 mole, 13.4 g.) keeping the temperature below 60°. After stirring for 1.5 hours, the reaction mixture was permitted to stand for 24 hours and worked up in the same way as compounds I, II and V. The resulting residue crystallized on standing giving rise to a material having a m.p. of 65-70°; yield 98%, recrystallized from benzene-petroleum ether (m.p. 68-69°).

*Anal.* Calcd. for  $C_{12}H_{17}N_3$ : C, 70.90; H, 8.43; N, 20.67. Found: C, 71.12; H, 8.43; N, 21.73.

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