Carbon-13 Magnetic Resonance Spectroscopy of Coumarins. Carbon-13–Proton Long-Range Couplings

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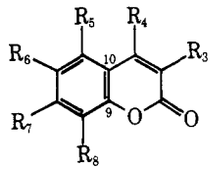
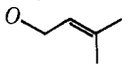
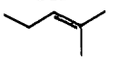
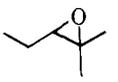
The high-resolution ^{13}C magnetic resonance spectra of eight coumarins have been determined. The ^{13}C–^{1}H long-range couplings are extensively analyzed, and utilized in the spectral interpretation, particularly for the differentiation of some very close resonance signals. The dynamic equilibrium of hydrogen-bonding and stereochemical effects on long-range couplings has been studied. The anti ^{13}C–^{1}H three-bond coupling constants are greater than the syn ones.

A large number of natural products incorporate the coumarin skeleton,[2] which is derived from a cinnamic acid unit. Biosynthetic isoprenylation of coumarins is common, frequently appearing in its simplest form, as the γ,γ-dimethylallyl substituent either on a phenolic oxygen or its adjacent carbon.[2] Progress on the structure elucidation of new coumarins has been tremendously enhanced by the application of proton magnetic resonance spectroscopy.[3] Lately, carbon-13 magnetic resonance (^{13}C NMR) spectroscopy has also been applied in the structural analysis of coumarins. The ^{13}C spectra of some coumarins have been analyzed,[4–8] based on the structural dissimilarily and the additivity principle of chemical shift. Until very recently, the ^{13}C–^{1}H coupling patterns have not been utilized in the spectral analysis of natural products and drugs. We have successfully applied the unique coupling information in the spectral analysis of sulfonamides,[9] antihistaminics,[10] flavonoids,[11,12] and a number of antibiotics.[12] Although Cussans and Huckerby[13] recently used the coupling patterns in their analysis of the ^{13}C spectra of coumarin and its bromo, hydroxy, methoxy, methyl, and glucosyl derivatives, some specific ^{13}C–^{1}H long-range couplings have not been properly assigned. Here we would like to present a detailed discussion of these long-range couplings, including the influence of stereochemical and substitution factors, and the dynamic equilibrium.

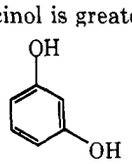
In previous reports,[7b,13] the ^{13}C–^{1}H-long-range coupling constants of coumarins have been partially assigned. An intensive analysis of the ^{13}C–^{1}H coupling patterns of nine coumarins is summarized in Tables I and II. The interpretation follows from the known data on simple aromatic compounds:[10,11,14] (1) $^{3}J_{CH}$ is normally in the range of 4–10 Hz; (2) $^{2}J_{CH}$ is no larger than 4 Hz; and (3) $^{4}J_{CH}$ is less than 2 Hz.

The ^{13}C–^{1}H coupling patterns of the C_9 and C_{10} resonance signals of coumarin (1) were not previously analyzed owing to the complex fine splittings.[7b,13] However, their patterns can be unraveled based on our high-resolution data, and further verified by analysis of the previously undefined coupling constants (Table III). The largest three-bond splitting of the C_9 signal is assigned to the coupling between C_9 and H_5 by comparison with the coupling patterns of 4-, 5-, 7- and 8-substituted coumarins. These comparative studies also indicate the relative magnitude of the other two three-bond couplings [$^{3}J(C_9–H_7) > {}^{3}J(C_9–H_4)$]. Similarly, the order of $^{3}J(C_{10}–H)$ can be determined [$^{3}J(C_{10}–H_6) \geq {}^{3}J(C_{10}–H_3) > {}^{3}J(C_{10}–H_8)$]. The reduction of $^{3}J(C_{10}–H_8)$ can be ascribed to the coupling through an oxygen-substituted carbon.[11] This characteristic reduced coupling has diagnostic value for the spectral analysis of the other oxygen-substituted coumarins except in 6,7- and 7,8-dioxygen-substituted systems.



