determined[19] to be 1.1×10^{-12} s at 21 °C. This is a measure of the time required for rotation of NH_4^+ by 34° about any axis, within its solvent cage. This time is so short as to signify that solvation and hydrogen bonding hardly retard the rotation. If we convert[20] this value to that for rotation of a tetrahedral NH_3^+ group by 60° about only one axis, subject to an additional barrier of 1.2 kcal/mol, we can calculate that $k_r = 3.0 \times 10^{10}$ s^{-1}. Therefore $2k_d = 6 \times 10^{10}$ s^{-1}.

This value represents quite a fast reaction. It is much too high to be consistent with the suggested pK_a of −1.8. Therefore we reject the conclusion[14] that proton-exchange kinetics support N-protonation of amides. However, the experimental rate constant is distinctly lower than some quite reasonable estimates and slower than two isoenergetic proton transfers.[8] It may be that the necessity for electronic reorganization has reduced the rate slightly. Indeed, an intrinsic barrier[21] $\Delta G_0^{\ddagger}$ of 6 kcal/mol would be sufficient to reduce the rate constant from kT/h to the 6×10^{10} s^{-1} observed.

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Registry No. 1 (R = CH_2=CH), 104213-85-6.

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Activation of the 2-Alkyl Group of a 2-Alkylindole toward Proton Loss and Subsequent Electrophilic Substitution[1]

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A basic tenant of heterocyclic chemistry[2] is that pyridine-like[3] nitrogen atoms cause the activation of ring C-methyl groups toward proton loss. In its simplest examples, 2- and 4-methylpyridine undergo a range of useful reactions which are initiated by this process. Even β-alkyl group such as those in 3-methylpyridine and 3-methylquinoline can be lithiated by lithium diisopropylamide.[4] Similar reactions are well-known and much employed in the chemistry of azines (six-membered rings with two or more nitrogen atoms) and in generalized azoles (five-membered rings containing two or more heteroatoms).

However, such activation is not caused by a pyrrole-like[5] nitrogen atom, and proton loss from C-methyl groups in pyrroles and indoles is difficult.[6] Although the generation of a γ-lithio enamine or a β-aminoallyl carbanion[7] could be anticipated, only one literature reference has been found for such a reaction of a methylpyrrole or -indole.[8] No report has not been found for the formation of a γ-lithio enamine or β-aminoallyl carbanion from a precursor with an N–H moiety. Indeed, our own effort to generate dilithiated species, such as *N*-lithium 2-(lithiomethyl)-indole failed.[9]

We now report that the 2-alkyl groups of N-unsubstituted 2-alkylindoles can be activated toward proton loss by using carbon dioxide both to protect the N–H position and to enable lithiation at the methyl group. Subsequent reaction with an electrophile affords the corresponding 2-(substituted alkyl)indole-1-carboxylic acid, and loss of CO_2 then occurs to reform the NH group. The whole sequence can be carried out in a one-pot procedure, which comprises the following individual operations:

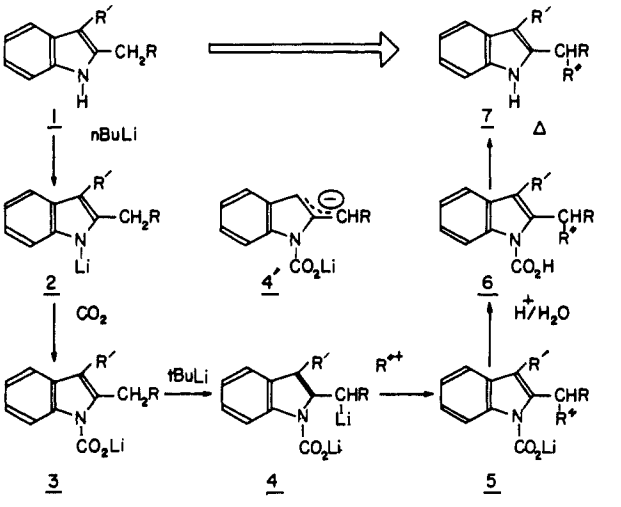
(i) Protection. The 2-alkylindole (**1**) was converted into the corresponding lithium carbamate (**3**) by reaction with *n*-butyllithium in tetrahydrofuran (**1** → **2**), followed by quenching with carbon dioxide (**2** → **3**).

(ii) Lithiation. Lithiation of this lithium carbamate (**3**) was accomplished by the addition of 1.1 equiv of *tert*-butyllithium in tetrahydrofuran at −20 °C for 45 min to give **4**.

(iii) Carbon–Carbon Bond Formation. Intermediate **4** was converted to **5** by adding 1.0 equiv of the electrophile at −70 °C for 2 h.

(iv) Deprotection. Aqueous 2 N sulfuric acid was slowly added to the mixture at −70 °C (**5** → **6**) to give the 1-indolecarboxylic acid (**6**). The isolated acid (**6**) could be decarboxylated under a variety of conditions, e.g., at 100 °C in acid condition. However, we found that brief thermolysis (up to 210 °C for 1 min) was a convenient and high-yielding procedure.

