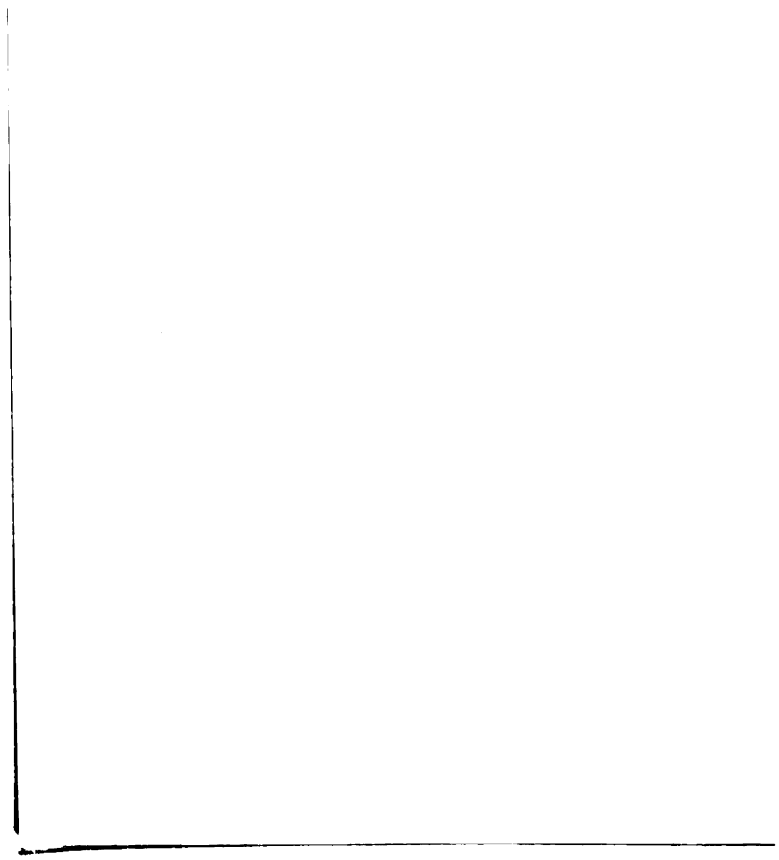
SOME MANNICH REACTIONS OF HYDROXYINDOLES

Thesis for the Degree of M. S.
MICHIGAN STATE UNIVERSITY

Wayne Orrin Johnson

1966



ABSTRACT

SOME MANNICH REACTIONS OF HYDROXYINDOLES

by Wayne Orrin Johnson

Mannich reactions with 5- and 6-hydroxyindoles are shown to result in the stereospecific substitution of the aromatic ring. The 5-hydroxyindoles furnish the C-4 adducts, while 6-hydroxyindoles yield C-7 adducts (indole numbering system). It is only when the active C-5-ortho-position is blocked, as in the case of 5-methyl-6-hydroxy-1,2,3,4-tetrahydrocarbazole (2), that condensation occurs at the indole nitrogen. If both the indole nitrogen atom and the hydroxyl function are blocked (e.g. 3), addition occurs at the C-7 position.

Of particular interest is the C-4 alkylation of 2-methyl-5-hydroxyindole (10) to give Mannich adduct 10a as well as the substitution at the C-4 carbon atom of 5-hydroxyindole (11) to give 11a. These results are contrasted with the normal C-3 alkylation of unsubstituted indoles and a possible rationale is presented.

Nmr spectra are offered as evidence in the structure elucidation of all the hydroxyindoles and their Mannich adducts.

SOME MANNICH REACTIONS OF HYDROXYINDOLES

By

Wayne Orrin Johnson

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To study at a graduate school in a department filled with professors of great integrity and who show wide ranges of interest is, to the author, one of the most exciting and productive aspects in the attainment of an advanced degree. Dr. Stephen Monti has truly displayed this vast sphere of academic awareness and has presented a most stimulating atmosphere through his guidance and counsel. I wish to thank him for the priviledge of studying under him.

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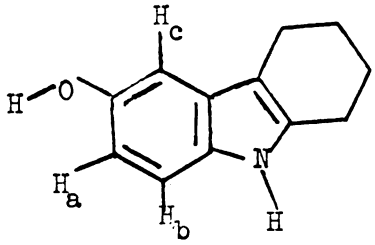
INTRODUCTION

The introduction of an aminomethyl substituent into an indole nucleus by means of a Mannich condensation has been reported to give, in most cases, condensation at the 3-position of the indole nucleus.[1] If this position is blocked, addition generally takes place at the indole nitrogen atom.[1,2] When the 3-position of the indole nucleus as well as the nitrogen atom are blocked, bond formation has been found to occur at the 2-position;[3a] with methyl substituents at all three sites of the indole ring, the Mannich addition took place on the C-2-methyl moiety.[3b]

The limited application of hydroxyindoles as substrates for the Mannich reaction, in contrast to work carried out on several other phenols[4] and heterocyclic phenols,[5] has led to further investigation on our part in this area.

RESULTS AND DISCUSSION

The partial synthesis of Voacamine, a dimeric indole alkaloid, employed a Mannich-like reaction of a 5-methoxyindole as did the Mannich condensation of 6-hydroxy-1,2,3,4-tetrahydrocarbazole (1) (Table I) to give Mannich adduct 1a (Table II).[6]



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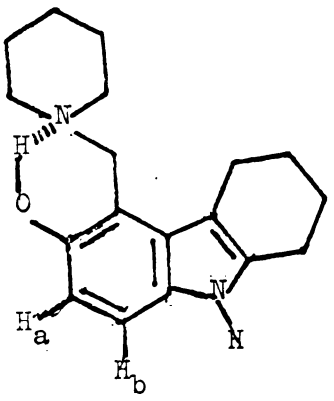
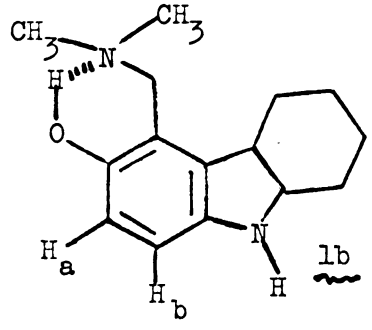
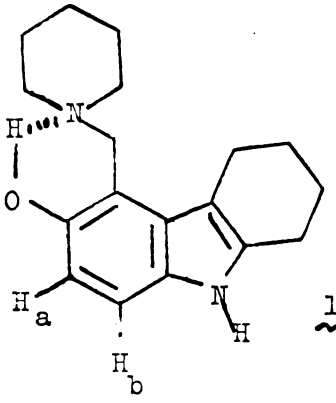


