

Reaction of Pyrrole Ketones with Formaldehyde.
Formation of *N*-Pyrrolemethanols.

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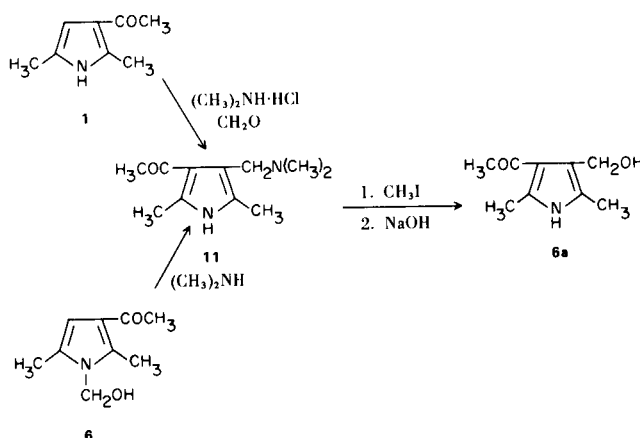
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In contrast to *C*-pyrrolemethanols (1), *N*-pyrrolemethanols are virtually unknown. Pyrrole itself reacts with formaldehyde under alkaline conditions at 40-50° to give pyrrole-1-methanol (2a-b); upon heating this material to 70° disproportionation occurs giving 2,5-bis-(hydroxymethyl)pyrrole (2a). If the reaction is conducted at 70-75°, the product is the diol (2a-b). More recently pyrrol-3-yl methyl ketone has been found to react with alkaline formaldehyde to give 1-hydroxymethylpyrrol-3-yl methyl ketone (3), and diethyl 1-benzyloxymethylpyrrol-3,4-dicarboxylate has been hydrogenolyzed to the corresponding pyrrole-1-methanol (4).

We have found that treatment of several types of pyrrole ketones with formaldehyde under basic reaction conditions leads to formation of *N*-pyrrolemethanols. Reaction of 2,5-dimethylpyrrol-3-yl methyl ketone **1** with 36% formaldehyde solution in the presence of small amounts of alkali on the steam bath results in formation of a product which elemental analysis shows to have incorporated one mole of formaldehyde. The nmr spectrum of this material (Table II) confirms the structure of this product as **6**. Salient features of the spectrum are: Presence of a single β -pyrrolic proton coupled weakly to the α -methyl group (5), a singlet methyl associated with the acetyl group, and absence of any pyrrolic proton attached to nitrogen on sweep offset to δ 15.0. Addition of deuterium oxide to the solution causes disappearance of the hydroxyl triplet at δ 6.21, and collapse of the spin-coupled doublet at δ 5.21 to a singlet. No other changes in the spectrum were observed. The product melts without any evidence of decomposition; it could also be recovered unchanged after reflux for 2 hours in xylene, indicating a somewhat unexpected degree of thermal stability.

Additional proof of structure was provided by the synthesis of the isomeric *C*-pyrrolemethanol **6a**. Reaction of **1** with formaldehyde and dimethylamine hydrochloride gave the Mannich base **11**, (6) which was quaternized with methyl iodide, then treated with strong alkali, affording **6a** (7). This material had melting point, infrared, and nmr spectra different from **6**. The nmr spectrum possesses

several noteworthy features: The hydroxylic and methylene protons have differences in chemical shift which must approximate the coupling constant since a complex 3-proton multiplet appears at about δ 4.38. Addition of deuterium oxide to the solution causes this multiplet to collapse to a two-proton singlet. The pyrrolic N-H resonance is also observed at δ 11.11 prior to deuterium oxide treatment.

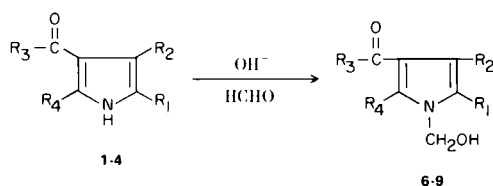


The pyrrole ketones **2-5**, possessing a variety of substitution patterns all react with formaldehyde to give *N*-pyrrolemethanols, (Table I) as determined by nmr (Table II). In all cases, no pyrrolic proton attached to nitrogen could be observed, and behavior on addition of deuterium oxide was the same as in the previous case.

