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POSITION SELECTIVE MANNICH REACTIONS OF SOME 5- AND 6-HYDROXYINDOLES[1]

S. A. MONTI[2] and W. O. JOHNSON

Departments of Chemistry, Michigan State University, East Lansing, Michigan 48823 and the University of Texas at Austin, Austin, Texas 78712

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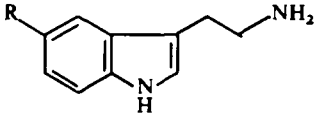
Abstract—Mannich condensation in the 5-hydroxyindole series (5-hydroxyindole and 6-hydroxy-1,2,3,4-tetrahydrocarbazole substrates) resulted in selective introduction of an aminomethyl substituent at C-4; if this position was blocked, condensation occurred at C-3 (if available) or at the indole N atom. In the 6-hydroxyindole series, preferential substitution at C-7 was observed for substrates bearing an indole N—H group. Mannich condensation of a 6-hydroxyindole derivative containing an N-Me group (7-hydroxy-9-methyl-1,2,3,4-tetrahydrocarbazole), however, occurred at C-5. The structures of the piperdine and dimethylamine adducts in each series were elucidated by NMR spectroscopy. The preferential condensation in the benzene ring of the hydroxyindole nucleus is ascribed to intermolecular H—bonded orientation of substrates prior to bond formation. The selective substitution at one of the two positions *ortho* to the aromatic OH group is discussed in terms of steric and electronic factors.

ELECTROPHILIC Mannich condensation of indoles generally results in selective reaction at the 5-membered pyrrole ring; substitution occurring preferentially at the 3-position, then the 1-position (indole N atom) and finally the 2-position.[3*] Accordingly this position selective introduction of an aminomethyl substituent has provided a facile entry into the synthesis of more complex molecules possessing 3-, 1- and/or 2-substituted indole nuclei. In particular these Mannich adducts serve as intermediates in the synthesis of biologically important amines such as tryptamine, serotonin and related derivatives.[5] In contrast to the ready accessibility of pyrrole ring substituted indole derivatives, there is a conspicuous absence of generally applicable methods for the selective introduction of carbon substituents into the benzene ring (positions 4–7).



R = H: Tryptamine
R = OH: Serotonin

In a general sense, electrophilic substitution of indole substrates bearing a *free* aromatic OH group appeared to offer an attractive approach to this problem. It was anticipated that the presence of a free OH moiety could facilitate benzene ring substitution over the normal pyrrole ring substitution.† Thus an investigation of the Mannich reaction of several hydroxyindoles was initiated.

* Mannich condensation of 1,2,3-trimethylindole is reported to occur at the C-2 Me group.[4]

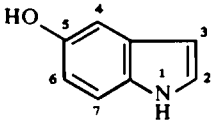
† For examples of substitution in the aromatic ring of C-5 oxygenated indoles see Ref. 6.

Although only fragmentary reports[7] of Mannich reactions involving hydroxyindoles existed at the outset of our investigation, the well documented[3] reactivity of phenols and heterocyclic phenols in the Mannich reaction provided support for the general approach envisioned. As briefly outlined in a preliminary communication,[8] this hypothesis of selective benzene ring substitution has been verified experimentally. Herein we wish to record our complete observations. Recently further support for the position selective Mannich reaction of hydroxyindoles has been documented elegantly by Troxler *et al.*[9] Furthermore, the utility of these hydroxyindole Mannich adducts as synthetic intermediates has been established.[9c-11]

METHODS AND RESULTS

Mannich condensation of the individual hydroxyindoles was effected by allowing an equivalent of hydroxyindole, formaldehyde and the appropriate amine to react in ethanol, 10% acetic acid–ethanol or glacial acetic acid. (See Experimental.) In each case the structure of resulting aminomethyl adduct(s) was elucidated by NMR spectroscopy. The three nonequivalent aromatic protons in the starting 5- and 6-hydroxyindoles were identified readily by first order analysis[12] of this well resolved region ($J_o \sim 8{\cdot}5$ Hz, $J_m \sim 2{\cdot}5$ Hz, $J_p < 1$ Hz). The C-2 and C-3 indole protons[13] (when present) were cleanly separable from the aromatic set. These data are summarized in Table 3. Thus the coupling pattern observed for the two nonequivalent aromatic protons of the resulting Mannich adduct established unambiguously the site of substitution (Table 4).