1a

In view of the preferential condensation on the benzene ring over the indole nitrogen with piperidine and paraformaldehyde in ethanol,[6,7] our interest turned to the synthesis of the hydroxy gramine analog 1b by usage of dimethylamine. Optimum yields were obtained by stirring the reaction mixture at room temperature to give the dimethylamino Mannich adduct 1b (Table II), which showed the expected two proton AB aromatic quartet (J_o ~8.5 cps),[8] and infrared spectrum.[7]

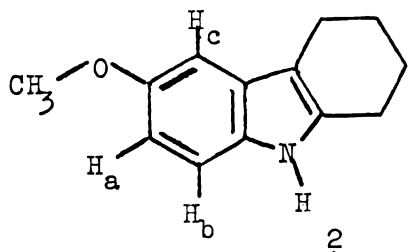


1b



1c

6-Methoxy-1,2,3,4-tetrahydrocarbazole (2) (Table I)[9] did not give substitution on the benzene ring under normal Mannich conditions with piperidine and paraformaldehyde in ethanol, but gave rather the N-alkylated product 2a. The nmr spectrum showed three aromatic protons (Table II), while the disappearance of the N-H stretching mode at 3475 cm.$^{-1}$ in the infrared confirmed such findings.



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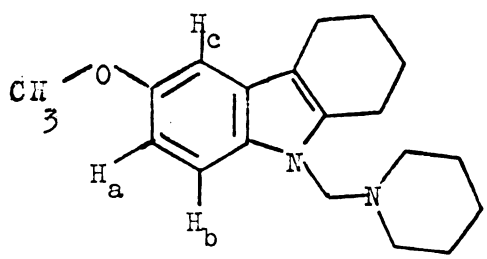
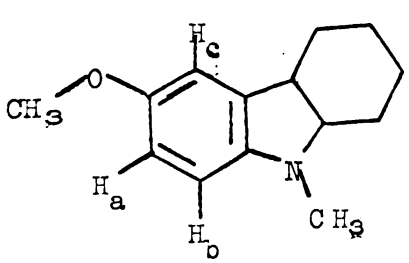


2a

The question now arose as to whether any Mannich condensation would occur if the indole nitrogen atom were also blocked. 9-Methyl-6-methoxy-1,2,3,4-tetrahydrocarbazole (3) (Table I)[10] gave Mannich adduct 3a (Table II) as the major product in a 55 per cent yield under forcing conditions of refluxing in glacial acetic acid. The nmr spectrum showed two aromatic one-hydrogen singlets, which indicated that the hydrogen atoms were para to each other[8] and that condensation had occured at C-7.



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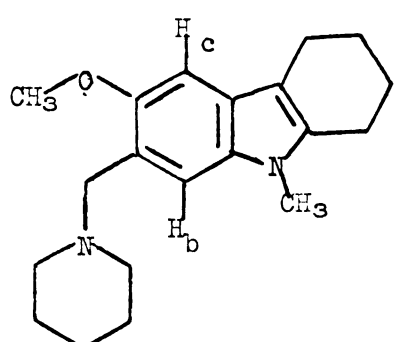
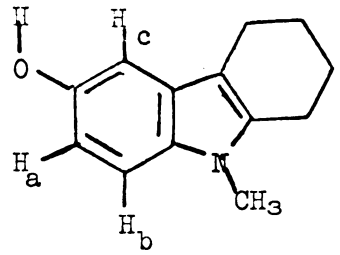


3a

If the 6-hydroxy Mannich adduct 1b was used as a substrate for a further condensation with an equimolar amount of piperidine and paraformaldehyde in ethanol at room temperature, the N-alkylated di-Mannich adduct 1c (vide supra) (Table II) was obtained. This was confirmed by the disappearance of the N-H stretching mode at 3470 $cm.^{-1}$ in the infrared and by the continued presence of the two proton aromatic AB quartet in the nmr.

The next area of interest was concerned with the mode of addition to 9-methyl-6-hydroxy-1,2,3,4-tetrahydrocarbazole (4) (Table I).[11] Condensation again occured at C-5 to give Mannich adduct 4a (Table II), which showed a two proton aromatic AB quartet and the expected infrared spectrum.[7]



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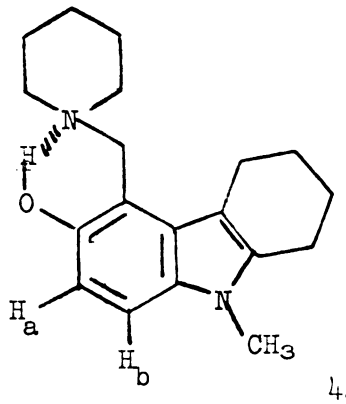
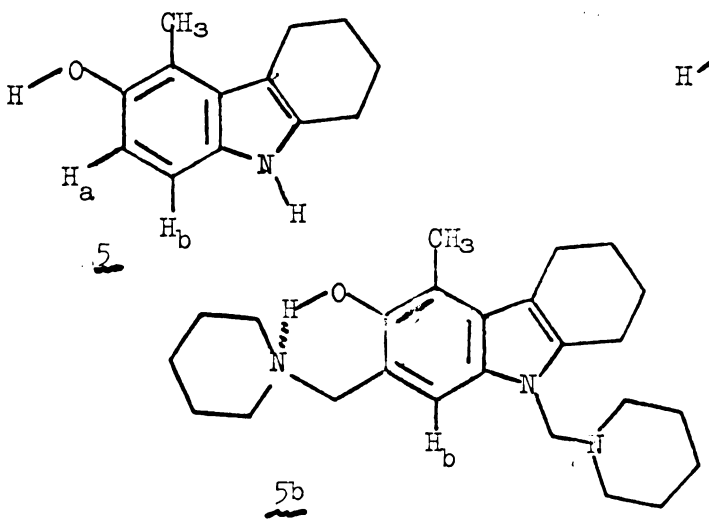


4a

The final condensation in the 6-hydroxy-model system involved the reaction of 5-methyl-6-hydroxy-1,2,3,4-tetrahydrocarbazole (5) (Table I). Compound 5 was prepared by hydrogenolysis of 1b in ethanol using a Pd/C catalyst at 80° and 50 psi of hydrogen. Condensation of 5 with the piperidine-Mannich intermediate in ethanol gave 5a (TableII) as the major product, which resulted from N-alkylation. The product showed free hydroxyl stretching at 3600 $cm.^{-1}$ by infrared analysis and displayed a two proton aromatic AB quartet

in the nmr. A second, minor product was assigned structure 5b. This di-Mannich adduct showed no N-H stretching in the infrared and had a one-proton singlet in the aromatic region of the nmr spectrum. No benzene ring monoalkylated product was observed as judged by infrared analysis of the various chromatography fractions. The upfield shift of the C-methylene group of the minor product (5b) to δ3.70 is in agreement with the chemical shift of the methylene group in Mannich adduct 3a (also note the upfield shift of all H_a-protons in Tables I, II, III and IV).