	R_3	R_4	R_6	R_5	R_7	R_8
1	H	H	H	H	H	H
2	CO_2H	H	H	H	H	H
3	OH	H	H	H	H	H
4	H	OH	H	H	H	H
5	H	H	OH	H	H	H
6	H	H	H	H	OH	H
7	H	H	H	H	OCH_3	H
8	H	H	H	H	*O*-β-D-Glu	H
9	H	H	H	H		H
10	H	H	OH	H	OH	H
11	H	H	*O*-β-D-Glu	H	OH	H
12	H	H	H	H	OH	OH
13	H	H	H	OCH_3	OCH_3	
14	H	H	H	H	OCH_3	
15	H	CH_3	H	H	OH	H
16	H	CH_3	H	H	*O*-β-D-Glu	H
17	H	CH_3	OH	H	OH	H
18	H	CH_3	H	H	OH	OH

A rather large two-bond coupling is observed in 7-oxygen substituted coumarins [$^{2}J(C_9–H_8)$], and 5,7-dihydroxyflavonoids[11,12] [$^{2}J(C_5–H_6)$ and $^{2}J(C_7–H_6)$] as well. It can most likely be attributed to the specific meta-dioxygen substitution which is manifested in the model studies. The $^{2}J(C_1–H_2)$ (4.1 Hz) of resorcinol is greater than that (2.5 Hz) of phenol.[11]



$^{3}J(C_1–H_5) = 11.0$ Hz
$^{2}J(C_1–H_2) = 4.1$ Hz
$^{3}J(C_2–H_4) = 4.8$ Hz

These ^{13}C–^{1}H two-bond coupling constants were tentatively assigned to the ^{13}C–OH coupling.[13] However, this ^{13}C–OH coupling can be ruled out in normal dimethyl sulfoxide solution because of the demonstrated fast dynamic equibration.[11] These two- and three-bond couplings can be very helpful in locating the oxygen substituents in the coumarin system.

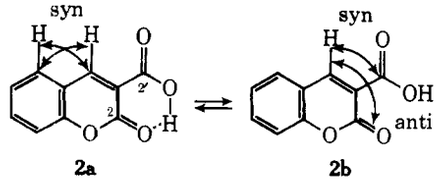
The assignments of $^{2}J(C_2–H_3)$ (4.5 Hz) and $^{3}J(C_2–H_4)$ (11.5

Table I. ^{13}C Chemical Shifts (δ) and ^{13}C–^{1}H Coupling Constants (Hz) of Coumarins [a]

