

The Synthesis of Pyrrolo[3,2,1-*hi*]indole

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We have for some time been interested in the study of heteroaromatic ring systems that owe their aromaticity to the presence of a pyrrolo-like nitrogen atom at a ring fusion position (1,2). An extension of these studies has led us to attempt the preparation of the parent pyrrolo[3,2,1-*hi*]indole (4), since this compound, if planar, should be aromatic according to Craig's rule (3).

Fischer syntheses of derivatives of compounds 4 and 5 have been reported (4,5,6).

When boron trifluoride etherate (7) was used for the cyclization of the hydrazone of ethyl pyruvate and *N*-aminoindoline, we obtained a 54 percent yield of the indole derivative 1, along with a 0.25 percent yield of 1,2-dihydro-4-oxo-5-hydroxypyrrolo[3,2,1-*ij*]quinoline which was obtained as major product by Rapoport and Tretter (6). Compound 1 could be dehydrogenated by treatment with a suspension of palladium on carbon suspended in refluxing nitrobenzene. It is of interest to note, that the dehydrogenation in *p*-cymene did not give the desired product. The ester 2 was readily hydrolyzed

to the carboxylic acid 3, which in turn could be decarboxylated by cupric oxide in quinoline, to yield the parent compound 4 (Scheme 1).

A comparison of the chemical shifts of the various protons in 7-methylindole with the corresponding ones in compound 5 (6) shows that there is no significant structural deformity introduced upon incorporation of the two-carbon bridge into the indole skeleton.

The benzene-induced solvent shifts of proton resonances in nmr spectra have recently been studied, largely by Williams and his coworkers (8). These investigators have shown that a benzene molecule will interact at electron deficient sites in the solute molecules in such a fashion that a nonplanar collision complex is formed in which the benzene ring lies as far as possible from the negative end and close to the positive end of the local dipole. This complexing causes the protons close to the shielding region of the benzene ring to appear at more shielded frequencies than they do in an "inert" solvent, such as carbon tetrachloride.