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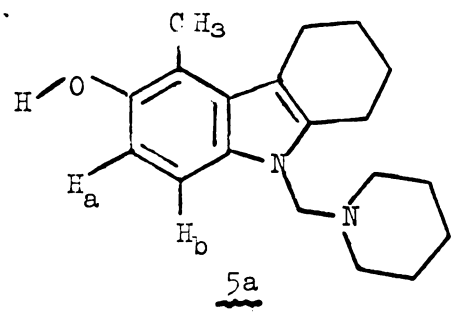
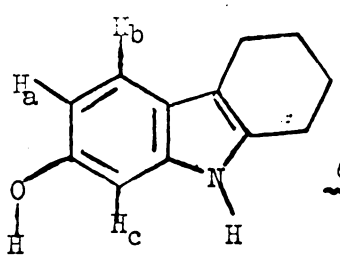


5a

5b

7-Hydroxy-1,2,3,4-tetrahydrocarbazole (6) (Table I)[12] underwent condensation at C-8 to give the piperidine-Mannich adduct 6a (Table II),[13] which gave the expected infrared spectrum and showed a two proton aromatic AB quartet, typical of ortho coupling,[8] in the nmr spectrum.



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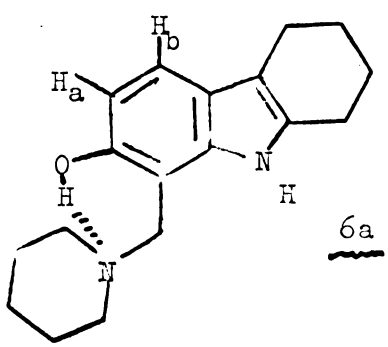
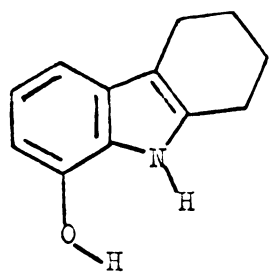


6a

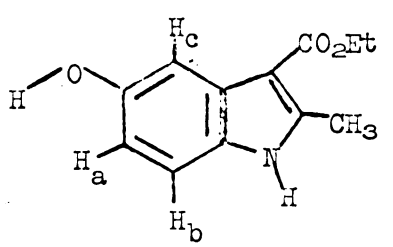
An attempt to synthesize 8-hydroxy-1,2,3,4-tetrahydrocarbazole (7) by the method employed for the preparation of 6 furnished a crystalline product. The combined chemical and spectral evidence for this material, however, are not in complete accord with the anticipated structure 7 (see Experimental Section).



7

The second phase of our research turned to hydroxyindoles with various substituents in the 2- and 3-positions. It has been reported that 2-methylindole and 2-carbethoxyindole give 3-alkylated Mannich adducts with dimethylamine or piperidine as bases,[14] while 5-methoxyindole[15] and 5-benzyloxyindole[16] are known to give the 3-substituted gramine analogs with dimethylamine.

2-Methyl-3-carbethoxy-5-hydroxyindole (8) (Table III)[17] underwent Mannich condensation with formaldehyde and piperidine[17a] or dimethylamine in acetic acid to yield the C-4 Mannich adducts 8a and 8b, respectively. The infrared spectrum of both products showed indole N-H stretching at 3470 cm.$^{-1}$ and had a two-proton aromatic AB quartet indicative of ortho coupling in the nmr.[8]



8

TABLE I

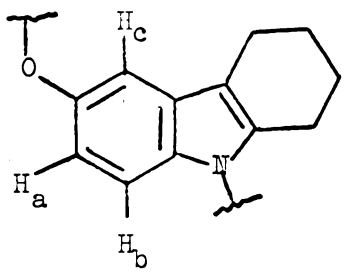
Nmr Spectral Data of Tetrahydrocarbazoles

Compound	Chemical Shifts in δ ppm[a]					
	H_a[b]	H_b[c]	H_c[d]	N-CH_3[e]	O-CH_3[e]	C-CH_3[e]
1	6.60	7.05	6.82	---	---	---
2[f]	6.72	7.02	6.90	---	3.81	---
3[f]	6.75	7.04	6.90	3.38	3.78	---
4	6.64	6.92	6.80	3.33	---	---
5	6.57[c]	6.88	---	---	---	2.47
6[g]	6.55	7.03	6.69	---	---	---

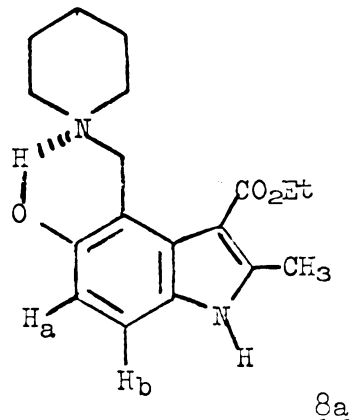
(a) Spectra were taken in CH_3OH with an internal TMS standard; (b) doublet of doublets ($J_o \sim 8.5$ cps, $J_m \sim 2.5$ cps); (c) doublet ($J_o \sim 8.5$ cps); (d) doublet ($J_m \sim 2.5$ cps); (e) singlet; (f) spectra were taken in $CDCl_3$ with an internal TMS standard; (g) C_5-H = H_b, C_6-H = H_a, C_8-H = H_c.