Carbon	1	2	6	10
2	159.2 dd 11.5 (H_4) 4.5 (H_3)	157.5 d 10.3 (H_4)	161.0 dd 11.5 (H_4) 4.9 (H_3)	161.2 dd 11.4 (H_4) 4.8 (H_3)
3	115.2 d 172.6 (H_3)	118.3 d 1.0 (H_4)	111.6 d 172.6 (H_3)	111.9 d 172.1 (H_3)
4	142.5 ddd 164.7 (H_4) 5.4 (H_5) 1.1 (H_3)	148.9 dd 168.0 (H_4) 4.4 (H_5)	144.5 dd 164.5 (H_4) 4.8 (H_5)	144.7 dd 164.6 (H_4) 4.9 (H_5)
5	127.0 dddd 162.7 (H_5) 8.2 (H_7) 4.0 (H_4) 1.3 (H_6)	130.5 ddd 165.6 (H_5) 8.0 (H_7) 4.0 (H_4)	129.8 dd 163.6 (H_5) 3.9 (H_4)	112.6 dd 160.7 (H_5) 4.2 (H_4)
6	123.2 dd 163.8 (H_6) 7.7 (H_8)	125.3 dd 165.3 (H_6) 7.6 (H_8)	113.4 dd 163.6 (H_6) 4.9 (H_8)	143.0 dd 7.0 (H_8) 3.3 (H_5)
7	130.6 ddd 163.4 (H_7) 8.9 (H_5) 0.6 (H_8 or H_6)	134.8 dd 164.4 (H_7) 8.5 (H_5)	161.5 dd 10.9 (H_5) 3.4 (H_8) 2.1 (H_6)	150.5 dd 8.1 (H_5) 3.7 (H_8)
8	115.1 dd 165.0 (H_8) 7.7 (H_6)	116.5 dd 166.3 (H_8) 7.1 (H_6)	102.5 dd 162.8 (H_8) 4.5 (H_6)	102.9 d 161.6 (H_8)
9	152.6 ddddd 10.2 (H_5) 7.4 (H_7) 5.6 (H_4) 2.8 (H_8) 1.3 (H_6 or H_3)	154.7 m	155.8 ddd 9.9 (H_5) 5.7 (H_4) 4.5 (H_8)	148.8 ddd 10.0 (H_5) 6.2 (H_4) 4.9 (H_8)
10	117.6 tdt 8.5 (H_6, H_3) 4.6 (H_8) 1.5 (H_5 or H_4)	118.2 dd 6.8 (H_6) 5.4 (H_8)	111.6 tdt 7.2 (H_6, H_3) 6.4 (H_8) 1.5 (H_5 or H_4)	111.2 ddd 8.1 (H_3) 5.4 (H_8) 1.5 (H_5 or H_4)

[a] The data for each carbon resonance are shown in the following order: chemical shift, multiplicity, and coupling constants (coupled protons). m: unresolved multiplet.

Hz) of coumarin are ascertained by studying the coupling pattern change of **2**, in which the smaller splitting [$^{2}J(C_2$–$H_3)$] is absent. The allocation of C_2 and $C_{2'}$ resonances of **2** is derived from simple chemical shift theory.[15] Their coupling analyses disclose the stereospecificity of the ^{13}C–^{1}H three-



2a **2b**

bond couplings, $^{3}J(C_2$–$H_4)$ (10.3 Hz) (anti) > $^{3}J(C_{2'}$–$H_4)$ (5.4 Hz) (syn). This result is consistent with Marshall's study on crotonic and isocrotonic acids.[16] The steric dependence of three-bond couplings can also account for the reduction of $^{3}J(C_4$–$H_5)$ and $^{3}J(C_5$–$H_4)$ since they are syn couplings. Based on the coupling analysis described above, the C_{10} peak [118.2 ppm; $^{3}J(C_{10}$–$H_6)$ = 6.8 and $^{3}J(C_{10}$–$H_8)$ = 5.4 Hz] of **2** can be easily distinguished from the C_3 peak [118.3 ppm; $^{2}J(C_3$–$H_4)$

Table II. ^{13}C Chemical Shifts (δ) and ^{13}C–^{1}H Couplings (Hz) of Isoprenyl Coumarins [a]