In the 5-hydroxyindole series, two general classes of substrates were examined: the 5-hydroxyindole (**1**) and the structurally analogous 6-hydroxy-1,2,3,4-tetrahydrocarbazole (**5**) systems.* The results for the Mannich reaction of these 5-hydroxyindoles are summarized in Table 1. These data show that condensation occurs preferentially at the C-4 position of **1** (the C-5 position of **5**) to yield aminomethyl adducts of part structure **A**. When the C-4 position is blocked, condensation takes place preferentially at C-3 if available, or at the indole N atom. No evidence for the formation of mono adducts at the alternative aromatic ring positions† was found.



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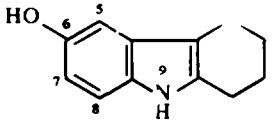

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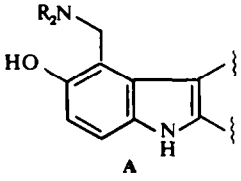
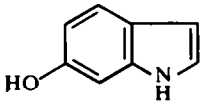


A

* The hydroxyindoles and Mannich adducts listed in Tables 1 and 2 have been numbered sequentially for convenient reference.

† Trace amounts of the C-6 mono adduct of 4 have been observed by Troxler.[9]

Both the 6-hydroxyindole (**8**) and the 7-hydroxy-1,2,3,4-tetrahydrocarbazole (**10**) nuclei were used to investigate Mannich reactions in the 6-hydroxyindole series. These data are summarized in Table 2. Once again preferential condensation occurs in the benzene ring of the hydroxyindole skeleton. In the absence of steric effects the aminomethyl substituent is introduced at C-7 of the indole ring (part structure **B**). If this position is blocked and the C-3 position is unsubstituted, condensation occurs at C-3[9a] Finally the data in Table 2 reveal a pronounced steric effect in the 7-hydroxytetrahydrocarbazole series. When the indole N atom (N-9) bears a Me substituent (**11**) the only mono Mannich adduct observed is the C-6 species **12**. The *peri* relationship between the N-9 Me group and the C-8 position (preferred site of condensation) does not present a major barrier to reaction at this position, however, since the bis-Mannich adduct **13** is also formed in this reaction. No evidence for the C-8 monoadduct was found (NMR analysis of crude reaction mixtures).



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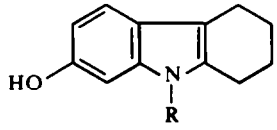
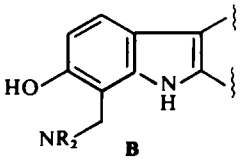
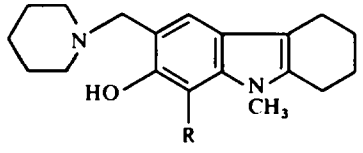


10: R = H
11: R = Me



B



12: R = H
13: R=CH_2—N

TABLE 1. MANNICH ADDUCTS IN THE 5-HYDROXYINDOLE SERIES

Substrate	Formula number	Condensation site	Amine	Mannich adduct Formula number
5-Hydroxyindole	**1**	C-4	Piperidine	**1p**
			Dimethylamine[9]	**1d**
5-Hydroxy-2-methylindole	**2**	C-4	Piperidine	**2p**
			Dimethylamine	**2d**
5-Hydroxy-2-methyl-3-carbethoxyindole	**3**	C-4	Piperidine	**3p**
			Dimethylamine	**3d**
5-Hydroxy-4-methylindole	**4**	C-3[15]	Dimethylamine[9]	**4d**
5-Hydroxy-4-dimethylaminomethyl-2-methylindole	**2d**	C-3	Dimethylamine	**2b**
6-Hydroxytetrahydrocarbazole	**5**	C-5	Piperidine	**5p**
			Dimethylamine	**5d**
6-Hydroxy-9-methyltetrahydrocarbazole	**6**	C-5	Piperidine	**6p**
6-Hydroxy-5-methyltetrahydrocarbazole	**7**	N-9	Piperidine	**7p**
6-Hydroxy-5-piperidinomethyltetrahydrocarbazole	**5p**	N-9	Piperidine	**5b**