SCHEME 1

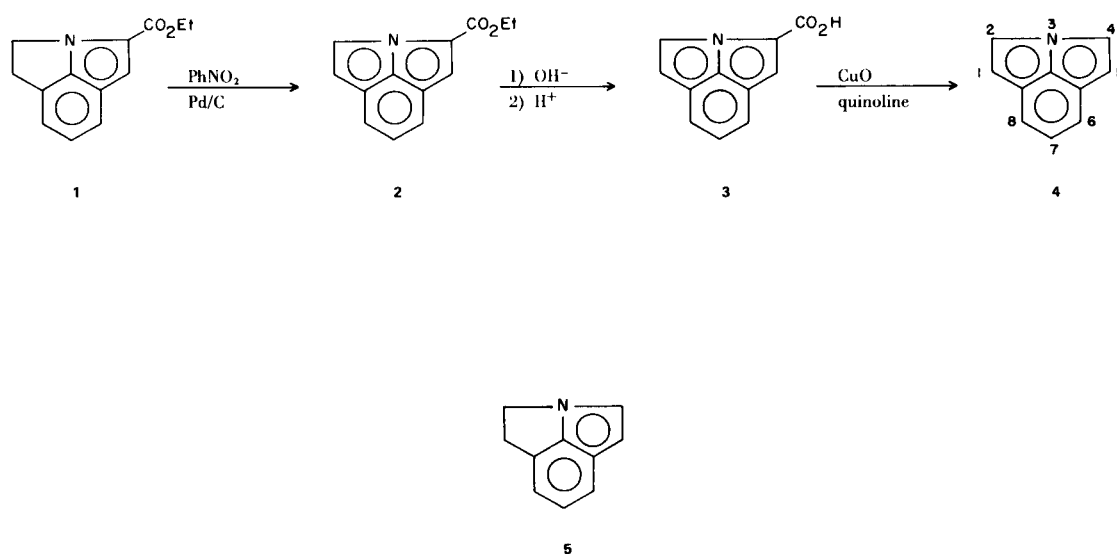


TABLE I
PMR Parameters of Pyrrolo[3,2,1-*h,i*]indole and Some of its Derivatives

Compound	Solvent	Chemical Shifts (τ)										Coupling constants (cps)					
		H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	J ₁₂	J ₂₃	J ₄₅	J ₅₆	J ₆₇	J ₇₈	J ₆₈	
5	CDCl ₃	6.74	6.07	—	3.19	3.70	2.72	3.10	3.27	7.5	—	2.6	—	—	7.5	—	—
	CCl ₄	6.34	5.64	—	3.06	3.72	2.83	3.16	3.26	7.5	—	2.6	—	—	7.5	—	—
	C ₆ D ₆	6.92	6.42	—	3.28	3.56	2.58	2.94	3.18	7.5	—	2.6	—	—	7.5	—	—
4	($\Delta(\tau_{\text{CCl}_4-\text{C}_6\text{D}_6}$)	0.58	0.78	—	0.22	0.16	0.25	0.22	0.08	—	—	—	—	—	—	—	—
	CDCl ₃	3.40	2.88	—	2.88	3.40	2.47(a)	2.65(a)	2.47(a)	2.8	—	2.8	—	—	1.0(b)	—	—
	CCl ₄	3.32	2.71	—	2.71	3.32	2.46(a)	2.63(a)	2.46(a)	2.8	—	2.8	—	—	1.0(b)	—	—
($\Delta(\tau_{\text{CCl}_4-\text{C}_6\text{D}_6}$))	C ₆ D ₆	3.48	3.18	—	3.18	3.48	2.47(a)	2.64(a)	2.47(a)	2.8	—	2.8	—	—	1.0(b)	—	—
		0.16	0.47	—	0.47	0.16	0.01	0.01	0.01	—	—	—	—	—	—	—	—
7-Methylindole	CDCl ₃	2.64	3.26	3.48	2.55	3.00	3.10	8.80(CH ₃)	—	2.8	7.5	7.0	—	—	—	—	—

(a) These protons appear as non-first order AB₂ patterns. The chemical shift assignments have been obtained from an appropriate non-first order analysis. (b) This, and the following coupling constants were obtained from an analysis of the C¹³ satellites. Compound **4**, J_{C¹³H-1} = 175 cps.; compound **5**, J_{C¹³H-4} = 172 cps.

These effects can potentially be used to compare, in a qualitative manner, and in closely related systems, the ground-state charge densities (which are, of course, reflected in the "local" dipoles) of closely related molecules. The $\Delta(\tau_{\text{CCl}_4} - \tau_{\text{C}_6\text{D}_6})$ shifts for the protons in 7-methylindole are -0.35 and 0.10 ppm for H-2 and H-3, respectively. The difference between these values (0.45 ppm) compares favorably with the difference (0.41 ppm) in those of the compound **5**, (**6**) where H-4 and H-5 (corresponding to H-2 and H-3 in 7-methylindole) are changed by -0.25 and 0.16 ppm, respectively. Thus, these data also indicate that there is no loss of "aromaticity" in the compound **5**, as compared to 7-methylindole.

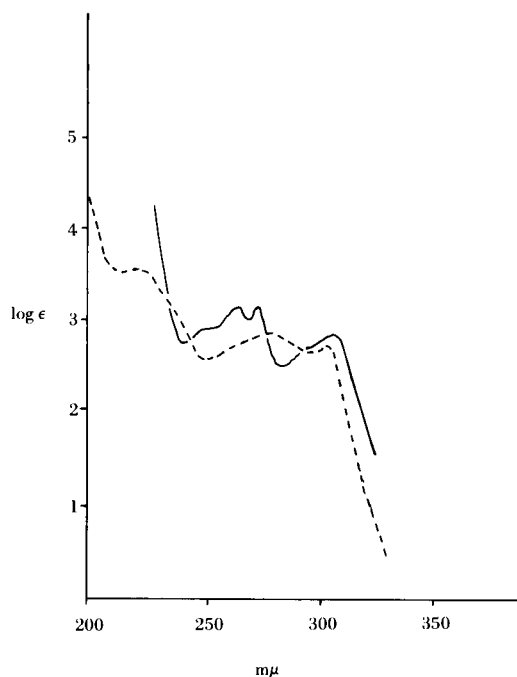


Figure 1. Ultraviolet spectra of compound **5** (---) and compound **4** (—).