Carbon	9	13	14	19[c]
2	160.1 dd 11.3 (H_4) 4.6 (H_3)	160.9 dd 11.6 (H_4) 4.3 (H_3)	161.1 dd 11.6 (H_4) 4.9 (H_3)	161.3 dd 11.6 (H_4) 3.9 (H_3)
3	111.9 d 172.1 (H_3)	112.4 d 172.1 (H_3)	110.5 d 172.7 (H_3)	110.4 d 172.7 (H_3)
4	142.7 dd 163.0 (H_4) 4.9 (H_5)	143.5 dd 162.4 (H_4) 4.9 (H_5)	138.6 d 165.4 (H_4)	138.7 d 166.0 (H_4)
5	128.1 dd 163.0 (H_5) 3.7 (H_4)	126.0 dd 163.3 (H_5) 2.8 (H_4)	155.7 m[b]	156.0 m[b]
6	112.1 dd 164.2 (H_6) 4.9 (H_8)	107.0 d 161.7 (H_6)	90.2 d 158.7	95.5 dd 160.8 (H_6) 5.2 (H_8)
7	161.2 dtd 10.0 (H_5) 5.7 (H_{11}) 3.0 (H_8)	159.8 m[b]	161.2 m[b]	163.5 sex.[b] 4.2 (H_6, H_8, OMe)
8	100.6 dd 163.1 (H_8) 4.3 (H_6)	117.3 m[b]	106.0 q 4.9 (H_6, H_{11})	92.5 dd 165.1 (H_8) 4.0 (H_6)
9	154.9 dt 9.8 (H_5) 5.5 (H_4, H_8)	152.4 dq 9.8 (H_5) 5.0 (H_4, H_{11})	153.9 m[b]	156.5 t 5.5 (H_4, H_3)
10	111.6 td 8.1 (H_3, H_6) 4.9 (H_8)	112.6 tt 8.2 (H_3, H_6) 1.8 (H_4, H_5)	103.5 dd 7.6 (H_3) 5.8 (H_6)	104.0 dt 7.9 (H_3) 5.2 (H_6, H_8)
11	64.6 td 143.6 (H_{11}) 2.7 (H_{12})	21.6 td 129.3 (H_{11}) 3.7 (H_{12})	21.8 td 130.6 (H_{11}) 4.3 (H_{12})	65.5 td 143.7 (H_{11}) 2.9 (H_{12})
12	118.1 dm[b] ca. 156 (H_{12})	120.8 dm[b] 161.1 (H_{12})	59.1 dm[b] 175.8 (H_{12})	118.3 dm[b] 151.4 (H_{12})
13	137.9 m[b]	132.1 m[b]	63.1 m[b]	141.8 m[2]
14	17.5 qdq 125.7 (H_{14}) 8.2 (H_{12}) 4.2 (H_{15})	17.6 qdq 125.4 (H_{14}) 8.1 (H_{12}) 4.2 (H_{15})	19.0 qq 126.5 (H_{14}) 3.4 (H_{15})	16.5 qdt 126.0 8.2 (H_{12}) 3.1 (H_{15})
15	25.0 qdq 125.7 (H_{15}) 6.8 (H_{12}) 4.0 (H_{14})	25.4 qdq 125.1 (H_{15}) 7.2 (H_{12}) 3.9 (H_{14})	24.6 bq[b] 126.9 (H_{15})	39.2 bt[b] 127.0 (H_{15})
OMe		55.7 q 144.5 (OMe)	55.9 q 144.7 (OMe) 55.8 q 144.7 (OMe)	55.5 q 144.7 (OMe)

[a] The data of each carbon resonance are shown in the following order: chemical shift, multiplicity, and coupling constants (coupled protons). [b] b = broad; sex. = sextet; m = unresolved multiplet. [c] C_{16} = 26.0, tq, 127.0 (H_{16}), 4.9 (H_{15}, H_{17}); C_{17} = 123.4, dm, 151.4 (H_{17}); C_{18} = 131.6, m; C_{19} = 17.5, qdq, 125.4 (H_{19}), 8.2 (H_{17}), 4.1 (H_{20}); C_{20} = 25.4, qdq, 125.1 (H_{20}), 7.3 (H_{17}), 4.0 (H_{19}).

Table III. ^{13}C–^{1}H Long-Range Couplings of Coumarins[13,a]

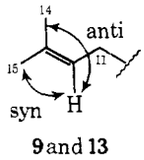
Compd	Coupled proton						
	C_9				C_{10}		
	H_5	H_7	H_4	H_8	H_6	H_3	H_8
3	7.5	6	6		5[c]		4.5[c]
4	9.5	8		2.5	8	5.5[c]	4.5[c]
5	8	8	6	2		8	5
7	*b*				8	8	5
8	*b*				7.5	7.5	5
11	10	6[c]	5[c]	?		8	6
12	8.5		6.5		8	8	
13							
14	10.5			5		b	
15	10.5			5		b	
16	10			4.5		b	
17	9					b	

[a] Carbon spectra were determined at 20 MHz using a Varian CFT-20 spectrometer with 4K data points. [b] The coupling patterns were not reported. [c] These assignments within the same line may be reversed.