TABLE 2. MANNICH ADDUCTS IN THE 6-HYDROXYINDOLE SERIES

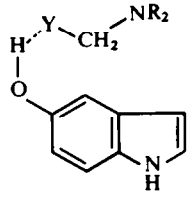
Substrate	Formula number	Condensation site	Amine	Mannich adduct Formula number
6-Hydroxyindole	**8**	C-7	Dimethylamine[9]	**8d**
6-Hydroxy-7-methylindole	**9**	C-3[a]	Dimethylamine[9]	**9d**
7-Hydrotetrahydro-carbazole	**10**	C-8	Piperidine	**10p**
7-Hydroxy-9-methyl-tetrahydrocarbazole	**11**	C-6	Piperidine	**12**
7-Hydroxy-9-methyl-6-piperidinomethyltetra-hydroxarbazole	**12**	C-8	Piperidine	**13**

[a] A small amount of the C-5 monoadduct was observed.[9]

DISCUSSION

A consideration of the position selectivity observed in the Mannich reactions of these 5- and 6-hydroxyindoles must account for the following two elements of selectivity: first, introduction of the aminomethyl group into the benzene ring instead of the pyrrole ring of the indole nucleus; and second, preferential condensation at *one* of the two available *ortho* positions.

Since both 5- and 6-alkoxyindoles undergo Mannich condensation exclusively at the C-3 position,[14] the presence of a *free* OH group must be crucial in determining the selectivity observed. One possible role for the free OH group involves initial formation of an intermolecular H-bonded complex such as **C** prior to C—C bond formation. This species can then collapse *via* a *quasi* 6-membered transition state to furnish selectively the *ortho* substituted Mannich adduct.*† Taken alone, however, this would suggest a nonspecific Mannich alkylation at both available *ortho* positions.



C: Y = NR_2, OH, or OEt.

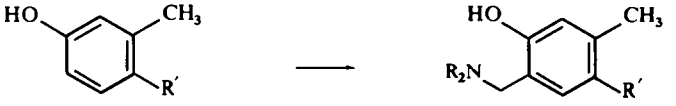
In theory, both steric and electronic factors could contribute to the positive selectivity observed. Experimentally the preferred site for substitution in both the 5- and the 6-hydroxyindole series is the *more* hindered‡ of the two *ortho* positions. In contrast Mannich reactions of phenols generally yield the less hindered product. For example reaction of 3-methyl-[17] and 3,4-dimethylphenol[18] (**14**) gave the C-6 adducts

* The formation of such a chelate was first proposed to account for the *ortho* substitution of phenol in the Mannich reaction.[15]

† For a discussion of the reactive amine-formaldehyde Mannich intermediate see Ref. 16.

‡ Based on the *peri* shielding of C-4 position by the C-3 H atom in the 5-hydroxyindole series and on the *peri* interaction of the indole H atom with C-7 position in the 6-hydroxyindole systems.

15 and 3-acetamidophenol (**16**) furnished the C-6 adduct **17**.[19] Consequently the products observed in the present work are not those anticipated from steric considerations.