TABLE II

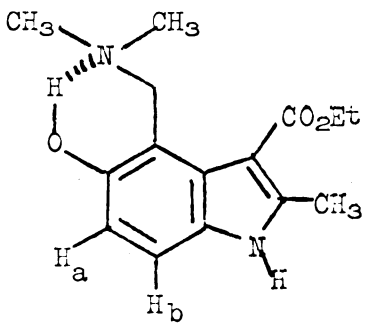
Nmr Spectral Data of Mannich Adducts

Mannich Adduct	Chemical Shifts in δppm[a]						
							
	H_a[b]	H_b[b]	H_c	N-CH_3[c]	O-CH_3[c]	C-CH_3[c]	CH_2NR_2[c]
1a	6.62	6.97	---	---	---	---	4.03
1b	6.67	6.98	---	---	---	---	4.02
1c	6.67	7.18	---	---	---	---	4.08, 4.43
2a	6.75	7.24	6.90[e]	---	3.83	---	4.46
3a	---	7.24[c]	6.89[c]	3.53	3.83	---	3.67
4a	6.72	7.02	---	3.43	---	---	4.03
5a	6.58	7.05	---	---	---	2.53	4.46
5b	---	6.85[c]	---	---	---	2.55	3.70, 4.43
6a[f]	6.60	7.17	---	---	---	---	3.70

(a) Spectra were taken in $CDCl_3$ with an internal TMS standard; (b) doublet ($J_o \sim 8.5$ cps); (c) singlet; (d) doublet of doublets ($J_o \sim 8.5$ cps, $J_m \sim 2.5$ cps); (e) doublet ($J_m \sim 2.5$ cps); (f) C_5-H = H_b, C_6-H = H_a.

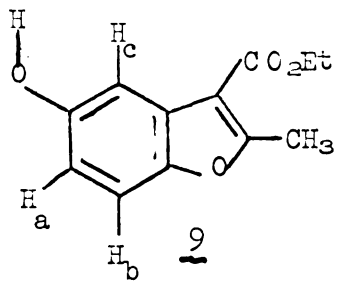


8a



8b

Also of interest was the condensation of 2-methyl-3-carbethoxy-5-hydroxybenzofuran (9) (Table III)[18] with dimethylamine and paraformaldehyde to give the 4-Mannich adduct 9a,[19] while the reaction using piperidine[13] as the base gave the corresponding Mannich adduct 9b (Table IV). Compound 9b showed only hydrogen-bonded hydroxyl in the infrared and displayed a two-proton aromatic AB quartet by nmr.



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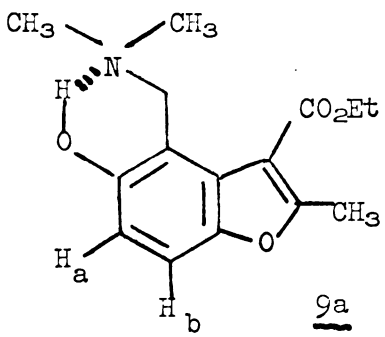
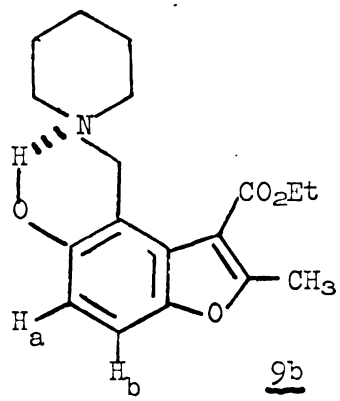


9a

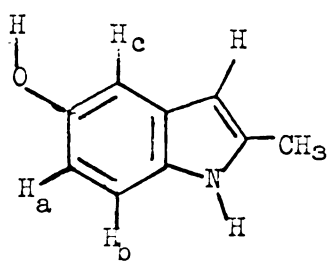


9b

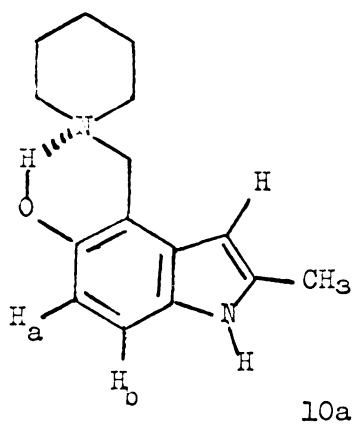
The last phase of our investigation involved the Mannich reactions of 2-methyl-5-hydroxyindole (10) (Table III)[17] and 5-hydroxyindole (11) (Table III).[20] The nmr spectrum of 10 displayed the normal aromatic ring pattern as observed for the other hydroxyindoles, but showed in addition the C_3-H at δ 6.32, which appeared

as a multiplet due to splitting by the C_2-methyl and the indole N-H.

Mannich condensation of 10 with piperidine and paraformaldehyde in ethanol at room temperature gave as the major product Mannich adduct 10a (Table IV) in a 72 per cent yield. Compound 10a showed a two-proton AB quartet in the aromatic region as well as the C_3-H as a multiplet at δ6.34. The infrared spectrum showed the expected absorptions.[7] A minor product was present in too small amounts to isolate, but may well have been the C_3-adduct.



10

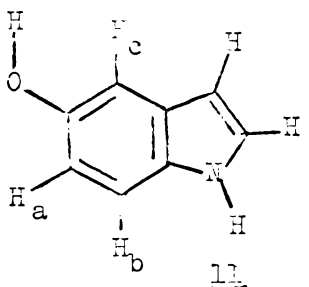


10a

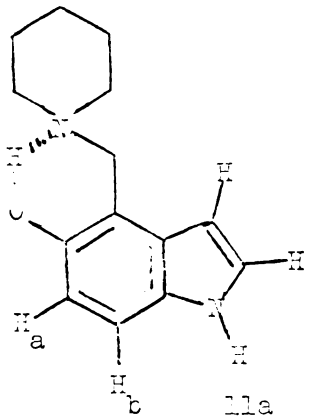
5-Hydroxyindole (11), which has five potential sites for addition (N-H, C_2, C_3, C_4, and C_6) was next subjected to the Mannich reaction. The parent compound 11 showed the expected aromatic protons H_a, H_b and H_c (Table III) as well as the C_2-hydrogen, doublet at δ7.02, and the C_3-hydrogen as a broadened doublet at δ6.34 in the nmr.

Condensation of 11 with piperidine and paraformaldehyde at room temperature, or at reflux in ethanol for a shorter time, gave principally the C_4- alkylated product 11a (Table IV) in an 87 per cent yield. Mannich adduct 11a showed the expected infrared

spectrum[7] while the nmr spectrum showed a two-proton aromatic AB quartet, which is indicative of C_4-addition, with retention of the C_2-hydrogen as a doublet at δ7.13 and the C_3-hydrogen as a broadened doublet at δ6.34.