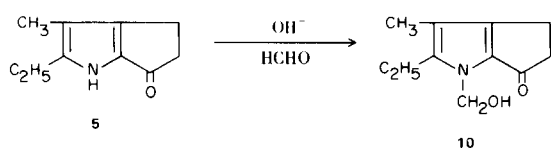
Reaction of **6**, which has a free β -position, with dimethylamine yields the *C*-Mannich base **11**. Reaction of the fully substituted pyrrolemethanol **9** with dimethylamine results in loss of formaldehyde to give **4**. It was established that under these conditions (experimental) **4** does *not* react with formaldehyde and dimethylamine.

These findings are interesting when compared with the results of a recent publication (4) which describes the facile elimination of formaldehyde from a pyrrole-1-methanol with base. The reaction leading to formation of the pyrrole-1-methanols thus appears to be reversible.

TABLE I



	R ₁	R ₂	R ₃	R ₄	
1	CH ₃	H	CH ₃	CH ₃	6
2	CH ₃	H	-(CH ₂) ₃ -		7
3	H	CH ₃	-(CH ₂) ₃ -		8
4	CH ₃	C ₂ H ₅	-(CH ₂) ₃ -		9



The rearrangement of **6** to **11** probably results from reaction of the secondary amine with the liberated formaldehyde to give the carbenium-immonium ion which then attacks the pyrrole nucleus.

Although it is very likely that the Mannich reaction of pyrroles proceeds *via* electrophilic attack of the π -excessive aromatic nucleus by the carbenium-immonium ion *initially* derived from formaldehyde and secondary amine, the intermediacy of *N*-hydroxymethyl compounds should not be discounted in those cases where the acidity of the pyrrole is enhanced by electron-withdrawing substituents.

EXPERIMENTAL

The nmr spectra were recorded on a Varian T-60 Spectrometer using TMS as internal standard. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Analyses by Spang Microanalytical Lab, Ann Arbor, Michigan.

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A mixture of the ketone, an equivalent amount of formal-

TABLE II

NMR Spectral Data
(60 MHz DMSO-d₆) (a)

Compound	(b) CH ₂ -OH	Ring H	Ring CH ₃	Other	
6	5.21 (<i>d</i>)	6.18 (<i>m</i>) (<i>c</i>)	2.30, 2.25 (<i>d</i>) (<i>c</i>)	CH ₃ CO- -OH	2.51 (<i>s</i>) 6.26 (<i>t</i>)
7	5.19 (<i>d</i>)	6.09 (<i>s</i>)	2.25 (<i>s</i>)	-CH ₂ CO- -OH	2.80 (<i>t</i>) 6.40 (<i>t</i>)
8	5.15 (<i>d</i>)	6.62 (<i>s</i>)	2.15 (<i>s</i>)	-CH ₂ CO- -OH	2.80 (<i>t</i>) 6.44 (<i>t</i>)
9	5.16 (<i>d</i>)	---	2.13 (<i>s</i>)	-CH ₂ CH ₃ -CH ₂ CO- -OH	1.00 (<i>s</i>) 2.80 (<i>t</i>) 6.29 (<i>t</i>)
10	5.39 (<i>d</i>)	---	1.95 (<i>s</i>)	-CH ₂ CH ₃ -OH	1.11 (<i>t</i>) 6.35 (<i>t</i>)

s = singlet; *d* = doublet; *t* = triplet; *m* = multiplet

(a) Integration of peak areas was consistent with assigned structure in each case. (b) *J* = 6-7 Hz. Coupled to hydroxyl proton. (c) *J* ~ 1 Hz.