14: R′ = H, or Me **15**: R′ = H, or Me

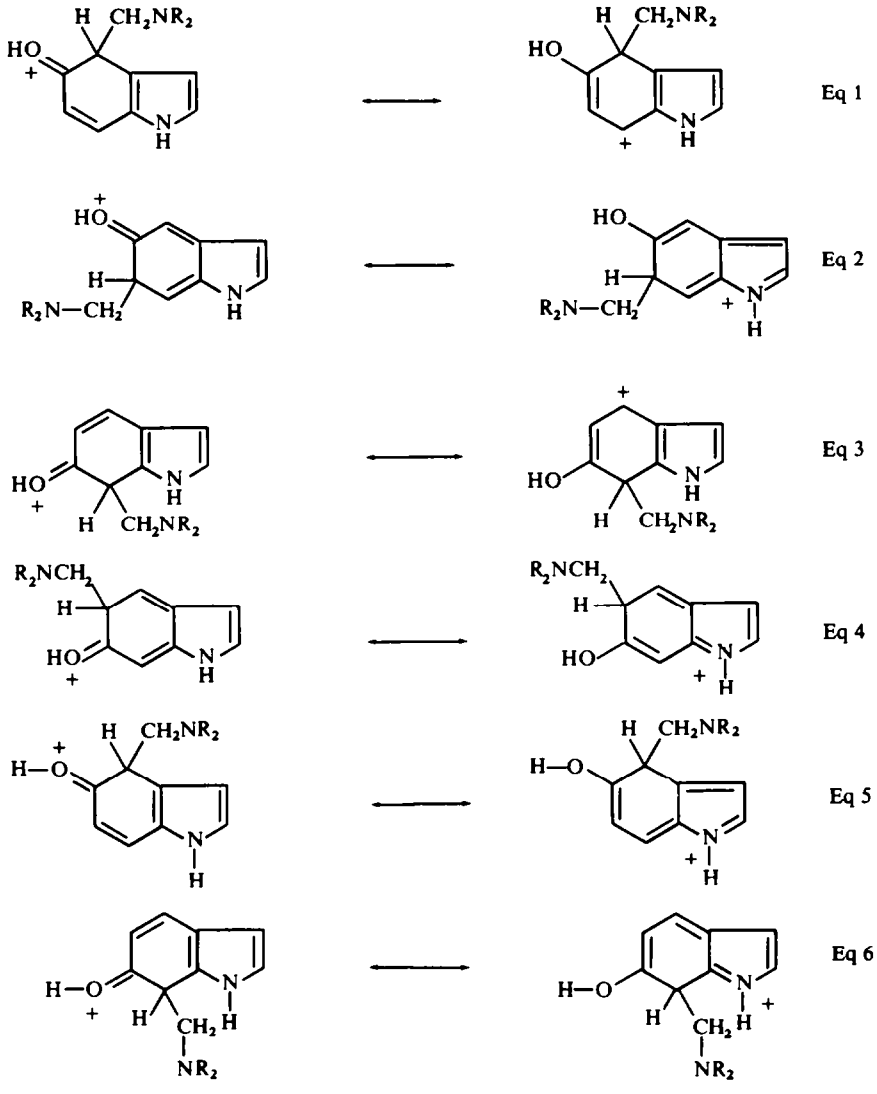
16 **17**

The position selectivity can be accounted for, however, by comparing the cationic intermediates (or transition states) for substitution at both positions. For the 5-hydroxyindole system, substitution at C-4 yields the resonance stabilized cation shown in Eq 1; substitution at C-6 results in the species given in Eq 2. In the 6-hydroxyindole series the analogous sets of intermediates are shown in Eqs 3 and 4.

In both series the preferred product results from the resonance stabilized intermediate (Eqs 1 and 3) in which allylic delocalization is possible *without* disruption of the π-system of the pyrrole ring. Clearly, in each case delocalization into the pyrrole ring is possible. Charge delocalization in the alternative set of intermediates (Eqs 2 and 4), however, requires participation of the π-electrons of the pyrrole ring. Accordingly reaction *via* this pathway would be energetically less favorable.

Alternatively one could consider formal delocalization of the positive charge in the preferred cations (Eqs 1 and 3) from the O atom of the phenol group to the indole N atom as shown in Eqs 5 and 6.[7c] In both the 5- and 6-hydroxyndole series the observed product results from the electronically preferred, more fully conjugated intermediate. For 5-hydroxyindole this comparison involves a conjugated 10π electron system (Eq 5) *versus* a conjugated 8π electron system (Eq 2); for the 6-hydroxyindole skeleton, an 8π electron system (Eq 6) *versus* a 6π electron system (Eq 4). The absence of significant amounts of C-6 substituted 5-hydroxyindoles, which in analogy with the observed C-7 substitution of 6-hydroxyindoles, involves a conjugated 8 π-electron delocalized intermediate suggests that preservation of the π-system of the pyrrole ring and not the extent of the conjugated π-system being delocalized is the major factor in determining the position of substitution.