11



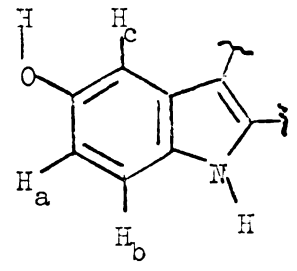
11a

The preferential alkylation of 6-hydroxy-1,2,3,4-tetrahydrocarbazoles at C-5 and of 5-hydroxyindoles at C-4 via the Mannich reaction requires some rationalization. It has been suggested[21] that the preferential ortho-alkylation of phenols over para-alkylation is a result of the hydroxyl group orienting the Mannich intermediate in a quasi-six-membered chelate ring preceeding carbon-carbon bond formation.

If one extends this argument to the hydroxyindole systems, the orientation by the hydroxyl group would seem to suggest a non-stereospecific alkylation of either of the two α-carbon atoms. Results of our work indicate a stereospecific alkylation at C-5 for 6-hydroxy-1,2,3,4-tetrahydrocarbazole (1) and for 9-methyl-6-hydroxy-1,2,3,4-tetrahydrocarbazole (4), and C_4-addition for 5-hydroxyindole (11), 2-methyl-5-hydroxyindole (10), 2-methyl-3-carbethoxy-5-hydroxyindole (8) as well as for 2-methyl-3-

TABLE III

Nmr Spectra of 5-Hydroxyindoles

Compound	Chemical Shifts in δ ppm[a]					
						
	H_a[b]	H_b[c]	H_c[d]	C_2-CH_3[e]	C_2-H	C_3-H
8	6.72	7.16	7.48	2.65	---	---
9 (N-H=O)	6.84	7.32	7.49	2.70	---	---
10	6.62	7.10	6.90	2.33	---	6.00[f]
11	6.73	7.23	7.04	---	7.13[g]	6.32[h]

(a) Spectra were taken in CH_3CH with an internal TMS standard; (b) doublet of doublets ($J_o \sim 8.5$ cps, $J_m \sim 2.5$ cps); (c) doublet ($J_o \sim 8.5$ cps); (d) doublet ($J_m \sim 2.5$ cps); (e) singlet; (f) multiplet; (g) doublet ($J \sim 3.3$ cps); (g) broadened doublet ($J \sim 3.3$ cps) [sic].

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TABLE IV

Nmr Spectra of Mannich Adducts

Mannich Adduct	Chemical Shifts in δppm[a]					
	H_a[b]	H_b[b]	C_4-CH_2-[c]	C_2-CH_3[c]	C_2-H	C_3-H
8a	6.67	6.98	4.25	2.55	---	---
8b[d]	6.67	7.00	4.25	2.52	---	---
9b(N-H=O)	6.73	7.15	4.15	2.58	---	---
10a	6.67	6.98	3.83	2.32	---	6.05[e]
11a	6.72	7.08	3.87	---	7.02[f]	6.34[g]

(a) Spectra were taken in $CDCl_3$ with an internal TMS standard; (b) doublet ($J \sim 8.5$ cps); (c) singlet; (d) dimethylamino Mannich adduct; (e) multiplet; (f) doublet ($J \sim 3.3$ cps); (g) broadened doublet ($J \sim 3.3$ cps) [nr].

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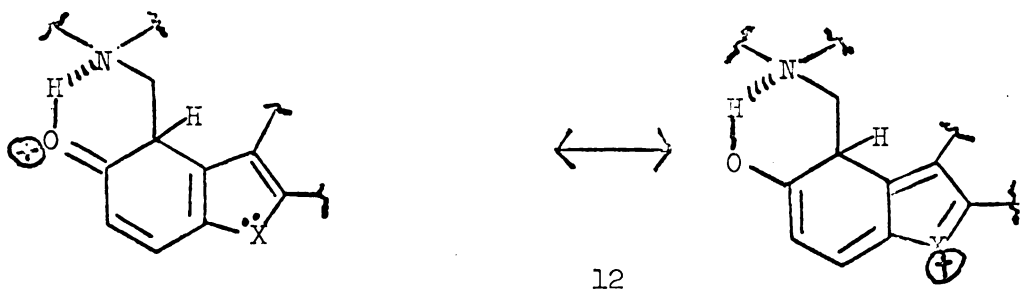
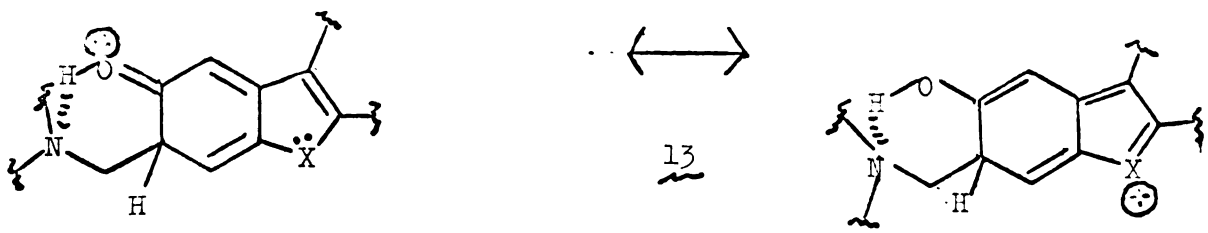
carbethoxy-5-hydroxybenzofuran (9).

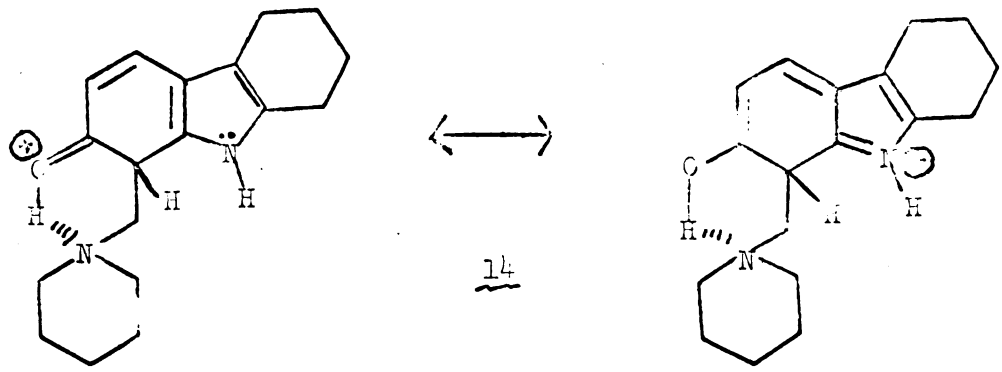
We consequently propose resonance stabilization of the developing transition state carbonium ion 12,[6] involving the electron pair on the hetero atom, to be the deciding factor for our stereospecific alkylations. Alkylation in the alternate ortho-position 13 would allow less delocalization of the positive charge and would consequently have a higher energy of activation. A similar argument would favor the C_8-alkylation of 7-hydroxy-1,2,3,4-tetrahydrocarbazole, in which greater charge delocalization is obtained in the transition state 14 than could occur for the C_6-alkylated product 15. Only the C_8-condensation is noted for this compound, which supports the delocalization theory.