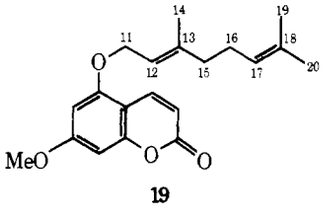
= 1 Hz] despite the fact that their shifts are almost identical, and they cannot be differentiated by conventional chemical shift theory. In the same manner, we can determine the resonance signals of C_3 [115.2 ppm; $^{1}J(C_3–H_3)$ = 172.6 Hz)] and C_8 [115.1 ppm; $^{1}J(C_8–H_8)$ = 165.0, $^{3}J(C_8–H_6)$ = 7.7 Hz] of **1**. Furthermore, in **2** there is no coupling between C_3 and the hydroxy proton, suggesting fast equilibration between conformers **2a** and **2b**, and/or fast intermolecular hydrogen exchange.[11]

The resonance signal assignments of other carbons of **2** can be achieved by analogy to coumarin. These results can then be applied to the spectral interpretation of umbelliferone (**6**) and esculetin (**10**). It is noted that $^{3}J(C_6–H_8)$ and $^{3}J(C_7–H_5)$ have the same magnitude as normal three-bond coupling constants although the coupling occurs through an oxygen-substituted carbon. This seems to be a special case in this particular system because no similar phenomena can be detected in the model study.[17] Further examination of this exception is desirable.

The carbon resonances of the γ,γ-dimethylallyl coumarins (**9** and **13**) can now be assigned, following the approach presented above to unambiguously differentiate C_2 from C_7, and



9 and **13**



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C_3 from C_6 in spite of their small chemical shift differences. Additionally, it is worth noticing that the stereospecificity of ^{13}C–^{1}H long-range coupling can again be used to distinguish the two methyl resonance signals $[^{3}J(C_{14}–H_{12}) > {}^{3}J(C_{15}–H_{12})]$. These assignments ($C_{14}$ = 17.5 ppm and C_{15} = 25.0 ppm) are in agreement with the chemical shift calculation derived from the well-known γ effect.[15] The complicated multiplicity of the C_{12} (118.1 ppm) and C_{13} (137.9 ppm) signals is attributed to the many ^{13}C–^{1}H long-range couplings. The resonance assignments of sibiricin (**14**) can then be made without difficulty based on the conventional chemical shift theory and coupling patterns. However, the stereospecificity of the ^{13}C–^{1}H long-range coupling in an epoxide system is still too uncertain to determine their accurate couplings.