The reaction of the N-Me derivative **11** to yield a mixture of the unexpected C-6 mono Mannich adduct (**12**) and the C-6, C-8 bisadduct (**13**) indicates that these electronic factors can be balanced to some extent by steric effects.



Acknowledgement—The skilful assistance of Messrs. G. D. Castillo, Jr., R. R. Schmidt, III, and Dr. F. G. Cowherd, III, is gratefully acknowledged.

EXPERIMENTAL

M.ps were observed on a Kofler micro hot stage. IR spectra were recorded on a Perkin–Elmer Model 237 grating IR spectrometer; UV spectra were measured on a Unicam SP 800 recording UV spectrometer; NMR spectra were taken on a Varian Associates Model A-60 NMR spectrometer. TLC on silica gel G was employed routinely. Microanalysis were performed by the Chemalytics, Inc., Tempe, Arizona and by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

General procedures for Mannich reactions

Reactions were run on a 1 to 10 mmole scale; yields reported are for crystalline material and are not necessarily optimum. Due to the air sensitivity of some of the Mannich adducts, chromatographic (TLC), physical (mp) and spectral (NMR) data were used as routine criteria of purity.

(a) A mixture of paraformaldehyde (1 eq), amine (1 eq) [piperidine or aqueous (25 or 40%) dimethylamine] and ethanol (ca. 5 ml per mmole) was warmed to give a homogeneous soln. This soln was cooled, the hydroxindole (1 eq) was added and the resulting mixture was stirred under N_2. The course of the reaction was monitored by TLC; reaction was usually complete after 4–10 hr at room temp or 0·5–3 hr at reflux. The crude product, obtained by evaporation of the final reaction soln, was purified by chromatography on alumina (activity III) and/or crystallization to yield pure material as judged by TLC, physical and spectral data.

(b) The procedure outlined in (a) was followed except that 10% AcOH-EtOH was used as a solvent. The final reaction mixture was neutralized with Na_2CO_3,aq and extracted with benzene or CH_2Cl_2. After drying ($MgSO_4$) the residue obtained from evaporation was purified as above.

(c) Procedure (b) was followed except glacial AcOH was used as a solvent. The reactions were usually complete after ca. 0·2–2 hr reflux.

5-Hydroxy-4-piperidinomethylindole (**1p**) was prepared from **1**[20] by procedure (a) in 81%; m.p. 91–92·5° (cyclohexane); UV max (95% EtOH) 217, 273, 301 and 308 (sh) nm (ε 18000, 7500, 4100 and 3800 resp); IR ($CHCl_3$);* NMR, Table 4. (Found: C, 73·33; H, 7·61; N, 12·65 calcd. for $C_{14}H_{18}N_2O$: C, 73·01; H, 7·88; N, 12·17).

5-Hydroxy-4-piperidino [*and dimethylamino*] *methyl-2-methylindole* (**2p,d**). The adduct **2p** was prepared from **2**[22] by procedure (a) in 72%; m.p. 98–99° (benzene-light petroleum); UV max (95% EtOH) 216, 276, 294 (sh) and 307 (sh) nm (ε 22,000, 9100, 5500 and 3900 resp); IR ($CHCl_3$),* NMR, Table 4. Hydrochloride salt of **2p**, m.p. 175–176°.

The adduct **2d** was prepared by procedure (a) in 50% yield; m.p. 130–131° (benzene:hexane); IR ($CHCl_3$),* NMR, Table 4. (Found: C, 70·23; H, 8·10; N, 13·79 calcd. for $C_{12}H_{16}N_2O$: C, 70·54; H, 7·90; N, 13·72).

5-Hydroxy-4-piperidino [*and dimethylamino*] *methyl-3-carbethoxy-2-methylindole* (**3p,d**). The adduct **3p** was prepared from **3**[22] by procedure (b) in 57%; m.p. 156–158° (EtOH); IR ($CHCl_3$),* NMR, Table 4. (Found: C, 68·38; H, 7·79; N, 8·99 calcd. for $C_{18}H_{24}O_3N_2$: C, 68·33; H, 7·65; N, 8·85).