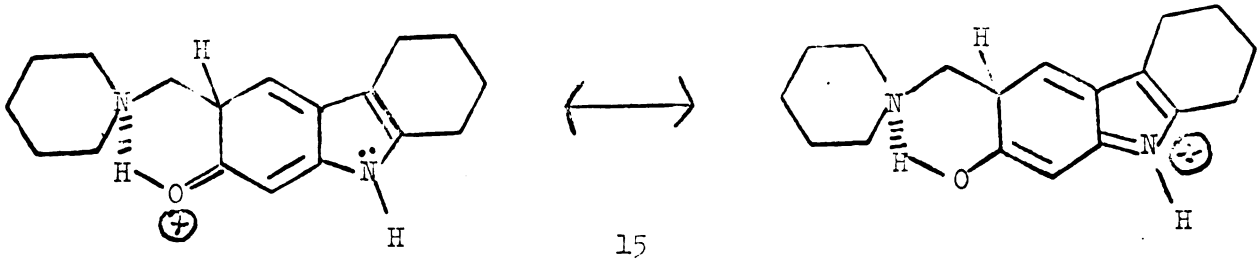
12



13



14



15

For 6-methoxy-1,2,3,4-tetrahydrocarbazole (2) one could not employ the hydrogen-bonded orientation and consequently alkylation involving the electron pair on the indole nitrogen would be expected and was observed.

The interesting case at hand is that of 5-methyl-6-hydroxy-1,2,3,4-tetrahydrocarbazole (3) where the preferred site of addition is blocked. In this case two products were obtained. The major product was the N-alkylated Mannich adduct 5a and the second, minor product was di-adduct 5b. At first glance this appeared to be a rather strange order for addition, expecially when the hydroxyl group was present to orient the Mannich intermediate, but the result is consistent with the stereospecific addition of the hydroxyindoles.

It could logically be assumed that the energy of activation for the alkylation of the two ortho-carbons is significantly different and consequently the energy of activation for the alternate site is in the region of that of N-alkylation or even somewhat higher, which would give the resulting product distribution.

An explaination for the anomalous, stereospecific orientation of 9-methyl-6-methoxy-1,2,3,4-tetrahydrocarbazole (3) is not perfectly clear at this point, but is perhaps analogous to the synthesis of Voacamine.[6] It might be pointed out that forcing conditions were used in this case, which were not necessary in the other Mannich reactions.

Hence, it appears that orientation of the Mannich intermediate by the hydroxyl group on the indole nucleus and resonance stabilization of the intermediate carbonium ion are the two dominant factors in the stereospecific alkylation of hydroxyindoles via the Mannich reaction.

EXPERIMENTAL

6-Hydroxy-1,2,3,4-tetrahydrocarbazole (1) was prepared by the method of Milne and Tomlinson[8] in a 60% yield. A modification of the method used by Asero and co-workers[22] was also employed to give a 64% conversion to the desired product. The crude product was purified by sublimation at 0.4mm. and 160° to yield white crystals, m.p. 170-172° (lit.[8] m.p. 172°); λ_{max}^{EtOH} 228, 282, 295 (shoulder) mμ (ε 20,300, 7500 and 6700, resp.); $\nu_{max}^{CHCl_3}$ 3600, 3470 cm.$^{-1}$. See Table I for nmr.

Mannich Adduct 1a was prepared according to the method of Büchi, Manning and Monti.[6] The product was crystallized from ethanol to give a 75% yield of a white crystalline solid, m.p. 163-164°(lit.[6] m.p. 163.5-164.5°). The reaction was also carried out at room temperature for 4 hours in ethanol and recrystallized to give a 78% yield, m.p. 163-164°; λ_{max}^{EtOH} 231, 284, 295 (shoulder) mμ (ε 20,800, 8600 and 7500, resp.); $\nu_{max}^{CHCl_3}$ 3470 cm.$^{-1}$.[7] See Table II for nmr.

Mannich Adduct 1b.--A mixture of 25% dimethylamine solution (1.0mmole) and paraformaldehyde (30 mg., 1.0mmole) was warmed in ethanol (3 ml.) on a steam bath until the solution became homogeneous. The solution was cooled to room temperature and 6-hydroxy-1,2,3,4-tetrahydrocarbazole (1) (185 mg., 1 mmole) was added. The mixture was stirred for 3 hours at room temperature, evaporated to dryness and chromatographed over activity III alumina with benzene to give 147 mg. (60%) of product, which was recrystal-

lized from a benzene-pet. ether mixture to give white crystals, m.p. 128-133.5°; λ_{max}^{EtOH} 231, 285, 295 (shoulder) mμ (ε19,800, 8000 and 7200, resp.); $\nu_{max}^{CHCl_3}$ 3470 cm.$^{-1}$.[7] The nmr showed the N,N-dimethyl group as a 6-hydrogen singlet at δ2.35 in addition to the protons shown in Table II.

Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.73; H, 8.25; N, 11.47. Found: C, 72.94; H, 8.16; N, 11.38. The reason for poor agreement might be due to the instability of the product. The compound has been noted by tlc to decompose on standing in alcohol.

Mannich Adduct 1c.--A mixture of piperidine (85 mg., 1.0 mmole) and paraformaldehyde (30 mg., 1.0 mmole) was warmed in ethanol (9 ml.) until the solution became homogenous. The mixture was cooled to room temperature and the piperidine-Mannich adduct 1a (282 mg., 1.0 mmole) was added. The reaction mixture was refluxed for 8 hours, during which time 318 mg. (84%) of a white solid crystallized, m.p. 172-181°(dec.); λ_{max}^{EtOH} 232, 286, 300 (shoulder) mμ (ε21,900, 9500 and 7400, resp.); $\nu_{max}^{CHCl_3}$ (see footnote 7). See Table II for nmr.

