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THE MANNICH REACTION OF HYDROXYINDOLES[1]

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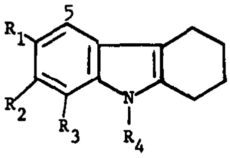
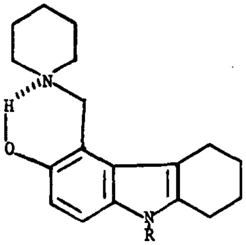
The introduction of an aminomethyl substituent into an indole nucleus by means of a Mannich condensation is well documented.[3] In general, condensation occurs at the 3-position of the indole ring; if this position is blocked, addition is reported to occur at the indole nitrogen atom.[3,4] The limited application of hydroxyindoles as substrates is somewhat surprizing in view of the extensive use of several other heterocyclic phenols.[3] The partial synthesis of Voacamine, a dimeric indole alkaloid, employed a Mannich-like reaction of a 5-methoxyindole and a 5-hydroxyindole model system was described briefly.[5] The Mannich reaction of 2-methyl-3-carbethoxy-5-hydroxyindole (10a) is reported[6] to yield the corresponding 6-aminomethyl adduct (vide infra for revised structure) and the condensation of a 5-hydroxybenzindole has been described.[7]

We wish to report the results of the Mannich reaction with several 6-, 7-, and 8-hydroxytetrahydrocarbazoles and three 5-hydroxyindoles. In general the reaction of an equivalent mixture of hydroxyindole, formaldehyde, and piperidine or dimethylamine in ethanol was complete after one to four hours. When more forcing conditions were necessary, 10% acetic acid in ethanol or glacial acetic acid was employed as solvent. All reactions were carried out in a nitrogen atmosphere at room temperature or at reflux. With the exception of 8-hydroxytetrahydrocarbazole (6), the nmr spectra of the starting hydroxyindoles showed a well resolved pattern for the aromatic protons. First order analysis of this region ($J_o \sim 8.5$ cps, $J_m \sim 2.5$ cps, $J_p \sim$ o cps) allowed unambigious identification of each proton.[8] This then provided a powerful tool for the structure elucidation of the resulting Mannich adducts.



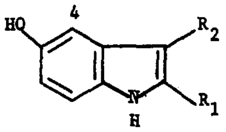


1 $R_1 = \mathrm{OH}$, $R_2=R_3=R_4=\mathrm{H}$
2 $R_1 = \mathrm{OH}$, $R_2=R_3=\mathrm{H}$, $R_4=\mathrm{CH_3}$
3a $R_1 = \mathrm{OCH_3}$, $R_2=R_3=R_4=\mathrm{H}$
3b $R_1 = \mathrm{OCH_3}$, $R_2=R_3=\mathrm{H}$, $R_4=\mathrm{C_5H_{10}NCH_2}$
4a $R_1 = \mathrm{OCH_3}$, $R_2=R_3=\mathrm{H}$, $R_4=\mathrm{CH_3}$
4b $R_1 = \mathrm{OCH_3}$, $R_2=\mathrm{C_5H_{10}NCH_2}$, $R_3=\mathrm{H}$, $R_4= \mathrm{CH_3}$
5a $R_1 = R_3=R_4=\mathrm{H}$, $R_2=\mathrm{OH}$
5b $R_1 = R_4=\mathrm{H}$, $R_2=\mathrm{OH}$, $R_3=\mathrm{C_5H_{10}NCH_2}$
6 $R_1 = R_2=R_4=\mathrm{H}$, $R_3=\mathrm{OH}$

7 $R=\mathrm{H}$
8 $R=\mathrm{CH_3}$
9 $R=\mathrm{C_5H_{10}NCH_2}$

As previously reported[5] substitution readily occurs at C-5 in the Mannich condensation of 6-hydroxytetrahydrocarbazole (1) to furnish adduct 7. The corresponding N-methyl derivative 2 also yielded the C-5 adduct 8, although more forcing conditions were required. 6-Methoxytetrahydrocarbazole (3a) gave the indole nitrogen (N-ind.) adduct 3b together with some dimeric material.[3] A more interesting example was provided by 7, the mono-adduct of 1. Both C-7 and N-ind. are potential sites for a second condensation. The infrared spectrum of 7, however, shows extensive intramolecular hydrogen bonding of the hydroxyl hydrogen atom to the basic nitrogen atom as illustrated in 7. In practice, the Mannich condensation of 7 furnished the N-ind. adduct 9 as the only observed product. In refluxing acetic acid, the relatively inert 6-methoxy-N-methyltetrahydrocarbazole (4a) yielded the C-7 adduct 4b.