The adduct **3d** was prepared by procedure (c) in 70%; m.p. 112–113° (cyclohexane) (lit.[9b] m.p. 114·5–116·5°) IR ($CHCl_3$),* NMR, Table 4; hydrochloride salt of **3d**, m.p. 215–216° (lit.[23] m.p. 224–225°).

5-Hydroxy-3,4-bis(dimethylaminomethyl)-2-methylindole (**2b**) was prepared from the adduct **2d** by procedure (b) in 61% yield; m.p. 151–153° (cyclohexane); IR ($CHCl_3$):* NMR, Table 4. (Found: C, 69·18; H, 9·00; N, 16·19 calcd. for $C_{15}H_{23}N_3O$: C, 68·91; H, 8·88; N, 16·09).

6-Hydroxy-5-piperidino [*and dimethylamino*] *methyl-1,2,3,4-tetrahydrocarbazole* (**5p,d**). The adduct **5p** was prepared from **5**[24] by procdure (a) in 78%; m.p. 163–164° (EtOH); UV max (95% EtOH) 231, 284, and 295 (sh) nm (ε 20,800, 8600 and 7500 resp); IR ($CHCl_3$);* NMR, Table 4. (Found: C, 76·24; H, 8·53; N, 9·80 calcd. for $C_{18}H_{24}N_2O$: C, 76·02; H, 8·51; N, 9·85).

The adduct **5d** was prepared by procedure (a) in 60%; m.p. 128–133° (benzene-light petroleum); IR;* NMR, Table 4. (Found: C, 72·94 and 74·89; H, 8·16 and 8·49; N, 11·38 calcd. for $C_{15}H_{20}N_2O$: C, 73·73; H, 8·25; N, 11·47).

6-Hydroxy-9-methyl-1,2,3,4-tetrahydrocarbazole (**6**). A soln of 6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole[25] (650 mg, 3 mmoles) in 48% HBr (3 ml) and AcOH (19 ml) was heated under reflux for 16 hr under N_2. The cooled soln was neutralized with Na_2CO_3,aq and extracted with CH_2Cl_2. The residue obtained from evaporation of the dried ($MgSO_4$) organic phase was chromatographed on alumina (activity III) to give 250 mg of **6** (41%). Sublimation at ca. 100° (0·5 mm) furnished pure **6** m.p. 112–114° (lit.[26] m.p. 101–102°); UV max (95% EtOH) 231, 286, and 299 (sh) nm (ε 21,000, 7000, and 5900 resp); IR ($CHCl_3$), 3600, 3377 (broad) cm^{-1}; NMR, Table 3.

6-Hydroxy-5-piperidinomethyl-9-methyl-1,2,3,4-tetrahydrocarbazole (**6p**) was prepared from **6** by procedure (b) in 84%, m.p. 147·5–148·5 (EtOAc); UV max (95% EtOH) 232, 287 and 308 (sh) nm (ε 19,600, 7000 and 5900 resp); IR ($CHCl_3$);* NMR, Table 4. (Found: C, 76·35; H, 9·05; N, 9·35 calc. for $C_{19}H_{26}N_2O$: C, 76·47; H, 8·78; N, 9·39).

6-Hydroxy-5-methyl-1,2,3,4-tetrahydrocarbazole (**7**) was prepared by hydrogenolysis[27] (Pd/C, 50 psi, 3 hr at 80° in 95% EtOH) of adduct **5d** in 90%, m.p. 125–128° (sublimation, ca. 105°, 0·5 mm); UV max (95% EtOH) 227, 279 and 294 (sh) nm (ε 15,300, 5700 and 4000 resp); IR ($CHCl_3$) 3600, 3470 cm^{-1}; NMR, see Table 3. (Found: C, 77·46; H, 7·39; N, 7·01 calcd. for $C_{13}H_{15}NO$; C, 77·58; H, 7·51; N, 6·96).