6-Methoxy-1,2,3,4-tetrahydrocarbazole (2) was prepared by the method of Milne and Tomlinson[9] in a 56% yield. The crude product was purified by recrystallization from ethanol to yield white crystals, m.p. 101-104°(lit.[9] m.p. 93-105°); λ_{max}^{EtOH} 229, 285, 296 (shoulder) mμ (ε23,000, 7800 and 7500, resp.); $\nu_{max}^{CHCl_3}$ 3470 cm.$^{-1}$. See Table I for nmr.

Mannich Adduct 2a.--A mixture of piperidine (85 mg., 1.0

mmole) and paraformaldehyde (30 mg., 1.0 mmole) was warmed in ethanol (2 ml.) to give a homogeneous solution. The mixture was cooled and the 6-methoxy-1,2,3,4-tetrahydrocarbazole (2) (199 mg., 1.0 mmole) was added. The mixture was refluxed under a nitrogen atmosphere for 2 hours and evaporated to a yellow syrup, which crystallized from ethanol to give 172 mg. (58%) of product, m.p. 54-65°(dec.); λ_{max}^{EtOH} 231, 283, 296 (shoulder) mμ(24,000, 8300 and 7200, resp.); $\nu_{max}^{CHCl_3}$ (no functional groups present). See Table II for nmr.

9-Methyl-6-methoxy-1,2,3,4-tetrahydrocarbazole (3) was prepared by the method of Stevens and Tucker[10] in a 85% yield. The crude product was purified by recrystallization from an ethanol-water mixture to yield a white product, m.p. 86.5-88.5° (lit.[10] m.p. 88-89°); λ_{max}^{EtOH} 231, 287, 292 (shoulder) mμ(ε23,900, 7500 and 6700, resp.); no identifiable functional groups in infrared spectrum. See Table I for nmr.

Mannich Adduct 3a.--A mixture of piperidine (43 mg., 0.50 mmole) and paraformaldehyde (15 mg., 0.50 mmole) was dissolved in glacial acetic acid (6 ml.) by warming on a steam bath. The mixture was cooled to room temperature and the 9-methyl-6-methoxy-1,2,3,4-tetrahydrocarbazole (3) (108 mg., 0.50 mmole) was added. The mixture was then refluxed under a nitrogen atmosphere for one and one half hours, neutralized by adding dropwise to a sodium carbonate solution and extracted with benzene to give 86 mg. (55%) of product, which was recrystallized from ethyl acetate to give slightly yellow crystals, m.p. 84-87.5°. See Table II for nmr.

9-Methyl-6-hydroxy-1,2,3,4-tetrahydrocarbazole (4).--A 650 mg. sample of 9-methyl-6-methoxy-1,2,3,4-tetrahydrocarbazole (3) was demethylated[11] by refluxing in a mixture of hydrobromic acid (3 ml. of 48%) and acetic acid (10 ml.) for 16 hours under nitrogen. The solution was neutralized with sodium carbonate and extracted with methylene chloride to give 250 mg.(41%) of product. The product was purified by sublimation at 0.5 mm to give a white solid, m.p. 112.5-114.5°; λ_{max}^{EtOH} 231, 286, 299 (shoulder) mμ(ε21,000, 7000 and 5900, resp.); $\nu_{max}^{CHCl_3}$ 3600, 3370 (broad) cm.$^{-1}$. See Table I for nmr.

Mannich Adduct 4a.--A mixture of piperidine (42.5 mg., 0.50 mmole) and paraformaldehyde (15 mg., 0.50 mmole) was warmed in a mixture of acetic acid in ethanol (1:10) to effect an homogeneous solution. The mixture was cooled and the 9-methyl-6-hydroxy-1,2,3,4-tetrahydrocarbazole (99.5 mg., 0.50 mmole) was added. The mixture was refluxed for 90 minutes under a nitrogen atmosphere, cooled to room temperature and added dropwise into a solution of sodium carbonate and then was extracted with benzene. The crude product was recrystallized from ethyl acetate to give 125 mg. (84%) of white needles, m.p. 142-144°, λ_{max}^{EtOH} 232, 287, 308 (shoulder) mμ(ε19,600, 7000 and 5900, resp.). The product showed the expected infrared[7] and nmr spectra (Table II).

5-Methyl-6-hydroxy-1,2,3,4-tetrahydrocarbazole (5).--Mannich adduct 1b (244 mg., 1.0 mmole) was dissolved in 50 ml. of 95% ethanol and 100 mg. of catalyst (Pd/C) was added. The mixture was shaken on a Paar shaker at 80° for 3 hours at a pressure of 50 psi

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of hydrogen to give 180 mg.(90%) of the desired product, m.p. 50.5-53.5°; λ_{max}^{EtOH} 227, 279, 294 (shoulder) mμ(ε15,300, 5700 and 4000, resp.); $\nu_{max}^{CHCl_3}$ 3604, 3470 cm.$^{-1}$. See Table I for nmr.

Mannich Adduct 5a.--A mixture of piperidine (85 mg., 1.0 mmole) and paraformaldehyde (30 mg., 1.0 mmole) was warmed to effect a clear solution in alcohol (6 ml.) containing 2 drops of acetic acid. The mixture was cooled and the 5-methyl-6-hydroxy-1,2,3,4-tetrahydrocarbazole (5) (202 mg., 1.0 mmole) was added. The mixture was stirred at room temperature for 8 hours, evaporated to dryness on Alumina III and eluted with benzene to give 193 mg. (65%) of product. This major product was recrystallized from ethanol to give white crystals, m.p. 146.5-147.5°; λ_{max}^{EtOH} 229, 281, 303 (shoulder) mμ(ε14,500, 5400 and 3700, resp.); $\nu_{max}^{CHCl_3}$ 3600 cm.$^{-1}$.7 See Table II for nmr.

Mannich Adduct 5b.--A second minor product was obtained by chromatography of the mother liquors from 5a over Alumina III. The second fraction (50% benzene-pet ether) furnished 50 mg. (13%) of a white solid, m.p. 146.5-148°; mixture melting point with 5a, 125-135°. The absence of N-H or free hydroxyl stretches in the infrared as well as the nmr spectrum (see Table II) confirm the di-addition formulation 5b for this material. No mono-alkylation product, resulting from addition to the benzene ring only, was obtained. This was concluded by the absence of an indole N-H stretch in the infrared in any of the chromatography fractions.