TABLE III

Characterization of New Compounds

Compound	% C	Analyses					M.p., °C	Yield %
		Calcd. % H	% N	% C	Found % H	% N		
6 C ₉ H ₁₃ NO ₂	64.65	7.84	8.38	64.70	7.80	8.30	135-137	65
7 C ₁₀ H ₁₃ NO ₂	67.02	7.31	7.82	66.91	7.10	7.78	145.5-147.5	34
8 C ₁₀ H ₁₃ NO ₂	67.02	7.31	7.82	67.08	7.03	7.84	150-152	67
9 C ₁₂ H ₁₇ NO ₂	69.54	8.27	6.76	69.35	8.37	6.92	165-168	38
10 C ₁₁ H ₁₅ NO ₂	68.37	7.82	7.25	68.90	7.86	7.27	130-132	93

dehyde (as 36% solution) and 0.1 equivalent of sodium hydroxide (as a 1*N* solution) was heated on the steambath until complete solution resulted. Approximately an equal volume of water was added, the solution cooled, and the precipitated product filtered, washed, and dried. Analytical samples were recrystallized from ethanol.

2,5-Dimethyl-4-[(dimethylamino)methyl]pyrrol-3-yl Methyl Ketone (**11**).

A mixture of **1** (27.4 g., 0.2 mole) dimethylamine hydrochloride (16.8 g., 0.2 mole) and paraformaldehyde (9.6 g.) in 200 ml. of ethanol was heated at reflux overnight. Solvent was removed *in vacuo*, the residue dissolved in a small amount of water, basified with sodium hydroxide, saturated with salt, and extracted continuously overnight with benzene. Concentration of the extracts and filtration through a short column of neutral alumina gave a pale yellow solution which on dilution with pentane yielded 17.2 g. of product, m.p. 140-142°.

Anal. Calcd. for C₁₁H₁₈N₂O: C, 68.00; H, 9.34; N, 14.42. Found: C, 68.28; H, 9.27; N, 14.34.

The methiodide was prepared by dissolving the Mannich base in ethanol and treating with 1.25 equivalents of methyl iodide. After several hours that salt was removed by filtration, m.p. 191-193° dec.

2,5-Dimethyl-4-hydroxymethylpyrrol-3-yl Methyl Ketone (**6a**).

A solution of **11** methiodide (2.5 g.) in about 200 ml. of water was added to a vigorously stirred mixture of 50 ml. of 10% sodium hydroxide and 75 ml. of ether. After stirring for 15 minutes, some pink solids were removed by filtration, the ether-water filtrate separated, and the water layer saturated with potassium carbonate. After several extractions with ether, the combined extracts were dried and evaporated. The solid residue was recrystallized from benzene to give 100 mg. of silky needles, m.p. 178-180°; nmr spectrum (DMSO-d₆): δ 2.14 (s, 3), 2.44 (s, 6), 4.38 (m, 3), 11.11 (broad s, 1).

Anal. Calcd. for C₉H₁₃NO₂: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.83; H, 7.90; N, 8.43.

Reaction of **6** with Dimethylamine.

Seven g. of **6** was heated with 50 ml. of 10% ethanolic dimethylamine at 100° for 7½ hours in a stainless steel bomb. The contents of the bomb were evaporated to dryness yielding a yellow oil which solidified on trituration under pentane. The solid was recrystallized twice from hexane-benzene to give 3.0 g. of white needles, m.p. 138-141°. This material did not depress

the melting point of **11**; the infrared spectra of the two materials were identical.

Reaction of **9** with Dimethylamine.

Treatment of 9.0 g. of **9** with 100 ml. of 25% ethanolic dimethylamine as above for 40 hours gave, after evaporation of solvent, 7.4 g. crude solid product. Thin layer chromatography of this material in two different solvent systems (8% diethylamine in benzene and 18:1:1 benzene:ethyl acetate:acetic acid) showed the absence of starting material, and formation of a product having the same R_f as authentic **4**. Recrystallization of the crude product from ethanol gave material of m.p. and mixed m.p. with authentic **4**, 179-180°. The infrared spectrum of this material was identical with that of **4**.

Treatment of **4** with equimolar quantities of 36% formaldehyde solution and 25% ethanolic dimethylamine under the above conditions resulted in no reaction as determined by tlc.

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