* A sharp absorption for the indole N—H at 3480–3470 cm^{-1}, H-bonded —OH from 3500 to 3050 cm^{-1} and a series of absorptions[21] from 2700 to 2200 cm^{-1} were characteristic of the Mannich adducts.

6-Hydroxy-9-piperidinomethyl-5-methyl-1,2,3,4-tetrahydrocarbazole (**7p**) was prepared from **7** by procedure (b) in 65% yield, m.p. 146·5–147·5° (EtOH); UV max (95% EtOH) 229, 281, and 303 (sh) nm (ε 14,500, 5400 and 3700 resp); IR ($CHCl_3$) 3600 cm^{-1}; NMR, Table 4. Attempts to purify this material for analysis were unsuccessful.

Chromatography of the mother liquors from above furnished a second product formulated as the 7,9-diadduct, 6-hydroxy-7,9-bis(piperidinomethyl)-1,2,3,4-tetrahydrocarbazole, in 13%; m.p. 147–148°, m.m.p. with **7p**, 125–135°; IR ($CHCl_3$) 3200–2600 cm^{-1} (broad); NMR ($CDCl_3$) δ 6·85 (s, 1, C-8 aromatic proton), 4·43 (s, 2) and 3·70 (s, 2) (two $-CH_2-N<$), 2·55 (s, 3, C-5 Me group).

6-Hydroxy-5,9-bis(piperidinomethyl)-1,2,3,4-tetrahydrocarbazole (**5b**) was prepared from adduct **5p** by procedure (a) in 84%; m.p. 182–184° (dec) (cyclohexane); UV max (95% EtOH) 232, 286, and 300 (sh) nm (21,900, 9500, and 7400 resp); IR ($CHCl_3$) 3200–2600 cm^{-1} (broad); NMR, see Table 4. (Found: C, 75·54; H, 9·51; N, 10·57 calcd. for $C_{24}H_{35}N_3O$: C, 75·55; H, 9·25; N, 11·01).

7-Hydroxy-8-piperidinomethyl-1,2,3,4-tetrahydrocarbazole (**10p**) was prepared from **10**[28] by procedure (a) in 69%; m.p. 163–164° (aqueous EtOH); UV max (95% EtOH) 230, 274, 303 nm (ε 27,000, 4600, and 4400 resp); IR ($CHCl_3$);* NMR, Table 4. (Found: C, 76·07; H, 8·41; N, 9·88 calcd. for $C_{18}H_{24}N_2O$: C, 76·02; H, 8·51; N, 9·85).

7-Hydroxy-9-methyl-1,2,3,4-tetrahydrocarbazole (**11**) was prepared from 7-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole by treatment with HBr-HOAc (as described for **6**) in 47%; m.p. 122–124° (sublimation, 94°, 0·05 mm); IR ($CHCl_3$) 3580, 3300 (broad) cm^{-1}; NMR Table 3. (Found: C, 77·14; H, 7·39; N, 7·31. Calc. for $C_{13}H_{15}NO$: C, 77·58; H, 7·51; N, 6·91%).

7-Methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole was prepared from 7-methoxy-1,2,3,4-tetrahydrocarbazole by treatment with excess Me_2SO_4 and KOH in aqueous acetone in 88%, m.p. 120–124° (sublimation, 90°, 0·1 mm) (lit.[29] m.p. 95–96); IR ($CHCl_3$), no OH or NH; NMR ($CDCl_3$) δ 3·81 (s, 3, —OMe), 3·44 (s, 3, $\diagdown\!\!\diagup$N—Me).

7-Methoxy-1,2,3,4-tetrahydrocarbazole was prepared from the **10**[26] by treatment with Me_2SO_4 and KOH in aqueous acetone in 78%; m.p. 144–146°, (aqueous EtOH) (lit.[30] m.p. 144–145°); IR ($CHCl_3$) 3480 cm^{-1} (sharp, indole N—H); NMR ($CDCl_3$) δ 3·78 (s, 3, $-OCH_3$).

Direct conversion of **10** to 7-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole using excess Me_2SO_4 and base was unsuccessful; the 7-methoxy derivative was isolated in good yield.