7-Hydroxy-1,2,3,4-tetrahydrocarbazole (6)[13] was prepared by the method of Jones and Tomlinson[12] in a 31% yield, m.p. 162.5-163.5°

(lit.[12] m.p. 163-164°); λ_{max}^{EtOH} 229, 273, 302 mμ (ε27,300, 4200 and 4700, resp.); $\nu_{max}^{CHCl_3}$ 3600, 3470 cm.$^{-1}$. See Table I for nmr.

Mannich Adduct 6a.[13]--A mixture of piperidine (85 mg., 1.0 mmole) and paraformaldehyde (30 mg., 1.0 mmole) was warmed on a steam bath to effect an homogeneous solution. The mixture was cooled to room temperature and the 7-hydroxy-1,2,3,4-tetrahydrocarbazole (6) was added. The mixture was stirred at room temperature for 30 min. to give 195 mg. (69%) of product, m.p. 161.5-163°; λ_{max}^{EtOH} 230, 274, 303 mμ (ε27,000, 4600 and 4400, resp.); $\nu_{max}^{CHCl_3}$ 3475 cm.$^{-1}$.[7] See Table II for nmr.

Anal. Calcd. for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85. Found: C, 76.07; H, 8.41; N, 9.88.

Attempted Synthesis of 8-Hydroxy-1,2,3,4-tetrahydrocarbazole (7).--An attempt was made to prepare 7 in a method similar to the preparation of 6.[12] Ortho-aminophenol (5.45 g, 50 mmoles) and 2-hydroxycyclohexanone (6.00g., 50 mmoles) were warmed in the presence of three drops of hydrochloric acid to 140° for eight minutes in an open flask with stirring. The syrupy product was crystallized from ethanol to give 6.30 g. of a white crystalline product, m.p. 161.5-163°; λ_{max}^{EtOH} 209, 243, 293 mμ (ε21,400, 4400 and 2500, resp.); $\nu_{max}^{CHCl_3}$ 3580 (shoulder), 3480 (broad), 3395 (sharp) and 3320 (shoulder) cm.$^{-1}$. The nmr spectrum showed a complex aromatic multiplet from δ6.5-6.7.

Anal. Calcd. for $C_{12}H_{13}NO$: C, 76.97; H, 7.00; N, 7.48. Found: C, 71.20; H, 7.41; N, 7.04. This analysis better fits

$C_{12}H_{15}NO_2$ calcd.: C, 70.22; H, 7.37; N, 6.82.

2-Methyl-3-carbethoxy-5-hydroxybenzofuran (9) was prepared by the method of Bernatek and Ledaal.[18] See Table III for nmr.

Mannich Adduct 9b.[13,19]--A Mixture of piperidine (0.43g., 5.0 mmole) and paraformaldehyde (0.15 g., 5.0 mmole) was warmed in a mixture of acetic acid in ethanol (1:10) to effect a clear solution. The mixture was cooled and the 2-methyl-3-carbethoxy-5-hydroxybenzofuran (8) (1.10 g., 5.0 mmole) was added. The mixture was refluxed under nitrogen for 4 hours and allowed to stand at room temperature for one week. The mixture was neutralized with sodium carbonate and extracted with chloroform. Crystallization from ether/hexane gave 380 mg. (24%) of a white material, m.p. 75-78°; $\nu_{max}^{CHCl_3}$ (footnote 7). See Table IV for nmr.

2-Methyl-5-hydroxyindole (10)[17] was purified by sublimation at 0.5 mm., m.p. 131-132.5° (lit.[19] m.p. 134-135°); λ_{max}^{EtOH} 212, 274, 294 (shoulder), 306 (shoulder) mμ (ε22,800, 8500, 5600 and 3600, resp.); $\nu_{max}^{CHCl_3}$ 3600, 3475 cm.$^{-1}$. See Table III for nmr.

Mannich Adduct 10a.--A mixture of piperidine (85 mg., 1.0 mmole) and paraformaldehyde (30 mg., 1.0 mmole) was warmed in ethanol (4 ml.) to effect an homogeneous solution. The mixture was cooled and 2-methyl-5-hydroxyindole (10) (147 mg., 1.0 mmole) was added. The mixture was stirred for one hour at room temperature and chromatographed over Alumina III using a benzene-pet. ether eluent (1:1). The yellow oil obtained was recrystallized from a mixture of benzene and pet. ether to give 175 mg. (72%) of a white crystalline product, m.p. 98-99°; λ_{max}^{EtOH} 216, 276, 294 (shoulder) and 307

(shoulder) mμ(ε22,000, 9100, 5500 and 3900, resp.); $\nu_{max}^{CHCl_3}$ 3475 cm.$^{-1}$.[7] See Table III for nmr.

5-Hydroxyindole (11),[20] melted from 106-10[illegible]°; λ_{max}^{EtOH} 209, 215 (shoulder), 271, 298, 307 (shoulder) mμ(ε20,700, 19,000, 6500, 3600 and 2900, resp.); $\nu_{max}^{CHCl_3}$ 3600, 3485 cm.$^{-1}$. See Table III for nmr.

Mannich Adduct 11a.--A mixture of piperidine (85 mg., 1.0 mmole) and paraformaldehyde (30 mg., 1.0 mmole) was warmed on a steam bath in ethanol (3 ml.) to effect an homogeneous solution. The reaction mixture was cooled and the 5-hydroxyindole (11) (133 mg., 1.0 mmole) was added. The mixture was stirred for 1.5 hours at room temperature, evaporated to dryness and chromatographed on activity III Alumina with a mixture of benzene and pet. ether (1:1). The yellow syrupy liquid was recrystallized from a small amount of benzene to give 200 mg. (87%) of product, m.p. 86-98°; λ_{max}^{EtOH} 217, 273, 301, 308 (shoulder) mμ(ε18,000, 7500, 4100 and 3800, resp.); $\nu_{max}^{CHCl_3}$ 3485 cm.$^{-1}$.[7] See Table IV for nmr.

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BIOGRAPHICAL NOTE

The author was born on May 26, 1942, in Valley City, North Dakota and received his secondary education in Hannaford, North Dakota. He undertook undergraduate study at Concordia College of Moorhead, Minnesota, where he received a Bachelor of Arts Degree in June, 1964. He then became a graduate student at Michigan State University, East Lansing, Michigan, where he worked for his Master's Degree. Upon completion, he has been accepted to the graduate school of the Department of Chemistry of the University of Oregon, Eugene, Oregon, in the fall of 1966.