7-Hydroxytetrahydrocarbazole (5a) readily furnished the C-8 adduct 5b while the 8-hydroxy derivative 6 gave no isolable products under a variety of conditions. These data are summarized in Table I.



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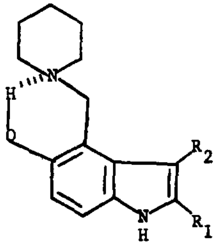

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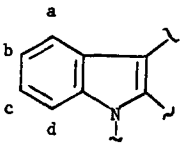
a $R_1 = CH_3$, $R_2 = CO_2Et$
b $R_1 = CH_3$, $R_2 = H$
c $R_1 = R_2 = H$

The previously reported[6] Mannich adduct of 2-methyl-3-carbethoxy-5-hydroxyindole (10a) was shown to be the C-4 adduct 11a by nmr spectroscopy. (See Table I.) A much more revealing system was provided by 2-

methyl-5-hydroxyindole (10b). Of the five potential sites for condensation, N-ind, C-2-CH_3,[9] C-3, C-4 and C-6, the most likely are C-3 and C-4. The piperidine adduct of 10b, obtained in 67% yield, was shown to be the C-4 adduct 11b by nmr. A minor, unidentified product was observed by thin layer chromatography of the reaction mixture (C-3 adduct ?). When 5-hydroxyindole (10c) was used as a substrate, the corresponding C-4 adduct 11c was formed in an 80% yield. Again a second, minor product was indicated by TLC.

TABLE I

Nmr Spectral Data for Mannich Adducts

Compound	Chemical Shifts in δ ppm (J cps)[a] 			
	Ha	Hb	Hc	Hd
7	-	-	6.62 (8.5)	6.97 (8.5)
8	-	-	6.72 (8.5)	7.02 (8.5)
3b	6.90 (2)	-	6.75 (8.5,2)[b]	7.24 (8.5)
9	-	-	6.67 (8.5)	7.18 (8.5)
4b	6.89[c]	-	-	7.24[c]
5b	7.17 (8.5)	6.60 (8.5)	-	-
11a	-	-	6.67 (8.5)	6.98 (8.5)
11b	-	-	6.67 (8.5)	6.98 (8.5)
11c	-	-	6.72 (8.5)	7.08 (8.5)

(a) Spectra were taken in $CDCl_3$ with an internal TMS reference; doublets were observed unless indicated otherwise; (b) two doublets; (c) singlet.

Inspection of these data reveals three general catagories. If a free hydroxyl group is present, substitution occurs *ortho* to it even in the presence of an unsubstituted C-3 position (i.e., 10b and 10c). This presumably occurs via the intermediacy of a six-membered chelate ring prior to carbon-carbon bond formation.[10] In support of this, the Mannich reaction of 5-benzyloxyindole yields only the C-3 adduct.[11] A rationale for substitution at C-5 in preference to C-7 (6-hydroxy-tetrahydrocarbazole system) has been advanced.[5] Extension of this hypothesis to the 7-hydroxy system 5a predicts addition at C-8, as is observed. If only the hydroxyl group is blocked (i.e., 3a and 7) condensation occurs at the indole nitrogen atom.

The third group consists of compounds 4a and 6. The infrared spectrum of the 8-hydroxy derivative 6 shows strong intramolecular hydrogen bonding. Apparently the interaction of the hydroxyl group with the indole nitrogen atom drastically reduces the reactivity of the molecule. An explanation for C-7 substitution in 4a is not immediately apparent but is reminiscent of the results obtained in the partial synthesis of Voacamine.[5]

Work is in progress to further define the scope and nature of this and related reactions of hydroxyindoles. The use of these Mannich adducts as alkylating agents will be reported shortly.

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2. National Science Foundation Undergraduate Research Program participant.

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