TABLE 3. NMR CHEMICAL SHIFT DATA FOR SOME 5- AND 6-HYDROXYINDOLE SYSTEMS

Compound[b]	Chemical shifts[a] Aromatic protons[c] H_4	H_5	H_6	H_7	Other groups[c]
1	7·04[d]	HO—	6·73[e]	7·23[f]	7·13(C_2H); 6·32(C_3H)
2	6·90[d]	HO—	6·62[e]	7·10[f]	6·00(C_3H); 2·33(C_2—Me)
3	7·48[d]	HO—	6·72[e]	7·16[f]	2·65(C_2—Me)
5	6·82[d]	HO—	6·60[e]	7·05[f]	
6	6·80[d]	HO—	6·64[e]	6·92[f]	3·33(indole N—Me)
7	—	HO—	6·57[f]	6·80[f]	2·47(C_4—Me)
10	7·03[f]	6·55[e]	HO—	6·69[d]	
11[g]	7·28[f]	6·60[e]	HO—	6·65[d]	3·45(indole N—Me)

[a] Reported in ppm downfield from internal TMS; MeOH solvent.

[b] See Tables 1 and 2 for compound identification.

[c] Indole ring numbering used for both indole and tetrahydrocarbazole nuclei.

[d] Doublet ($J_m \sim 2·5$ Hz). [e] Doublet of doublets ($J_o \sim 8·5$ Hz, $J_m \sim 2·5$ Hz).

[f] Doublet ($J_o \sim 8·5$ Hz). [g] $CDCl_3$ solvent.

* A sharp absorption for the indole N—H at 3480–3470 cm^{-1}, H-bonded —OH from 3500 to 3050 cm^{-1} and a series of absorptions[21] from 2700 to 2200 cm^{-1} were characteristic of the Mannich adducts.

7-Hydroxy-6-piperidinomethyl [and 6,8-*bis*(*piperidonomethyl*)]-9-*methyl*-1,2,3,4-*tetrahydrocarbazole* (**12**, **13**). Mannich condensation of **11** under procedure (a) gave little or no reaction (TLC); using procedure (b) a mixture of the C-6 mono adduct **12** (major product) and the C-6, C-8 bisadduct **13** (minor product) were formed, together with trace amounts of unidentified material (TLC). Partial separation of **12** and **13** was effected by chromatography (alumina, activity III); structural assignments were based on the NMR data presented in Table 4.

TABLE 4. NMR CHEMICAL SHIFT DATA FOR SOME 5- AND 6-HYDROXYINDOLE MANNICH ADDUCTS

Compound[b]	Chemical shift[a]					
	Aromatic protons[c]				CH_2NR_2[d]	Other groups[c]
	H_4	H_5	H_6[e]	H_7[e]		
1p	—	HO—	6·72	7·08	3·87	7·02(C_2H); 6·34(C_3H)
2p	—	HO—	6·67	6·98	3·83	6·05(C_3H); 2·32(C_2—CH_3)
2d	—	HO—	6·67	6·93	3·75	6·00(C_3H); 2·24(C_2—CH_3)
3p	—	HO—	6·67	6·98	4·25	2·55(C_2—CH_3)
3d	—	HO—	6·67	7·00	4·25	2·52(C_2—CH_3)
2b	—	HO—	6·67	6·90	3·37, 4·18	
5p	—	HO—	6·62	6·97	4·03	
5d	—	HO—	6·67	6·98	4·02	
6p	—	HO—	6·72	7·02	4·03	3·43(indole N—CH_3)
7p	—	HO—	6·58	7·05	4·46	2·53(C_4—CH_3)
5b	—	HO—	6·67	7·18	4·08, 4·43	
10p	7·17[e]	6·60[e]	HO—	—	3·70	
12	7·03[d]	—	HO—	6·70[d]	3·74	3·47(indole N—CH_3)
13	7·0[d]	—	HO—	—	3·8, 3·7	3·94(indole N—CH_3)

[a] Same as Table 3; $CDCl_3$ solvent. [b, c] See Table 3. [d] Singlet.
[e] Doublet ($J_o \sim 8·5$ Hz).

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