(v) Workup. The crude **7** was chromatographed on silica gel (*n*-hexane) to give the product in high yield.



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(7) Enamines with γ-positions which are also conjugated benzylic systems (e.g., a pyrrolidine enamine of indan-2-one, 1,3-diphenylacetone, or 3,4-diphenylcyclopentenone) can form a γ-lithio enamine or β-aminoallyl carbanion (Thompson, H. W.; Huegi, B. S. *J. Chem. Soc., Chem. Commun.* **1973**, 636. Thompson, H. W.; and Huegi, B. S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1603. Inagaki, S.; Iwase, K.; Goto, N. *J. Chem. Soc., Perkin Trans. 2* **1984**, 2019).
(8) 3-(Hydroxydiphenylmethyl)-1-methyl-2-[2,2-bis(hydroxyphenyl)-ethyl]indole was obtained in 30% yield by reaction of 1,2-dimethylindole with 1 equiv of *n*-butyllithium followed with 1 equiv of benzophenone at reflux in diethyl ether (Szmuszkovicz, J. *J. Org. Chem.* **1962**, *27*, 511).
(9) Dianions of indole derivatives having a δ-amino substituent carrying a dipolar stabilizing group on the amino, such as Li–C(1), formamidine–N(2), and K–N(9) of tetrahydro-β-carboline, were reported: Meyers, A. I.; Loewe, M. F. *Tetrahedron Lett.* **1984**, *25*, 2641.

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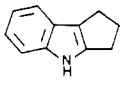
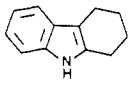
Table I. Preparation of 2-(Substituted alkyl)indoles

entry	R	R′	electrophiles	R″	yield, %[a]	mp, °C	lit. mp, °C
1	H	H	D_2O	D	90	58.0	
2	H	H	CH_3I	CH_3	52	44.5–45.0	43[14]
3	H	H	$CH_3(CH_2)_3I$	$(CH_2)_3CH_3$	58	43.5–44.0	44–44.5[15]
4[b]	H	H	$CH_3(CH_2)_5I$	$(CH_2)_5CH_3$	93	60.0–60.5	61[16]
5	H	H	$CH_3(CH_2)_{11}I$	$(CH_2)_{11}CH_3$	78	69.5–70.0	
6	H	H	$CH_3(CH_2)_{15}I$	$(CH_2)_{15}CH_3$	63	78.0–78.5	
7	H	H	$(CH_2)_4CO$	$C(OH)(CH_2)_4$	58	95.5–96.0	
8	H	H	Ph_2CO	$C(OH)(C_6H_5)_2$	67	134.0–134.5	
9	H	H	*t*-BuNCO	CONHBu-*t*	61	165.0–165.5	
10	H	H	CO_2	CO_2H	70	95.0 dec	93 dec[17]
11	CH_3	H	CH_3I	CH_3	95	65.0–67.0	73–74[18]
12	$(CH_2)_3CH_3$	H	*t*-BuNCO	CONHBu-*t*	60	158.5–159.0	
13	$(CH_2)_5CH_3$	H	*t*-BuNCO	CONHBu-*t*	47	141.5–142.0	
14	H	CH_3	D_2O	D	88	102.0–102.5	
15	H	CH_3	$CH_3(CH_2)_5I$	$(CH_2)_5CH_3$	75	oil	
16	H	CH_3	*t*-BuNCO	CONHBu-*t*	77	179.0	
17	CH_3	CH_3	D_2O	D	0		
18			D_2O		0		
19			D_2O		0		

[a] Isolated yield. [b] 2-Methylindole (10.0 g) was used.

A wide variety of electrophiles were employed to give the corresponding 2-(substituted alkyl)indoles.[10] The results of the preparations of 2-(substituted alkyl)indoles are summarized in Table I.

Deprotonation in all cases proceeded selectively to give the product of electrophilic attack at the α-carbon of the 2-alkylindole. Thus, 2-alkylindole and 2,3-dimethylindole afforded selectively 2-(substituted alkyl)- and 2-(substituted methyl)-3-methylindole products (entries 14–16). No deuteration was observed for 2-ethyl-3-methylindole, for 2,3-trimethyleneindole, and for tetrahydrocarbazole even with prolonged lithiation times, in striking contrast with the successful results obtained with 2-alkylindoles and 2,3-dimethylindole.

Heterocyclic enamines like indole and pyrrole never contain cis hydrogens in the enamino system.[11] Therefore, potential lithiation site of such enamines is limited to be 2-alkyl, 3-alkyl, indole C(3), or aromatic carbons. The results in the table eliminate the possibility of a 3-(lithioalkyl) enamine, a *trans*-β-lithio enamine,[11] or an ortho-lithiated species as intermediate, although selective ortho lithiation was observed for the lithium carbamates of *N*-methyl- and *N*-ethylaniline.[1] The selective alkylation we now find can be rationalized by chelation of the oxygen of the protecting carbamate group[12] stabilizing the γ-lithio enamine. We do not yet understand the reason for the nonreactivity of some 2,3-dialkylindoles as mentioned above. Further study is necessary regarding the precise nature of the intermediate, i.e., the γ-lithio enamine **4** and/or β-aminoallyl carbanion **4′**.