From Roberts' extensive chemical shift analysis of alkenes[18] and the previous interpretation of the γ,γ-dimethylallyl unit, the chemical shifts of the geranyl portion of 5-geranyloxy-7-methoxycoumarin (**19**) can be determined. The relative position of the resonance peaks for C_{12} and C_{17}, and C_{13} and C_{18} are predictable,[18] i.e., $C_{12} < C_{17}$ and $C_{18} < C_{13}$. Therefore, we can assign the peaks at 118.3, 123.4, 131.6, and 141.8 ppm to C_{12}, C_{17}, C_{18}, and C_{13}, respectively. The assignment of the C_{14} signal (16.5 ppm) is derived from the long-range fine splittings $[^{3}J(C_{14}–H_{12})$ (anti) = 8.2 and $^{3}J(C_{14}–H_{15})$ = 3.1 Hz]. On the other hand, the splitting patterns of the C_{19} and C_{20} signals are identical with those in **9** and **13**. The determination of the other resonances is straightforward except the differentiation of C_5 from C_9, and C_6 from C_8. The triplet at 156.5 ppm is assigned to C_9 because of the specific ^{13}C–^{1}H couplings $[^{3}J(C_9–H_4) = {}^{2}J(C_9–H_8)]$ while the partially resolved quintet at 156.0 ppm is designated as the C_5 signal. This splitting is probably due to the less well-defined couplings $[^{3}J(C_5–H_4) \approx {}^{3}J(C_5–H_{12}) \approx {}^{2}J(C_5–H_6)]$. Comparing the C_6 chemical shifts and ^{13}C–^{1}H one-bond coupling constants of osthol (**13**) and umbelliferone (**6**), the shielding effects ($\Delta\delta$ 6.4 ppm and ΔJ = 1.9 Hz) of the large alkyl group (γ,γ-dimethylallyl) at C_8 on the C_6 signal can be predicted. The corresponding values for the C_6 resonance of **19** may then be approximately estimated from those of sibiricin (**14**). The calculated values, 96.6 ppm and 160.6 Hz, permit us to assign the peak at 95.5 ppm $[^{1}J(C_6–H_6)$ = 160.8 Hz] to the C_6 resonance.

Experimental Section

The ^{13}C NMR spectra were obtained in a 10-mm spinning tube. The ^{13}C resonances of deuteriodimethyl sulfoxide and/or deuteriochloroform served as internal references, and converting to the Me_4Si scale involved the following corrections: $\delta(Me_4Si) = \delta(Me_2SO\text{-}d_6) + 39.6$ ppm; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. The instrument employed was a JEOL PFT-100 Fourier transform NMR spectrometer operating at 23 kG, interfaced with a JEOL EC-100 Fourier transform computer with 20K memory. The normal spectra were recorded at ambient temperature using an internal deuterium lock, the chemical shifts were measured at 5 kHz spectral width for proton-decoupled spectra, and at 1.25 kHz (resolution 0.19 Hz) (coumarin in $CDCl_3$), 2 kHz (resolution 0.24 Hz) (umbelliferone and esculetin in $Me_2SO\text{-}d_6$), 4 kHz (resolution 0.48 Hz) (coumarin-3-carboxylic acid in $Me_2SO\text{-}d_6$), and 5 kHz (resolution 0.61 Hz) (*O*-γ,γ-dimethylallylumbelliferone in $CDCl_3$; osthol in $CDCl_3$; sibiricin in $CDCl_3$; 5-geranyloxy-7-methoxycoumarin in $CDCl_3$) for proton-coupled spectra. The typical pulse width was 27.5 μs, and the repetition time between pulses was 8 s. All proton resonances were decoupled by a broad band (2.5 kHz) irradiation from an incoherent 99.99-MHz source for proton noise-decoupled spectra. The absolute magnitudes of the long-range coupling constants of coumarin are determined less accurately than those of the others owing to the strong couplings of H_5, H_6, H_7, and H_8. All deuterated solvents were purchased from Norell Chemical Co. Normal deuteriodimethyl sulfoxide usually contains 0.2–0.5% of water. The coumarin samples analyzed were either obtained commercially, isolated from natural sources, or had been synthesized earlier in these laboratories using published standard procedures.

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Substituent Effects on the Carbon-13 Spectra of Oxindoles

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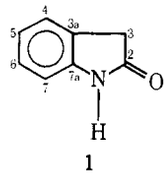
A detailed study of the ^{13}C NMR spectra of oxindoles has been made. A series of 40 oxindoles with varying substitution in the 3, 4, 5, 6, and 7 positions was investigated. Substituents on the 3 position were hydrogen, methyl, and thiomethoxyl. Substituents on the 4, 5, 6, or 7 positions were methoxyl, methyl, hydrogen, chloro, carboethoxy, cyano, and nitro. A set of shift parameters were established for each of these substituents. These were closely related to (but not identical with) previously published shift effects reported for substituents on simple derivatives of benzene. Certain long-range effects were correlated with σ inductive parameters.