A comparison of the chemical shifts of the different protons in the parent compound **4** with the corresponding ones in its precursor compound **5** reveals that the introduction of the double bond has caused all of the protons to become more deshielded. This is consistent with the interpretation that the compound **4** is "more aromatic" than its dihydro derivative **5**, and consequently is also planar.

Since the nitrogen lone pair of electrons in the aromatic compound **4** can be delocalized over two more carbon atoms than in the compound **5**, we anticipate that its electron density will decrease. This decrease will be reflected in a large benzene-induced solvent shift at H-1,2,4 and 5, since the local dipoles in compound **4** will be larger than those in the compound **5**. The solvent shift

data reported in Table I are in agreement with those predictions.

Finally, a comparison of the ultraviolet spectra (Figure 1) clearly shows the enhanced conjugation present in the compound **4** in comparison to the compound **5** (Anet (5) also reported the ultraviolet spectrum of the 1,2,4,5-tetramethyl derivative of **4** and commented on its similarity to indole). The nonbasic nature of these two compounds is demonstrated by the insensitivity of the ultraviolet spectra of the compounds **4** and **5** to acid.

In summary, we can state that the parent pyrrolo[3,2,1-*hi*]indole is an aromatic, nonbasic and planar heteroaromatic compound.

EXPERIMENTAL (9)

2-Carboxypyrrolo[3,2,1-*h,i*]indole (**3**).

A mixture of 1 g. (0.004 mole) of compound 1 and 1 g. of 10% palladium on charcoal suspended in 20 ml. of nitrobenzene was heated under reflux in a nitrogen atmosphere for 12 hours. The reaction mixture was filtered followed by dilution with 10 ml. of quinoline. The solution was further concentrated *in vacuo* and the concentrate was dissolved in ether. The ether solution was successively washed with 5% hydrochloric acid and water. Removal of the ether left an oily residue which was distilled *in vacuo* to afford a yellow oil, b.p. 126°/0.05 mm. This oil was hydrolyzed with 20% aqueous sodium hydroxide, and the solid product that separated upon acidification with concentrated hydrochloric acid was recrystallized from dilute ethanol to give a felted mass of fine colorless needles (0.6 g., 70%) of compound **3**, m.p. 210° dec.; ir (potassium bromide) 1650 cm^{-1} (C=O).

Anal. Calcd. for $\text{C}_{11}\text{H}_7\text{NO}_2$: C, 71.34; H, 3.81; N, 7.57. Found: C, 71.49; H, 3.82; N, 7.86. Mol. wt. (mass spectrometry), 185.

Pyrrolo[3,2,1-*h,i*]indole (**4**).

A mixture of 270 mg. (0.0014 mole) of compound **3** and 500 mg. of cupric oxide in 8 ml. of quinoline was heated under reflux for 5 minutes, cooled, diluted with chloroform and washed with 5% aqueous hydrochloric acid until the washings were acidic. The solution was then washed once with water and the organic layer was dried (magnesium sulfate) and concentrated. The resulting dark oil was distilled in a molecular still (100°/30 mm.) to give a slightly yellow oil (180 mg., 88%), which, on cooling, solidified, m.p. 33-36°; $\text{uv } \lambda \text{ max } 305, 271, 262 \text{ and } 255 \text{ (sh) m}\mu$ ($\log \epsilon, 3.87, 4.22, 4.20 \text{ and } 4.09$).

Anal. Calcd. for $\text{C}_{10}\text{H}_7\text{N}$: C, 85.08; H, 5.00; N, 9.92. Found: C, 84.97; H, 4.97; N, 10.07. Mol. wt. (mass spectrometry), 141.

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Received March 6, 1969

Athens, Ohio 45701