The effectiveness of the methodology now reported is demonstrated by novel routes to 1*H*-2-indoleacetic acids, the corresponding amides, and 2-(β-hydroxy) indoles (entries 7–10, 12, 13, and 16). These rare compounds were previously prepared in seven–eight steps and very low overall yield from 1*H*-2-indolecarboxylic acid.[17]

The results described herein thus provide a new methodology for carbon–carbon bond formation which could be useful, e.g., in alkaloid synthesis. A wide variety of electrophiles can be used: experiments with aromatic aldehydes indicate that the expected products were formed but were unstable.

Registry No. 1 (R = H; R′ = H), 95-20-5; **1** (R = H; R′ = CH_3), 91-55-4; **7** (R = H; R′ = H; R″ = D), 104196-88-5; **7** (R = H; R′ = H; R″ = CH_3), 3484-18-2; **7** (R = H; R′ = H; R″ = $(CH_2)_3CH_3$), 92039-39-9; **7** (R = H; R′ = H; R″ = $(CH_2)_5CH_3$), 54687-20-6; **7** (R = H; R′ = H; R″ = $(CH_2)_{11}CH_3$), 104196-89-6; **7** (R = H; R′ = H; R″ = $(CH_2)_{15}CH_3$), 102874-86-2; **7** (R = H; R′ = H; R″ = $C(OH)(CH_2)_4$), 104196-90-9; **7** (R = H; R′ = H; R″ = $C(OH)(Ph)_2$), 104196-91-0; **7** (R = H; R′ = H; R″ = CONHBu-*t*), 104196-92-1; **7** (R = H; R′ = H; R″ = CO_2H), 32588-36-6; **7** (R = CH_3; R′ = H; R″ = CH_3), 17790-93-1; **7** (R = $(CH_2)_3CH_3$; R′ = H; R″ = CONHBu-*t*), 104196-93-2; **7** (R = $(CH_2)_5CH_3$; R′ = H; R″ = CONHBu-*t*), 104196-94-3; **7** (R = H; R′ = CH_3; R″ = D), 104196-95-4; **7** (R = H; R′ = CH_3; R″ = $(CH_2)_5CH_3$), 104196-96-5; **7** (R = H; R′ = CH_3; R″ = CONHBu-*t*), 104196-97-6; D_2O, 7789-20-0; CH_3I, 74-88-4; $CH_3(CH_2)_3I$, 542-69-8; $CH_3(CH_2)_5I$, 638-45-9; $CH_3(CH_2)_{11}I$, 4292-19-7; $CH_3(CH_2)_{15}I$, 544-77-4; $(CH_2)_4CO$, 120-92-3; Ph_2CO, 119-61-9; *t*-BuNCO, 1609-86-5; CO_2, 124-38-9.

(10) The indole (15.2 mmol) was placed in a three-necked flask flushed with (dry, CaH_2) argon. Tetrahydrofuran (25.0 mL, dried over CaH_2, freshly distilled) was added. The resulting solution was cooled to −70 °C and *n*-butyllithium (Aldrich, 5.8 mL, 2.6 M hexane solution) added slowly. After the mixture was kept at −70 °C for 5 min, the cooling bath was removed. Carbon dioxide gas (Matheson, dried with $CaSO_4 \cdot 0.5H_2O$) was passed into the solution at −70 °C for 10 min. The solvent was removed at ca. 0 °C under reduced pressure to give colorless residue. The interior of the flask was flushed with the argon, and tetrahydrofuran (25.0 mL) was added. The solution was cooled in liquid nitrogen and degassed at 1.0 mmHg. The solution was warmed to −70 °C. *tert*-Butyllithium (Aldrich, 9.9 mL, 1.7 M pentane solution) was added slowly, to give a bright yellow solution. The cooling bath was replaced by an ice–salt bath, and the solution was kept at −20 °C for 45 min. The whole was cooled to −70 °C and the electrophile (15.2 mmol) was added. The reaction mixture was kept at −70 °C for 3 h. Aqueous 2 N sulfuric acid (10 mL) was added slowly at −70 °C, and the solution was extracted with diethyl ether (2 × 50 mL) and the extract was washed with water and dried ($MgSO_4$). Evapolation of the solvent under reduced pressure gave the solid, 2-(substituted alkyl)-3-methyl-indole-1-carboxylic acid. The acid was heated at 210 °C for 1 min to afford the crude product which was chromatographed on silica gel with *n*-hexane as an eluent. Alternatively, another deprotection method was employed for entries 7–9, 12, 13, and 16. After adding the electrophile at −70 °C, the reaction mixture was allowed to regain 25 °C over 10 h. The protecting group was automatically removed. Purification was carried out by column chromatography (silica gel, benzene or dichloromethane) and recrystallization. Deprotection for entry 10: The 2-indole-1-carboxylic acid was dissolved in dimethyl sulfoxide for 5 min at 25 °C. Gas was evolved. The whole was added to cold 2 N sulfuric acid.

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