Recently, we described a simple process for the preparation of oxindoles in high overall yield from readily available, inexpensive starting materials.[1-4] This has made oxindoles attractive precursors for a wide variety of synthetic schemes designed for the preparation of indole type alkaloids. Since our process for the preparation of oxindoles permitted the presence of both electron-withdrawing and electron-donating substituents on the aromatic nucleus, it also provided the potential for a wide variation in the substitution patterns of the desired indole derivatives. Since ^{13}C NMR is an extremely powerful tool in the elucidation of structure in the alkaloid field,[5] it became of interest to know the exact effect of substituents on the ^{13}C chemical shifts in indole and oxindole type systems. We report here a detailed study of substituent effects on the ^{13}C chemical shifts in oxindoles.

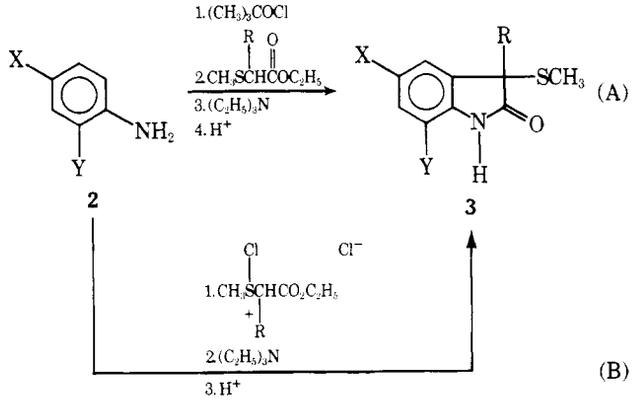
Relatively little is known about the ^{13}C NMR spectral properties of oxindoles. Wenkert and his co-workers have studied the ^{13}C NMR spectrum of oxindole (1) and of a few



1

oxindole derived alkaloids.[6] In the case of 1, the chemical shifts were based on analogy with aniline.[6] Our current study concurs with the literature assignments and adds considerable supporting evidence for the assignments.

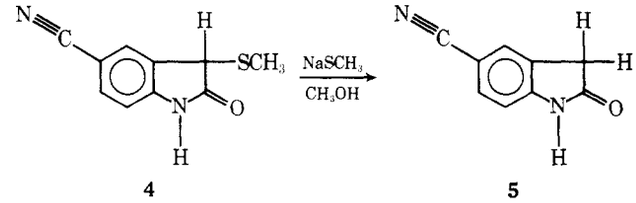
Synthesis of Oxindoles. With the exception of 5-nitrooxindole, which was prepared by the direct nitration of oxindole,[7] all of the oxindoles investigated as part of this study were prepared through either procedure A[1,3] or B.[2,4] In general, method A was used for the preparation of oxindoles bearing electron-withdrawing substituents and process B was used to prepare those oxindoles with electron-donating substituents. Table I lists the yields of oxindoles prepared specifically for this study. All of the other oxindoles investigated were prepared either as previously reported,[1-4] as part of a



(A)

(B)

study of isatin synthesis,[8] or as part of a detailed study of substituent effects on [2,3]-sigmatropic rearrangements of ylides derived from azasulfonium salts.[9] The desulfurization was accomplished in most cases through Raney-nickel reduction. However, in the case of nitro and cyano substituted oxindoles, where side reactions could be noted on Raney-nickel reduction, the thiomethoxyl group was removed via reaction with sodium thiomethoxide in methanol. For example, 4 could be converted into 5 in 62% yield by this method.



4 5

NMR Spectral Studies and Discussion. The ^{13}C NMR spectra of all of the oxindoles studied were obtained in dimethyl sulfoxide-d_6 as solvent with all shifts listed in parts per million relative to tetramethylsilane. Since the values obtained for oxindole (1) were slightly different from those reported by Wenkert and co-workers in chloroform-d, we also